TOXICOLOGICAL REVIEW

OF

BORON AND COMPOUNDS

(CAS No. 7440-42-8)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

February 2001

[Note to Editor: Remove Disclaimer at top and Notice for final reports]

NOTICE

This document is a preliminary draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for peer review on its technical accuracy and science policy implications.

U.S. Environmental Protection Agency
Washington, DC

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FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to boron. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of boron and compounds.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response. Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 513-569-7254.

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This document and summary information on IRIS have received peer review both by EPA scientists and by independent scientists external to EPA. Subsequent to external review and incorporation of comments, this assessment has undergone an Agency-wide review process whereby the IRIS Program Manager has achieved a consensus approval among the Office of Research and Development; Office of Air and Radiation; Office of Prevention, Pesticides, and Toxic Substances; Office of Solid Waste and Emergency Response; Office of Water; Office of Policy, Planning, and Evaluation; and the Regional Offices.

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Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix A.

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CONTENTS (continued)

1. INTRODUCTION

This document presents background and justification for the hazard and dose-response assessment summaries in EPA's Integrated Risk Information System (IRIS). IRIS summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC) and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for noncancer dose-response assessments. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as some carcinogenic responses. 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. The inhalation RfC is analogous to the oral RfD. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral exposure and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. 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 $\mu g/m^3$ air breathed. Another form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

Development of these hazard identification and dose-response assessments for boron has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA,1986a), *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Proposed Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1995a), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Proposed Guidelines for Carcinogen Risk Assessment* (1996a), and *Reproductive Toxicity Risk Assessment Guidelines* (U.S. EPA, 1996b); *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988); (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a); *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b); *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (U.S. EPA, 1994c); *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA,

1995b); *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998); and memorandum from EPA Administrator, Carol Browner, dated March 21, 1995, Subject: Guidance on Risk Characterization.

Literature search strategy employed for this compound was based on the CASRN and at least one common name. At a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

Boron is a non-metallic element that belongs to Group IIIA of the periodic table and has an oxidation state of +3. It has an atomic number of 5 and atomic weight of 10.81. Boron is actually a mixture of two stable isotopes, ^{10}B (19.8%) and ^{11}B (80.2%) (WHO, 1998a). The chemical and physical properties of boron and selected boron compounds are shown in Table 1.

Because boric acid is a weak acid with a pK_a of 9.2, it exists primarily as the undissociated acid (H_3BO_3) in aqueous solution at physiological pH, as do the borate salts (Woods, 1994). Therefore, the toxicity associated with these compounds is expected to be similar based on boron equivalents. Boron oxide will also produce similar effects because it is an anhydride that reacts exothermically with water in the body to form boric acid (WHO, 1998a). Boric acid can form complexes with carbohydrates and proteins in the body (ECETOC, 1994).

Boric acid and sodium salts of boron (primarily borax, or disodium tetraborate decahydrate) are widely used for a variety of industrial purposes including manufacture of glass, fiberglass insulation, porcelain enamel, ceramic glazes and metal alloys. These compounds are also used as fire retardants in cellulose insulation, laundry additives, fertilizers (boron is an essential element for plants), herbicides (at high concentrations boron is toxic to certain plant species) and insecticides (Woods, 1994). Elemental boron has only limited industrial applications.

Boron is a naturally-occurring element that is widespread in nature, albeit at relatively low concentrations (Woods, 1994). Boron concentrations in rocks and soils are typically less than 10 ppm, although concentrations as high as 100 ppm have been reported in shales and some soils. The overall average concentration in the earth's crust has been estimated to be 10 ppm. Concentrations reported in sea water range from 0.5 to 9.6 ppm, with an average of 4.6 ppm. Fresh water concentrations range from <0.01 to 1.5 ppm. Boron in the environment is always found chemically bound to oxygen, usually as alkali or alkaline earth borates, or as boric acid (IEHR, 1997; U.S. EPA, 1987). Elemental boron is not found in nature.

Table 1. Physical and Chemical Properties of Boron and Selected Boron Compounds

	Boron	Boric Acid	Borax	Borax Pentahydrate	Anhydrous Borax	Boron Oxide
CAS Registry Number	7440-42-8	10043-35-3	1303-96-4	12179-04-3	1330-43-4	1303-86-2
Molecular Formula	B	H_3BO_3	$Na_2B_4O_7 \cdot 10H_2O$	$Na_2B_4O_7 \cdot 5H_2O$	$Na_2B_4O_7$	B_2O_3
Molecular Weight	10.81	61.83	381.43	291.35	201.27	69.62
Boron Content (%)	100	17.48	11.34	14.85	21.49	31.06
Physical Form	black crystal or yellow-brown amorphous powder	white or colorless crystalline granules or powder	white or colorless crystalline granules or powder	white or colorless crystalline granules or powder	white or colorless vitreous granules	white or colorless vitreous granules
Specific Gravity (@ 20 °C)	2.34	1.51	1.73	1.81	2.37	2.46
Melting Point (°C)	2300	169	75, decomposes	742	741	450
Boiling Point (°C)	2550	300	320	320	1575, decomposes	1500
Water Solubility (% w/w)	insoluble	4.72 @ 20 °C 27.53 @ 100 °C	4.71 @ 20 °C 65.63 @ 100 °C	3.6 @ 20 °C 50.15 @ 100 °C	2.48 @ 20 °C 34.5 @ 100 °C	rapidly hydrates to boric acid
Vapor Pressure (mm Hg)	1.56×10^{-5} atm @ 2140 °C	No Data	No Data	No Data	No Data	No Data

Sources: ATSDR, 1992; ECETOC, 1994; U.S. EPA, 1987; WHO, 1998a

Boron is not transformed or degraded in the environment, but depending on environmental conditions (e.g., pH, moisture level), changes in the specific form of boron and its transport can occur (ATSDR, 1992). Natural weathering is expected to be a significant source of environmental boron (ATSDR, 1992). The most important source of exposure for human populations is ingestion of boron from food (primarily fruits and vegetables) (Anderson et al., 1994; Naghii and Samman, 1996a; WHO, 1998a). Occupational exposure to borate dust and exposure to borates in consumer products (e.g., cosmetics, medicines, insecticides) are other potentially significant sources.

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

3.1.1. Gastrointestinal Absorption

Boron is well absorbed from the gastrointestinal tract in humans. Schou et al. (1984) administered approximately 131 mg B as boric acid in both water (750 mg) and water-emulsifying ointment (740-1473 mg, approximately 130-258 mg B) to 6 volunteers and found that an average of 92-94% of administered boron was excreted in the urine within 96 hours, indicating that at least that much had been absorbed in that time. Although there was no significant difference in cumulative excretion for the two different vehicles, it was noted that excretion in the first 2-hour sampling period was lower using the ointment, suggesting delayed absorption of boron from the ointment in comparison to the water vehicle. Similarly, two women who ingested approximately 62 mg B as boric acid (in addition to 80-140 mg of boron in food) excreted greater than 90% of ingested boron in the urine in the first week after dosing (Kent and McCance, 1941). Volunteers (n=10) who drank spa waters containing approximately 100 mg daily dose of boron for 2 weeks were also determined to have had over 90% absorption of boron based on urinary excretion data (Job, 1973). Naghii et al. (1977) studied the effect of boron supplementation (10 mg B/d) into the normal diet of male volunteers (n+8). Supplementation of the 10 mg B/day for 4 weeks resulted in 84% recovery in the urine.

Studies in animals have shown that boron is readily absorbed following oral exposure in rats (Ku et al., 1991; Usuda et al., 1998), rabbits (Draize and Kelley, 1959), sheep (Brown et al., 1989) and cattle (Owen, 1944; Weeth et al., 1981). Using mass spectrometry and the boron-10 isotope, Vanderpool et al. (1994) showed that fasted rats fed 20 µg of ^{10}B in the diet eliminated 95% of the ^{10}B in the urine and 4% in the feces within 3 days of dosing, producing a 77% increase in the ratio of ^{10}B to ^{11}B in the urine. Moreover, ^{10}B in the liver peaked within 3 hours of dosing with over 90% recovery and a 56% increase in ^{10}B:^{11}B ratio, which returned to normal within 24 hours. This result suggests that >90% of orally administered boron is absorbed from the gastrointestinal tract within 3 hours, and that absorption is complete within 24 hours.

3.1.2. Respiratory Tract Absorption

Boron is absorbed during inhalation exposure. 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.

Similar evidence of absorption of airborne boron in rats was obtained by Wilding et al. (1959), who monitored urinary boron levels in rats exposed to aerosols of boron oxide (average concentration of 77 mg/m^3). Urinary boron was much higher in exposed rats than controls throughout the 22-week exposure period (average of 11.90 vs. 0.24 mg B/kg-day) and quickly reverted to control levels following cessation of exposure. These data show that inhalation exposure to boron oxide particulate produced high levels of urinary boron, but do not rule out a contribution by gastrointestinal absorption of particles transported from the upper respiratory tract by mucociliary activity. No toxic effects were observed.

3.1.3. Dermal Absorption

Boron is apparently not absorbed across intact skin. Draize and Kelley (1959) found no increase in urinary boron in a volunteer given topical application of powdered boric acid (15 g) to the forearm and held under occlusion for 4 hours. Friis-Hansen et al. (1982) reported no evidence of boron absorption in 22 newborn infants treated dermally with ointment containing 3% boric acid for 4-5 days (total dose of approximately 16 mg B); plasma boron levels fell over the 5-day study period as expected for neonates, and did not differ from 10 untreated controls. Vignec and Ellis (1954) found minimal difference in blood or urinary boron levels in twelve 1-10 month old infants exposed to talcum powder containing 5% boric acid 7-10 times per day for at least one month (estimated daily dose of 2.33 g boric acid or 407 mg B) compared with an equal number of untreated controls. An additional group of 12 infants with mild to moderate diaper rash during the test period were continued on the powder regimen for 48-72 hours after rashes appeared.

Their boron blood levels were similar to controls. However, there is evidence that boron will be absorbed through more severely damaged skin, at least from an aqueous vehicle. Blood and urinary boron levels were increased in 6 male volunteers with severe skin conditions (e.g., psoriasis, eczema, urticaria) following topical application of an aqueous jelly containing 3% boric acid (Stuttgen et al., 1982). However, urinary boron levels did not increase in skin-damaged volunteers given 3% boric acid in an emulsifying ointment.

Studies in laboratory animals have produced similar results. Boron was not absorbed across intact or mildly abraded skin in rabbits topically administered boric acid as the undiluted powder or at 5% in talc or aqueous solution (1.5 hr/day under occlusion for 4 days; 10-15% of body surface exposed) (Draize and Kelley, 1959). However, boron was readily absorbed across severely damaged skin in rabbits, and in proportion to the exposure concentration. Rats with intact skin treated topically with 3% boric acid (ointment or aqueous jelly) did not absorb boron, but urinary boron was increased 4- to 8-fold (to 1% of dose) following exposure to boric acid oleaginous ointment and 34-fold (to 23% of dose) following exposure to aqueous boric acid in rats with damaged skin (Nielsen, 1970).

3.2. DISTRIBUTION

Available studies suggest that boric acid and borate compounds in the body exist primarily as undissociated boric acid, which distributes evenly throughout the soft tissues of the body. Lack of appreciable accumulation of boron in the testis was demonstrated by Lee et al. (1978) and Treinen and Chapin (1991), and in the epididymis by Treinen and Chapin (1991). Ku et al. (1991) studied tissue distribution in male rats fed 9000 ppm of boric acid (1575 ppm boron) for 7 days. The authors estimated the 9000 ppm dose to be 93-96 mg B/kg-day. The tissue levels of boron on day 7 of exposure are listed in Table 2. Boron levels in all tissues except adipose increased rapidly after the start of exposure (2- to 20-fold increase over controls after 1 day). The greatest increase (20-fold) was in bone. Levels in adipose tissue increased only 1.3-fold. Boron levels in plasma and soft tissues other than adipose tissue reached steady-state (12-30 µg/g) within 3-4 days. Variability in levels of boron in all tissues except adipose tissue and bone were approximately 2-fold for any given day of examination (days 1,2,3,4,7). Levels in bone and adipose continued to increase throughout the 7-day study period. In comparison to plasma levels, there was no appreciable accumulation of boron in any soft tissue. However, boron did accumulate in bone, showing a 2- to 3-fold increase over plasma levels after 7 days. Accumulation of boron in bone in rats was also shown by Forbes and Mitchell (1957). Boron levels in adipose tissue remained at 20% of plasma levels after 7 days.

In a follow-up to Ku et al. (1991), Chapin et al. (1997) monitored bone boron concentrations in rats fed 200-9000 ppm of boric acid for 9-12 weeks. Bone boron was significantly increased over controls at 200 ppm and increased proportionally up to 6000 ppm, above which the increase in bone was slightly less than the increase in the feed. Bone boron levels reached steady state within 1 week at doses up to 3000 ppm and after approximately 4 weeks at higher doses. Steady-state bone boron levels were approximately 4-fold greater than serum boron levels.

Table 2. Tissue Levels of Boron in Male Rats on Day 7 of Exposure to 9000 ppm Boric Acid (1575 ppm Boron) in the Diet (µg boron/g tissue)

Tissue	Control	Day 7
Plasma	1.94 ± 0.17	16.00 ± 0.71
Liver	0.66 ± 0.10	13.13 ± 0.54
Kidney	1.55 ± 0.03	19.80 ± 1.65
Adipose	1.71 ± 0.17	3.78 ± 0.13
Muscle	3.69 ± 0.54	14.23 ± 0.19
Bone	1.17 ± 0.19	47.40 ± 1.14
Large Intestine[a]	3.08 ± 0.17	14.90 ± 0.7
Brain	0.76 ± 0.02	13.50 ± 0.86
Hypothalmus[b]	0.91	14.30
Testis	0.97 ± 0.10	16.00 ± 1.19
Epididymis[a]	0.81 ± 0.15	16.81 ± 3.7
Seminal vesicles[a]	1.64 ± 0.23	23.70 ± 6.56
Seminal vesicle fluid[b]	2.05	19.20
Adrenals[b]	7.99	21.90
Prostate[b]	1.20	14.80

Source: Ku et al., 1991

Note: Values are means +/- SE: N = 3 animals unless indicated by footnote

[a] Mean +/- SE N = 3 samples, each sample represents a pool of tissue from two animals

[b] A single sample was analyzed representing a pool from six animals

In a drinking water study using multiple dose levels of boric acid in rats, Naghii and Samman (1996) found, like Ku et al. (1991), that levels of boron in soft tissues were very similar to levels in plasma (the only exception being a 1.5- to 2-fold increase in the kidney that may have been due to contamination with urine because the organ was not perfused prior to analysis). These researchers also found that boron plasma and tissue levels increased proportionally with dose. Bone was not analyzed in this study. WHO (1998a) reported a preliminary comparison of blood boron levels across species in rats exposed to boron in the diet or drinking water and humans exposed in the diet, drinking water or accidental ingestion. Rat and human blood boron levels had a good overlap in the dose range of 0.01-100 mg B-kg body weight. Locksley and Sweet (1954) found that concentration of boron in the tissues was directly proportional to dose over a range of 1.8-71 mg B/kg in mice given borax by intraperitoneal injection.

Evidence that boron does not accumulate in the blood in humans was obtained by Culver et al. (1994). These researchers found no progressive accumulation of boron across the work week as measured by blood and urine levels in mine workers.

3.3. METABOLISM

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). Boron deprivation studies with animals and three human clinical studies have shown that boron affects macromineral and cellular metabolism of other substances that affect life processes such as calcium and magnesium (Section 4.4.4. Nutrition Studies).

Inorganic borate compounds are present as boric acid in the body. Boric acid is the only boron compound that has been identified in urine, and it has repeatedly been found to account for >90% of the ingested boron dose (WHO, 1998a). There is no evidence that boric acid is degraded in the body. Metabolism may not be feasible because a large amount of energy is apparently required to break the boron-oxygen bond (WHO, 1998a). Boric acid can form complexes with various biomolecules (IEHR, 1997; WHO, 1998a). It has an affinity for hydroxyl, amino and thiol groups. Complex formation is concentration dependent and reversible.

3.4. ELIMINATION AND EXCRETION

3.4.1. Urine

The elimination and excretion of boron have been evaluated in humans and rodents, and have demonstrated that more than 90% of an orally administered dose of boric acid is excreted unchanged in the urine a short time after treatment (see Section 3.1.1. for descriptions of several such studies). In humans, Jansen et al. (1984a) and Schou et al. (1984) reported that boron's primary route of elimination was in the urine, and that approximately 93% of an orally administered dose is eliminated within 96 hours. Jansen et al. (1984b) reported that approximately 60-75% of an orally administered dose of 750 mg boric acid (131 mg B) in a water solution or 740-1473 mg boric acid (129.5-261.3 mg B) in a water emulsifying ointment, to

humans is eliminated in urine over the initial 24 hours, with the urinary route of elimination accounting for 93% of the dose at 96 hours post administration. Astier et al. (1988) reported an acute boron intoxication of 45 g boric acid (7.9 g B) where >50% of the dose was eliminated through the kidneys over the first day following ingestion (renal clearance: 0.77 L/hour; tubular reabsorption: 80%; total clearance 10.5 g). Kent and McCance (1941) also reported that 92-93% of an administered oral dose (352 mg as boric acid) in humans was eliminated in urine during the first week following administration. Additional minor elimination pathways include saliva, sweat and feces (Jansen et al., 1984a).

During the development of the toxicological review for boron the body of scientific knowledge on boron revealed that developmental toxicity in the offspring of the pregnant Sprague-Dawley rat was the most sensitive toxic endpoint for development of a Reference Dose (RfD) for boron. Existing pharmacokinetic studies with boric acid also revealed similarities in rats and humans in absorption, distribution and metabolism. Boric acid is not metabolized in rats and humans and is readily absorbed orally; there is no evidence for accumulation, it is distributed throughout the body water and is excreted primarily unchanged in the urine. However, good pharmacokinetic information on the clearance and half-life of boron was not available. Pregnant women were considered to be a sensitive sub-population for intraspecies uncertainty because the most sensitive toxic effect was the developmental effect in the offspring of the rat. Good clearance data for boric acid in pregnant and non-pregnant women were also not available.

Due to this lack of good pharmacokinetic data on renal clearance of boric acid and the importance of these data to the assessment of the toxicity of boric acid, U.S. Borax volunteered to fund three different pharmacokinetic studies in rats and humans to determine renal clearance of boric acid. One study was conducted to determine the renal clearance rate of boric acid in the female rat (both non-pregnant and pregnant) at three different concentrations of a single oral dose. Another study used the highest concentration from this study to determine the half-life of boric acid in the non-pregnant and pregnant rat. A similarly designed study was also conducted in humans to determine the renal clearance rate of boric acid in non-pregnant and pregnant humans. Results of these recently conducted studies can be found in Sections 3.4.1. and 3.4.2.

Following an intravenous dose in humans of 28.52-31.9 mg boric acid (5-5.6 mg B) per minute or a total dose per subject of 520-620 mg boric acid (91-108.5 mg B), high volumes of distribution were reported by Jansen et al. (1984a), who also reported that boron's primary route of elimination was in the urine. When quantified over 120 hours, the fraction of dose eliminated in urine accounted for 98.7$\pm$9.1% of administered dose. Urinary elimination of boron in humans occurs rapidly and is the primary route of elimination. These data indicate almost total bioavailability of an orally administered boron dose in the human.

The urinary elimination of boron administered to male rats has been investigated following the oral administration of sodium tetraborate (at 11 different doses ranging from 0-4 mg

B/kg) by Usuda et al. (1998). The recovery of boron in 24-hour urine accounted for 99.6±9.7% of the administered dose, demonstrating essentially total bioavailability of an orally administered boron dose in rats. In a study conducted in rats with stable-labeled boron, Vanderpool et al. (1994) reported that 95% of the administered (20 µg/kg) dose was eliminated in the urine and 4% in the feces over the initial 3 days post-dosing.

Urinary elimination of boric acid in Sprague-Dawley female rats (non-pregnant and pregnant) was examined in a pharmacokinetic study sponsored by U.S. Borax at the University of California, Irvine (U.S. Borax, 2000 rat study). Three groups of 10 non-pregnant and 10-11 pregnant rats were started on the initial 7-day adequate boron diet on gestation day 9 (GD9). On the morning of the eighth day, the diet for all rats was switched to a low casein diet containing 0.2 mg B/kg diet for a total of 24 hours. This low boron diet was given before and during the initial sampling period to minimize any cross-contamination. After the initial 24 hours, groups of pregnant and non-pregnant rats were given a single oral dose of 0.3, 3.0 or 30 mg/kg of boric acid (0.052, 0.52, and 5.2 mgB/kg, respectively) by gavage in deionized water (ultrapure). The purpose of the choice of doses in this study were as follows: the low dose was chosen as an estimate of the high end human dietary dose level, the highest dose tested was approximately half of the NOAEL from the rat developmental toxicity study (Price et al., 1996).

Two blood samples were drawn from each rat. The first sample was taken 3 hours after gavage dosing on the assumption that the peak boron concentration in the blood had been achieved (based on data from Usuda et al., 1998). The second blood sample was taken 12 hours after the initial sample. Rats were placed in metabolic cages after the first blood sample was taken and urine was collected during the 12 hours between the first and second blood sampling.

The urinary concentration of boron at the high dose was significantly higher in pregnant rats compared with nonpregnant rats but not at the low and mid dose. The concentration of boron in the urine during the 12 hour collection period in the non-pregnant rats was 1.67±0.62 10.12±8.16 and 66.82±47.00 μg B/mL for the low, mid and high dose respectively and in the pregnant rats 1.62±0.49, 12.30±5.12 and 121.45 μg B/mL in the low, mid and high dose respectively. The urine volume was not significantly different in pregnant and non-pregnant rats. The amount of boron (μg/mL) excreted in the urine increased proportionately with increasing dose and during the 12-hour collection period was higher (32-37%) in pregnant rats compared to the non-pregnant rats in the high dose level. This was attributed by the authors to the higher dose of boron administered due to body weight and to the higher fractional excretion of boron(boric acid clearance/creatinine clearance) in the pregnant rats which was statistically significant at the high dose level. The percentage of administered dose of boric acid recovered in the urine was significantly higher in the low dose group compared to the mid and high dose groups for both the non-pregnant and pregnant animals and higher in the pregnant compared to the non-pregnant rats across dose groups which was statistically significant at the high dose only (see urinary data in Table 3).

Clearance rates of boric acid, creatinine and urea were expressed in three different ways mL/min, mL/min/kg of body weight and mL/min/cm^2 of body surface area (see Table 4). Boric

acid clearance was independent of dose within the range of dose levels tested and no significant dose-related differences in boric acid clearance were observed in non-pregnant or pregnant rats.

Table 3. Urinary Boron Concentration, Volume, Mean Excretion, and Percent Recovered in 12 Hours in Non-Pregnant and Pregnant Rats Given Boric Acid by Gavage[a]

Dose (mg BA/kg/day)	Urinary B (µg/mL)		Urine Volume (mL)		12-hr Urinary B Excretion (µg/12 hr)		Percent of Dose in 12-Hr Urine (3-15 Hr)	
	Non-pregnant[b]	Pregnant[b]	Non-pregnant	Pregnant	Non-pregnant[b]	Pregnant[b]	Non-pregnant[b,c]	Pregnant[b,c]
0.3	1.7±0.6[d] (9)	1.6±0.5 (9)	4.3±1.4 (9)	6.1±3.2 (9)	6±1[d] (9)	8±3 (9)	50.4±10.6%[d] (9)	55.6±21.4% (9)
3.0	10.1±8.2 (10)	12.3±5.1 (9)	5.2±3.4 (10)	5.3±2.4 (9)	32±7 (10)	56±16 (9)	24.6±4.5% (10)	35.6±9.4% (9)
30.0	66.8±47.0 (10)	121.4±47.1[e] (11)	6.8±3.9 (10)	5.4±2.5 (11)	324±61 (10)	561±114[e] (11)	24.6±4.3% (10)	34.7±6.4%[e] (11)

[a] Source: U.S. Borax, 2000

[b] Statistically significant difference in urinary boron concentration across dose levels based on two-way ANOVA, $p<0.05$

[c] Statistically significant difference across groups (non-pregnant vs. pregnant) based on two-way ANOVA, $p<0.05$

[d] Mean ± standard deviation (number of rats)

[e] Statistically significant difference between non-pregnant and pregnant rats based on multiple range test, $p<0.05$

Table 4. Clearance of Boric Acid (BA) Creatinine and Urea in Non-Pregnant and Pregnant Rats Given Boric Acid by Gavage expressed as mL/min, mL/min/cm^2 and mL/min/kg[a]

Dose (mg BA/kg)	Boric Acid Clearance (mL/min)		Creatinine Clearance (mL/min)		Urea Clearance (mL/min)	
	Non-pregnant[b]	Pregnant[b]	Non-pregnant	Pregnant	Non-pregnant	Pregnant
0.3	0.77±0.2[c] (9)	1.01±0.2 (9)	1.3±0.4[c] (9)	1.3±0.5 (9)	0.85±0.2 (9)	0.89±0.3 (9)
3.0	0.76±0.2 (10)	0.95±0.2 (9)	1.2±0.4 (10)	1.3±0.4 (9)	0.84±0.3 (10)	1.14±0.4 (9)
30.0	0.81±0.1 (10)	1.07±0.2[d] (11)	1.3±0.4 (10)	1.3±0.3 (11)	0.96±0.3 (10)	1.10±0.3 (11)
expressed as mL/min/cm^2						
0.3	0.0017±0.0004 (9)	0.0020±0.0004 (9)	0.0029±0.0007 (9)	0.0025±0.0009 (9)	0.0019±0.0005 (9)	0.0017±0.0005 (9)
3.0	0.0017±0.0003 (10)	0.0019±0.0003 (9)	0.0027±0.0008 (10)	0.0025±0.0006 (9)	0.0018±0.0006 (10)	0.0022±0.0008 (9)
30.0	0.0018±0.0003 (10)	0.0020±0.0003 (11)	0.0029±0.0008 (10)	0.0025±0.0006 (11)	0.0021±0.0006 (10)	0.0021±0.0004 (11)
expressed as mL/min/kg						
0.3	3.1±0.8 (9)	3.3±0.6 (9)	5.2±1.1[b] (9)	4.3±1.5[b] (9)	3.4±0.9 (9)	2.9±0.9 (9)
3.0	3.0±0.6 (10)	3.2±0.5 (9)	4.8±1.3[b] (10)	4.2±1.1[b] (9)	3.3±1.1 (10)	3.8±1.3 (9)
30.0	3.2±0.5 (10)	3.4±0.5 (11)	5.3±1.6[b] (10)	4.3±1.0[b] (11)	3.8±1.0 (10)	3.5±0.7 (11)

[a] Source: U.S. Borax, 2000
[b] Statistically significant difference across groups (non-pregnant vs. pregnant) based on two-way ANOVA, $p<0.05$
[c] Mean ± standard deviation (number of rats)
[d] Statistically significant difference between non-pregnant and pregnant rats based on multiple range test, $p<0.05$

Individual rat clearance data results presented in Table 5 demonstrate that the clearance of boron (mL/min/kg body mass) is not dependent on the dose of boron administered. Further, there appeared to be no statistically significant difference in the urinary clearance of boron between pregnant and non-pregnant rats.

A further statistical assessment of these data was performed. Because there was no significant difference in the urinary elimination of boron between doses in rats, the values from each of the three dose groups were pooled for further analysis. Results indicated that due to the low number of sample values, no statistically sound determination of the distribution (normal versus log normal) could be ascertained for this sample set. Results presented in Table 6 demonstrate the urinary clearance values for relevant points within either distribution type.

A human study to measure renal clearance of boron normally consumed in the daily diet in non-pregnant and pregnant women was conducted (U.S. Borax, 2000). This study was conducted in 32 women in good health between the ages of 18-40 years. Sixteen women in their second trimester (14-28 weeks) were chosen for this study. Sixteen age-matched non-pregnant women were also chosen for this study. At the beginning of the study all subjects were asked to empty their bladder and a baseline blood sample was taken. During the 2 hours following the blood sample all urine samples were collected. At the end of this 2 hours another blood sample was taken. The subjects were asked to collect all urine for the next 22 hours (24 hours from the baseline). A-24 hour blood sample was also collected. Boron intake was estimated from the renal excretion of boron in 24 hours which was 1.3 mgB/day, from which an average consumption was estimated at 0.02 mgB/kg per day.

Urine collected over the 24-hour period was pooled. Boron content of blood and pooled urine was analyzed via capillary zone electrophoresis by a contract laboratory following scrutinized laboratory analytical standards and practices and employing adequate quality control measures. Urinary clearance was measured by quantifying the amount of boron (mg) in the urine and blood, making the assumption that the blood concentration of boron ascertained at the study's initiation represented the blood boron levels over the period of the study. The urinary clearance of boron in humans was determined in all individuals and presented as mL blood cleared of boron per minute per kg body mass (Table 7). The results indicated that the clearance rate for boron in pregnant women was 0.92 ± 0.59 (mean $\pm$ standard deviation; range 0.265-2.149 mL/min/kg) and the clearance rate for boron in non-pregnant women was 0.64 ± 0.34 (mean $\pm$ standard deviation; range 0.224-1.468 mL/min/kg) mL/min/kg body mass (see Table 8). These results indicate that pregnant women clear boron more effectively than non-pregnant women. These results are consistent with increased measures of renal function in humans during pregnancy. Pregnant rats also clear boron more rapidly than non-pregnant rats as shown in Table 8.

Using the data from the rat and the human renal clearance study, clearance of boric acid in pregnant rats and pregnant humans can be compared. Table 9 shows selected percentiles of the boron clearance distributions for pregnant women and pregnant rats. The observations from all

rat dose groups were combined, as there were no dose-related differences in the clearance values. An empirical distribution function is chosen to represent both rat and human boron

Table 5. Urinary Clearance of Boron in Pregnant Rats[a]

Test Animal	0.3 mg/kg/day[b, c]	3.0 mg/kg/day[b, c]	30.0 mg/kg day[b, c]	Combined[c]
1	not pregnant	2.954	3.329	
2	3.714	2.532	2.670	
3	4.443	--	3.089	
4	3.592	3.822	2.849	
5	3.447	3.784	2.996	
6	2.983	3.564	3.574	
7	3.023	3.064	3.957	
8	3.109	2.640	3.757	
9	2.499	3.116	4.103	
10	3.114	2.978	4.101	
11			3.075	
Mean	3.325	3.162	3.409	3.306
Standard Deviation	0.56 (9)[d]	0.47 (9)	0.52 (11)	0.506 (29)

[a] Adapted from U.S. Borax (2000) rat study.

[b] Dose is presented as mg boric acid/kg/day.

[c] Results presented as mL/min/kg body mass.

[d] N values are presented in parentheses.

Table 6. Urinary Clearance of Boron in Non- Pregnant Rats[a]

Test Animal	0.3 mg/kg/day[b, c]	3.0 mg/kg/day[b, c]	30.0 mg/kg day[b, c]	Combined[c]
1	3.02	3.422	2.896	
2	4.073	2.982	3.927	
3	3.423	2.823	3.203	
4	3.717	3.368	2.647	
5	3.161	3.176	3.252	
6	3.428	3.010	3.213	
7	3.396	3.338	3.691	
8	1.651	3.002	3.834	
9	2.013	3.642	2.579	
10	died	1.514	3.106	
Mean	3.098	3.028	3.235	3.121
Standard Deviation	0.78 (9)	0.59 (10)	0.47 (10)	0.603 (29)

[a] Adapted from U.S. Borax (2000) rat study.

[b] Dose is presented as mg boric acid/kg/day.

[c] Results presented as mL/min/kg body mass.

[d] N values are presented in parentheses.

Table 7. Urinary Clearance of Boron in Women[a]

Test Subject	Non-pregnant[b]	Pregnant[b]
1	0.378	0.265
2	0.224	0.336
3	0.353	0.400
4	0.245	0.936
5	0.624	0.512
6	0.664	1.110
7	0.983	0.906
8	0.438	1.734
9	0.628	2.149
10	0.970	0.612
11	0.601	1.158
12	0.890	0.609
13	1.468	0.741
14	0.549	0.683
15	no subject	2.051
16	no subject	0.492
Mean	0.64	.92
Standard Deviation	0.34	.59

[a] Adapted from U.S. Borax, 2000. (Human Study).

[b] Data are presented as mL blood cleared of boron per minute per kg body mass.

Table 8. Clearance of Boron in Pregnant and Non-Pregnant Rats and Humans

Species	Dose[a]	Boron Clearance (mL/min/kg)	
		Pregnant	Non-Pregnant
Rat[b]	0.3 mg/kg/day	3.36 ± 0.6 (9)[c]	3.10 ± 0.78 (9)
	3.0 mg/kg/day	3.2 ± .05 (9)	3.02 ± 0.59 (10)
	30.0 mg/kg/day	3.4 ± 0.5 (9)	3.24 ± 0.47 (10)
	Combined	3.3 ± 0.51 (29)	3.12 ± 0.60 (29)
Humans[d]	0.114 mg/kg/day [e]	0.92 ± 0.59 (16)	0.64 ± 0.34 (14)

[a] Dose is presented as mg boric acid/kg/day

[b] Data adapted from U.S. Borax, 2000 rat study

[c] Data are presented as mean ± standard deviation (n).

[d] Data adapted from U.S. Borax, 2000 human study

[e] Dietary intake was estimated by U.S. Borax, 2000 human study as 0.02 mg boron/kg/day (equivalent to 0.114 mg boric acid/kg/day)

Table 9. Statistical Analysis of Boron Clearance Values in Pregnant Humans and Pregnant Rats

Parameter	Measured Value (mL/min/kg body mass)	
	Human	**Rats**
Number of Observations	16	29
Mean	0.9184	3.31
Standard Deviation	0.5896	0.506
Empirical Percentiles[a]:		
5th	0.286	2.53
10th	0.342	2.65
25th	0.502	2.98
50th	0.712	3.11
75th	1.13	3.72
90th	2.02	4.04
95th	2.12	4.12

[a] Values calculated by linear interpolation assuming that the observations (i) are distributed as (i - 0/5)/n, where n is the number of observations (Wilk and Gnanedisikan, 1968).

clearance, as no mathematical function well fits the rat boron clearance data. The boron clearance observations (i) are assumed to be distributed as the percentiles 100 x (i - 0.5)/n, where i is the rank order of the observation and n is the number of observations (Wilk and Gnanedisikan, 1967). Values at percentiles not directly observed are estimated by linear interpolation. The data show that, on average, pregnant rats clear boron 3.6 times faster than pregnant women. The difference becomes greater at lower points in the distribution, with relative rat:human clearance ratios of 4.4 and 8.9 at the median and 5th percentiles, respectively.

3.4.2. Plasma

In a study conducted with human volunteers and carefully administered doses of 570-620 mg boric acid (91-108.5 mg B), plasma concentration-time curves were followed over 3 days and were markedly biphasic. Terminal elimination half-lives were calculated for individuals (n=6) and demonstrated a range of 12.5-26.6 hours and a mean value of 21.0$\pm$4.9 hours when calculated from the data collected over the initial 72 hours post-dose (Jansen et al., 1984a). From this study a total mean volume of distribution of 104.7 mL/100 g body weight can be calculated A second study reported by Litovitz et al. (1988) investigated incidences of boron poisoning. Although this study did not document many important data (dose, time post-dose that examination began, number of concentrations used to estimate half-lives, etc.), the range of half-lives compares favorably with the well-controlled study presented by Jansen et al. (1984a). When linear regression analysis was used to fit the plasma concentration data, estimates of half-lives ranged from 4.0 to 27.8 hours, with an overall mean value of 13.4$\pm$7.1 hours. Astier (1988) reported a plasma half-life of 28.7 hours after acute ingestion of 45 g boric acid (7.9 g B) in two doses over a 20-hour period.

A pharmacokinetic study (Usuda et al., 1998) in 10 rats following an oral administration of sodium tetra-borate containing 0.4 mg boron/100g body weight where 0.5-1 mL samples were drawn at nine different times during a 24-hour time period reported a monophasic elimination of boron from plasma, demonstrating a plasma half-life mean of 4.64$\pm$1.19. This study also cited a high volume of distribution of 142.0$\pm$30.2 mL/100 g body weight. One of the limitations of this study is that a large amount of blood was drawn from the rats in the 24 hour period which may have physiologically compromised the rats.

In a plasma clearance study of boron sponsored by U. S. Borax in pregnant and non-pregnant rats given boric acid at dose levels of 0.3, 3.0 and 30 mg boric acid, plasma concentrations of boron were markedly lower 15 hours after dosing compared with that obtained 3 hours after dosing (see description of studies in Section 3.4.1.). Mean plasma levels of boron were slightly higher in pregnant rats compared with non-pregnant rats (statistically significant in only the high dose) given the same dose of boric acid.

In a study conducted to estimate the plasma half-life of boric acid in the Sprague-Dawley rat, six non-pregnant and six pregnant rats were given low B in the diet for 7 days as described previously in the clearance study (see Section 3.4.1.). On day 8 of the study all rats received a single oral dose of 30 mg/kg of boric acid at approximately 9:00 a.m. This dose was the high

dose used in the renal clearance study and was selected as the best to examine the liniarity of the boron plasma curve at the highest concentration. Six 0.25 mL blood samples were drawn from each animal during a 12-hour period starting at noon on day 8 of the study. The blood samples were taken at 2- to 3-hour intervals. Gavage administration of 30 mg/BA/kg/day resulted in plasma levels of 1.82±0.32 and 1.78±0.32 μ/mL among pregnant and nonpregnant rats in the first blood sample taken 3 hours after dosing. This was followed by a monophasic decline in plasma boron concentration in both the pregnant and non-pregnant rats. The plasma concentration curves were consistent with a one-compartment model. Based on the shape of the plasma concentration curve there was no evidence of saturation kinetics in either the non-pregnant or pregnant rats. The estimated half-life of boric acid in non-pregnant and pregnant rats were 2.9 and 3.2 hours, respectively, which was not statistically different.

A human study (U.S. Borax, 2000) was conducted to measure renal clearance of boron normally consumed in the daily diet in non-pregnant and pregnant women (see description of the study in Section 3.4.1.). At the beginning of the study a baseline blood sample was taken, during the 2 hours following the baseline blood sample all urine samples were collected, 2 hours after baseline another blood sample was taken and a final blood sample was collected at 24 hours. Plasma boron levels were measured at these three time periods. Mean plasma boron levels obtained at baseline and 2 hours after the beginning of the study were similar between the pregnant and non-pregnant subjects. After 24 hours plasma boron levels were lower in the pregnant women when compared with non-pregnant women, however there was a significant variability in the plasma values in both groups.

3.4.3. Bone

Elimination of boron from bone was studied in rats by Chapin et al. (1997). Bone (tibia) boron levels were monitored for 32 weeks following cessation of exposure in rats that had been fed boron in the diet at 4500-9000 ppm for 9 weeks. Levels of boron in the bone declined slowly. After 8 weeks of recovery, bone levels of boron were reduced to roughly 10% of levels at the end of exposure (e.g., at 9000 ppm: ≈6 µg B/g bone from ≈60 µg B/g bone) but still remained 5- to 6-fold higher than bone levels in unexposed controls (≈1 µg B/g bone). Even after 32 weeks of recovery (and ≈31.5 weeks after the return of blood boron levels to normal, which took only 4 days), bone boron concentrations remained 3-fold higher in treated groups than bone concentrations in controls. Accumulation of boron in skeletal bones of human cadavers has also been reported by Alexander et al. (1951) and Forbes et al. (1954)**.**

3.5. TOXICOKINETIC SUMMARY

Examinations in rats have revealed a fairly uniform distribution of boron outside the blood compartment across various tissues (liver, kidney, muscle, large intestine, brain hypothalamus, testis, epididymis, seminal vesicles, seminal vesicle fluid, adrenals and prostate). Notable exceptions are that consistently lower concentrations of boron were found in fat and consistently higher concentrations were observed in bone (Ku et al., 1991). Accumulation of boron in fat was 20% of plasma levels after day 7 and boron in bone was increased 2- to 3-fold over plasma levels

after day 7. The pharmacokinetic study of boron by Usuda et al. (1998) cited a high volume of distribution of 142.0±30.2 mL/100 g body weight. When this finding is combined with the relatively uniform distribution of boron to the tissues, the likelihood for sequestration of boron by a given tissue is minimal. When these data from rodents (plasma half-life, urinary elimination time course and tissue distribution) are compared with the data available for humans (plasma elimination half-life reports and high volume of distribution of 104.7 mL/100 g body weight), it seems reasonable that the distribution of boron to human tissues quite likely parallels that observed in rodents. Because of the extent to which boron's residence time in the body and pharmacokinetic profile are influenced by urinary elimination, a more thorough investigation of the urinary clearance of boron was undertaken to determine the difference in the urinary clearance of boron in pregnant and non-pregnant rats and humans. Reports from studies (U.S. Borax, 2000) indicated that the renal clearance of boron from female rats was greater than in humans, and that pregnant rats and pregnant women cleared boron slightly more efficiently than non-pregnant rats and women. The magnitude of the difference (rat:human) between average clearance values was approximately 3.6-fold and 4.9-fold for pregnant and non-pregnant individuals, respectively, in close agreement with differences in kinetic parameters predicted by allometric scaling (approximately 4-fold). The variance of boron clearance in humans was slightly greater than in rats (0.35%), but the coefficient of variation (s.d.÷ mean) was 4-fold higher in humans than in rats. Overall, the available pharmacokinetic data support a high degree of qualitative similarity (lack of metabolism, highly cleared through renal filtration mechanisms, and apparently consistent extravascular distribution characteristics) between the relevant experimental species and humans.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS — EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

4.1.1. Oral Exposure

Sayli et al. (1998) reported on a study of the relationship between exposure to boron in the drinking water and fertility in two geographic regions of Turkey. Drinking water boron concentrations were markedly higher in one region (2.05-29 mg/L) than in the other (0.03-0.4 mg/L). The study population comprised ever-married residents (primarily males) from these regions who could provide reproductive histories for three generations of family members (n=159 in one region and 154 in the other, 6.7% of the population in both). There was no difference between the regions regarding percentage of married couples with live births in any generation. Secondary sex ratios appeared to differ, with an excess of female births in the high-boron region (M/F = 0.89) and a slight excess of male births in the low-boron region (M/F = 1.04), but no statistical analysis was performed and other factors reported to affect sex ratio (parental age, rate of elective abortion, multiple births) were not taken into account.

A large number of accidental poisioning cases are reported in the literature; however, quantitative estimates of absorbed dose are limited. Baker et al. (1986) reported quantitative estimates of two sibling infants who ingested formulas accidentally prepared from a boric acid eyewash solution These infant doses ranged from 30.4-94.7 mg B/kg-day. The sibling who ingested 30.4 mg B/kg-day had a serum level of 9.79 mg B/mL and displayed a rash on his face and neck but later remained asymptomatic. The sibling who ingested 94.7 mg B/kg-day had serum boron values of 25.7 mg B/mL and experienced diarrhea, erythema of the diaper area and vomiting a small amount of formula.

Acute adult quantitative dose response data range from 1.4 mg B/kg to a high of 70 mg B/kg (Culver and Hubbard, 1996). In cases where ingestion was less than 3.68 mg B/kg, subjects were asymptomatic. Data in the 25-35 mg B/kg range were from patients undergoing boron neutron capture therapy for brain tumors. They displayed nausea and vomiting at 25 mg B/kg and at 35 mg B/kg additional symptoms included skin flush. A patient recovering from surgery had boric acid solution (70 mg B/kg) injected into the subcutaneous fluid infusion, which resulted in severe cutaneous and G.I. symptoms but recovery occurred after hydration and diuresis.

Because boron compounds were used for various medical conditions including epilepsy, malaria, urinary tract infections and exudative pluritis from the mid 1800's until around 1900, some data are available on longer term exposure. Culver and Hubbard (1996) report on early literature cases of boron treatment for epilepsy from 2.5 to 24.8 mg B/kg-day for many years. Signs and symptoms reported in patients receiving 5 mg B/kg/day and above were indigestion, dermatitis, alopecia and anorexia. One epilepsy patient who received 5.0 mg B/kg-day for 15 days displayed indigestion, anorexia and dermatitis but the signs and symptoms disappeared when the dose was reduced to 2.5 mg B/kg-day. In a "short report" in *Archives of Disease in Childhood,* O'Sullivan and Taylor (1983) report seizures (and other milder effects) in seven infants who had consumed boron in a honey-borax mixture applied to pacifiers. Five of the infants had a history suggestive of a familial reduced convulsive threshold. The seizures ceased when the honey-borax treatment was stopped. The infants, who ranged in age from 6 to 16 weeks (at the end of the exposure period), were exposed to the honey-borax mixture over a period of 4 to 10 weeks. Total ingested borax was calculated by the authors based on an estimated daily ingestion of honey-borax mixture and an analysis of the borax content in the mixture. Details of the analytic methods were not provided. Average estimated daily intakes of borax ranging from 143 to 429 mg can be calculated directly from data provided by the authors. Average body weights over the exposure period for the infants in this study ranging from 4.3 to 5.3 kg were estimated from the Exposure Factors Handbook (U.S. EPA, 1997). Using the estimated body weights and a factor of 0.113 to estimate the boron content in borax, the equivalent boron exposure levels would have been about 3.2 to 11 mg/kg-day. The lowest exposure level of 3.2 mg/kg-day would be considered a LOAEL for a fairly severe effect. Concentrations of boron in blood of 2.6, 8.4 and 8.5 µg/mL were reported for three of the subjects. Blood boron concentrations did not correlate well with estimated ingestion levels; the lowest blood boron concentration was measured for the infant with the highest estimated boron intake. Blood boron levels were also reported for a control group of 15 children aged 2 to 21 months, who had received no boron supplement and, presumably, had suffered no seizures. The

control group blood boron values ranged from 0 to 0.63 µg/mL and averaged 0.21 µg/mL, with a standard deviation of 0.17 µg/mL. The lowest boron blood level associated with seizures of 2.6 µg/mL was about 4 times the highest control level and 12 times the average control level, suggesting that the standard 10-fold uncertainty factor may be adequate for estimating a NOAEL. However, we don't know if any infants predisposed to seizures were in the control population. The presumptive boron NOAEL would be 0.32 mg/kg-day for a senstive human subpopuation. Given the relatively uncomplicated boron toxicokinetics, the lack of correlation of blood boron and estimated ingestion rates suggests that the data may not be completely reliable. Based on the latter consideration, the indirect exposure estimation, and the lack of detail in the publication (a "short report") this study should not be considered as the critical factor for derivation of the RfD, but the potential for seizures in infants should be considered in establishing the RfD.

Case reports and surveys of poisoning episodes were recently reviewed by Craan et al. (1997), WHO (1998a), Culver and Hubbard (1996) and Ishii et al. (1993). The most frequent symptoms of boron poisoning are vomiting, abdominal pain, and diarrhea. Other common symptoms include lethargy, headache, lightheadedness and rash. For boric acid, the minimum lethal dose by oral exposure is approximately 15-20 g in adults, 5-6 g in children and 2-3 g in infants.

4.1.2. Inhalation Exposure

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 vapors and aerosols of boron salts (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 (SBR is less sensitive than direct measures of testicular effects, exposure information was limited, applicability of total U.S. fertility rates as control is questionable). 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.

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 (93% of those eligible) employed for 5 or more years at the plant and employed in an area with heavy borax exposure at the time of the study. Workers were categorized into four 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 tests (FEV_1, Forced Expiratory Volume in 1 sec and FVC, Forced Vital Capacity) 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.

4.2. PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS — ORAL AND INHALATION

4.2.1. Oral Exposure

In the following studies, when not reported by the investigators, approximate dosages were calculated from dietary or drinking water concentrations of boron using food factors (rat: 0.05; dog: 0.025; mouse: 0.1) (1 ppm = 0.025 mg/kg-day assumed dog food consumption) and body-weight and water consumption values (mouse: 0.03 kg and 0.0057 L/day; rat: 0.35 kg and 0.049 L/day) specified by the U.S. EPA (1980, 1988). 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 subchronic and chronic toxicity of borax and boric acid has been studied in dogs administered these compounds in the diet (Weir and Fisher, 1972; U.S. Borax Research Corp., 1963, 1966, 1967). In the 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% (9.6 g) in males fed borax and 39% (10.5 g) in males fed boric acid 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 (175 ppm) boric acid group. Microscopic pathology revealed severe testicular atrophy in all high-dose male dogs, with complete degeneration of the spermatogenic epithelium in 4/5 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 ratio (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 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) based on systemic toxicity in dogs 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 not used to calculate the RfD due to several limitations, including 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 adequate for establishment of a defensible NOAEL.

Weir and Fisher (1972) also conducted studies of boron toxicity in rats. Sprague-Dawley rats (10/sex/dose) were fed borax or boric acid in the diet for 90 days at levels of 0, 52.5, 175, 525, 1750 and 5250 ppm boron (approximately 0, 2.6, 8.8, 26.3, 87.5 and 262.5 mg B/kg-day, respectively) calculated by assuming reference values of 0.35 kg bw and a food factor of 0.05 for rats. Both borax and boric acid produced 100% mortality at the highest dose and complete atrophy of the testes in all males fed diets containing 1750 ppm boron. Overt signs of toxicity at these two dose levels included rapid respiration, eye inflammation, swelling of the paws and desquamation of the skin on paws and tails. At 1750 ppm boron, both compounds produced significant ($p<0.05$) decreases in body weight and in the mean weights of the liver, kidneys, spleen and testes. At lower doses, changes in organ weights were inconsistent. At 52.5 ppm boron, increases in the mean weights of the brain, spleen, kidneys and ovaries were seen in females fed borax, and an increase in mean liver weight was seen in females fed boric acid; no organ weight changes were seen in the males. At 175 ppm boron, the only change in organ weight reported by the investigators was increased kidney weights in males fed borax. These changes, however, were not observed at 525 ppm boron for either compound. Microscopic examination revealed complete testicular atrophy at 1750 ppm in all males fed borax or boric acid, and partial testicular atrophy at 525 ppm boron in four males fed borax and in one male fed boric acid. Changes in

organ weights that were reported at 52.5 ppm were not dose related and were not confirmed in follow-up chronic studies by the same investigators. This study identified a NOAEL of 175 ppm boron (8.8 mg B/kg-day) and a LOAEL of 525 ppm boron (26.3 mg B/kg-day) boron for systemic toxicity in rats following subchronic dietary exposure.

In the chronic study, 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. Testes weights and testes:body weight ratios were significantly ($p<0.05$) decreased. Brain and thyroid:body weight ratios were significantly ($p<0.05$) increased. No treatment-related effects were observed in rats receiving 350 or 117 ppm boron as borax or boric acid. This study identified a LOAEL of 1170 ppm (58.5 mg B/kg-day) and a NOAEL of 350 ppm (17.5 mg B/kg-day) for testicular effects. 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.

A subchronic study in rats using drinking water exposure is also available. Borax was administered in the drinking water to male Long Evans rats (15/group) at levels of 0, 150 and 300 mg B/L for 70 days; the basal diet contained approximately 54 µg B/g of feed (Seal and Weeth, 1980). The approximate intake of boron for the treated rats was 23.7 and 44.7 mg B/kg-day, respectively, using reference values for body weight, food and water consumption. Treatment with borax at both doses produced significant ($p<0.05$) decreases in body weight, testis, seminal vesicle, spleen and right femur weight, and plasma triglyceride levels. At the highest dose level, spermatogenesis was impaired and hematocrit was decreased slightly. From this study, a LOAEL of 23.7 mg B/kg-day can be identified. A NOAEL was not identified.

The subchronic and chronic toxicity of boron (boric acid) in mice was studied by NTP (1987; Dieter, 1994). In the subchronic study, groups of 10 male and 10 female B6C3F1 mice were fed diets containing 0, 1200, 2500, 5000, 10,000 or 20,000 ppm boric acid (0, 210, 437, 874, 1748 or 3496 ppm boron) for 13 weeks (NTP, 1987; Dieter, 1994). These dietary levels correspond to approximately 0, 34, 70, 141, 281 and 563 mg B/kg-day for males and 0, 47, 97, 194, 388 and 776 mg B/kg-day for females, respectively, based on reported average values for feed consumption (161 g/kg bw/day for males, 222 g/kg bw/day for females) by controls in week 4 of the experiment. At the highest dose level, hyperkeratosis and acanthosis of the stomach and

>60% mortality were observed. At 10,000 ppm boric acid, 10% mortality was observed among the males. At 5000 ppm and higher, degeneration or atrophy of the seminiferous tubules was observed in males, and weight gain was suppressed in animals of both sexes. Minimal to mild extramedullary hematopoiesis of the spleen was observed in all dosed groups. The lowest dose tested, 1200 ppm (34 mg B/kg-day for male mice), appears to be the LOAEL for this study. The NOAEL (no toxicity in absence of body weight loss) was at or below 1200 ppm (34 mg/kg-day for males and 47 mg/kg-day for females). From this study dietary doses of 2500 ppm (70 mg B/kg-day for males and 97 mg B/kg-day for females) and 5000 ppm (141 mg B/kg-day for males and 194 mg B/kg-day for females) were selected to be tested in both sexes in the chronic 2-year study based on body weight depression and mortality in the two highest doses tested in the subchronic study.

In the chronic study, 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), respectively. 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). Administration of boric acid to male mice induced testicular atrophy and interstitial cell hyperplasia in the high-dose group. There were also dose-related increased incidences of splenic lymphoid depletion in male mice. According to NTP (1987), this lesion is associated with stress and debilitation and is reflected in the increased mortality in these groups of male mice. Increased incidences of other nonneoplastic lesions were not believed to have been caused by the administration of boric acid because they either were not consistently dose-related or did not occur in both sexes.

There were increased incidences 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 considered to be 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 longevity body weights (at 30 days treated animals were lighter than controls and at 90 days treated males were significantly heavier than controls). 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.

4.2.2. Inhalation Exposure

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

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES — ORAL AND INHALATION

4.3.1. Developmental Studies

Heindel et al. (1994, 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%, 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 0.200% 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.

Price et al. (1997) provides an analysis of maternal whole blood taken on gestation day 20 from the previously described study (Price et al., 1996a, 1994) where dietary concentration of added boric acid yielded average daily intakes equivalent to 0, 3, 6, 10, 13, or 25 mg boron/kg body weight. Blood samples were analyzed using inductively coupled plasma optical emission spectrometry. Increasing dietary concentrations of boric acid were positively associated with whole blood concentration in pregnant rats. Whole blood concentrations in confirmed pregnant rats were 0.229 ±0.143, 0.564±0.211, 0.975±0.261, 1.27±0.298, 1.53±0.546, 2.82±0.987µg boron/g whole blood (mean±SD) for the control through the high-dose groups. Positive correlations between maternal blood boron concentrations and indices of maternal dietary intake of boron with embryo/fetal toxicity (Price et al., 1996a, 1994) were observed at average daily concentration of 13 and 25 mg B/kg. Blood boron concentrations of 1.27±0.298 and 1.53±0.546 µg boron/g were associated with the NOAEL (10 mg boron/kg/day) and the LOAEL (13 mg boron/kg/day) for the developmental toxicity reported in Price et al. (1996a, 1994).

The developmental effects of boric acid also have been studied in mice and rabbits. Heindel et al. (1994, 1992; Field et al., 1989) examined the developmental effects of boric acid in pregnant CD-1 mice using the same experimental design as in the initial study with rats (Price et al., 1990) except that a 0.8% dietary level was not used in the mouse study. The diets containing 0, 0.1, 0.2 or 0.4% boric acid were estimated by the investigators to provide 0, 248, 452 or 1003 mg boric acid/kg-day (0, 43.4, 79.0 or 175.3 mg B/kg-day); the mice were treated during gd 0-17. Neither survival rates nor pregnancy rates were affected by treatment with boric acid. Pale kidneys were noted in several treated dams, particularly in the high-dose group, and one dam in this group had fluid accumulation in the kidney. Maternal body weight was significantly reduced by 10-15% during gd 12-17 in the high-dose group. Maternal weight gain was significantly

reduced during treatment in the high-dose group, but was not affected when corrected for gravid uterine weight. At the 0.4% dietary level, food intake was increased between days 12 and 15 and water intake was increased on days 15-17 (statistical significance not provided for either effect). Organ weight changes were limited to significant increases in relative kidney weight and absolute liver weight in the 0.4% groups. A dose-related increase in maternal renal tubular dilation and/or regeneration was observed; the incidence was 0/10, 2/10, 8/10 and 10/10 in the 0, 0.1, 0.2 and 0.4% dosage groups, respectively. Treatment with boric acid did not affect preimplantation loss or the number of implantation sites per litter, but significantly increased the percentage of resorptions per litter and the percent of litters with one or more resorptions at the 0.4% level. There was a significant dose-related decrease in average fetal body weight (all fetuses or male or female fetuses) per litter at 0.2% or more. The percentage of malformed fetuses per litter increased significantly at 0.4%, whereas the percentage of fetuses with variations per litter was decreased at 0.1 and 0.2% and was not affected at 0.4%. The most frequent malformation observed among fetuses of the 0.4% group was a short rib XIII. In contrast, full or rudimentary lumbar I rib (a variation) was less frequent in fetuses of treated mice. Although the level of 0.1% boric acid in the diet induced an increase in renal lesions in mice, the increased incidence did not achieve statistical significance (Fisher Exact Test). The 0.1% level (43.4 mg B/kg-day) is a maternal NOAEL and the 0.2% level (79 mg B/kg-day) is a maternal LOAEL. For developmental effects, the 0.2% dietary level of boric acid is a LOAEL based on decreased fetal body weight per litter and the 0.1% level is a NOAEL.

Artificially inseminated New Zealand White rabbits (30/group) were administered 0, 62.5, 125 or 250 mg boric acid/kg-day (0, 10.9, 21.9 and 43.7 mg B/kg-day) in aqueous solution by gavage on gd 6-19 (Price et al., 1996b, 1991; Heindel et al., 1994). Food consumption, body weight and clinical signs were monitored throughout the study. At day 30, the animals were sacrificed and the following endpoints were examined: pregnancy status, number of resorptions, fetal body weight, viability, and external, visceral and skeletal malformations. No treatment-related clinical signs of toxicity were observed during the study, except for vaginal bleeding noted in 2-11 does/day on gd 19-30 at the high dose; these does had no live fetuses on day 30. Vaginal bleeding was also observed in one female in the low-dose group and in one in the mid-dose group. Two maternal deaths occurred (one each at the low and mid dose), but were not treatment-related. Food intake was decreased relative to that of controls on treatment days 6-15 at the high dose, and was increased after treatment ceased on days 25-30 at the mid and high doses. Body weight on gd 9-30, weight gain on gd 6-19, gravid uterine weight and number of corpora lutea per dam were each decreased in the high-dose group. After correction for gravid uterine weights, however, maternal body-weight gain was increased at both the mid and high doses. Treatment with boric acid did not affect absolute or relative liver weight. Relative, but not absolute kidney weight increased at the high dose; kidney histopathology was unremarkable. Boric acid caused frank developmental effects at the high dose. These effects consisted of a high rate of prenatal mortality (90% of implants/litter were reabsorbed compared with 6% in controls). Also, the percentage of pregnant females with no live fetuses was greatly increased (73% compared with 0% in controls), whereas the number of live fetuses per litter on day 30 was significantly reduced (2.3/litter compared with 8.8/litter in controls). Malformed live fetuses per litter increased significantly at the high dose, primarily due to the incidence of fetuses with cardiovascular defects,

the most prevalent of which was interventricular septal defect (8/14 at high dose compared with 1/159 in controls). The incidence of skeletal malformations was comparable among groups. Relative to controls, the percent of fetuses with variations (all types combined) was not significantly increased in any treated group, but the percent with cardiovascular variations was significantly increased from 11% in controls to 64% in the high dose group. Fetal body weights per litter at the high dose were depressed relative to control, but the difference was not statistically significant; however, this could have been due to the small sample size in the high-dose group. No developmental effects were found in the low and mid dose groups. In this study, the mid dose of 125 mg boric acid/kg-day (21.9 mg B/kg-day) represents the NOAEL based on maternal and developmental effects. The high dose of 250 mg boric acid/kg-day (43.7 mg B/kg-day) is the LOAEL.

4.3.2. Reproductive Studies

4.3.2.1. *Male-Only Exposure*

Studies of subchronic and chronic toxicity of boron compounds in dogs, rats and mice have identified the testes as a primary target organ in males of these species (e.g., Weir and Fisher, 1972; NTP, 1987). These studies were described in Section 4.2.1. Several other studies have been conducted to investigate the effects of boron compounds on male reproductive performance and testicular morphology in more detail.

Dixon et al. (1976) studied the effects of borax on reproduction in male rats following acute and subchronic exposure. In the acute study, groups of 10 adult male Sprague-Dawley rats were given single oral doses of borax at 0, 45, 150 and 450 mg B/kg. Fertility was assessed by serial mating trials in which each male was mated with a series of untreated virgin females in sequential 7-day periods (for up to 70 days). The females were sacrificed 9 days after the end of their breeding periods (when they would be 9-16 days pregnant), and uteri and fetuses were examined. Male rats were sacrificed on days 1 and 7, and at subsequent 7-day intervals for histopathological examination of the testes. No effect on male fertility was found at any dose in this study. Testicular lesions were not reported. This study found a NOAEL of 450 mg B/kg for reproductive effects in male rats following single-dose oral exposure.

In the subchronic study, male Sprague-Dawley rats (10/group) were given 0, 0.3, 1.0 or 6.0 mg B/L, as borax, in the drinking water for 30, 60 or 90 days (Dixon et al., 1976). As estimated by the investigators, the highest exposure level provided 0.84 mg B/kg-day. Based on this estimate, the lower two levels provided 0.042 and 0.14 mg B/kg-day. There were no noticeable reproductive effects or changes in serum chemistry, plasma levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH), or weight of the body, testes, prostate or seminal vesicles. Fructose, zinc and acid phosphatase levels in the prostate were unchanged. Breeding studies revealed no effects on male fertility. Therefore, the dose of 0.84 mg B/kg-day, the highest dose tested, represents a NOAEL for this study.

In a follow-up study, Dixon et al. (1979); Lee et al. (1978) administered diets containing 0, 500, 1000 or 2000 ppm boron, as borax, to male Sprague-Dawley rats (18/group) for 30 or 60 days (approximately 0, 25, 50 or 100 mg B/kg-day). Significant ($p<0.05$) decreases in the weight of liver, testes and epididymis were observed at the 1000 and 2000 ppm dietary levels. Seminiferous tubule diameter was significantly ($p<0.05$) decreased in a dose-dependent manner in all treatment groups; however, significant loss of germinal cell elements was observed only at the 1000 and 2000 ppm dietary levels. Aplasia was complete at the highest dose. Plasma levels of the hormone FSH were significantly ($p<0.05$) elevated in a dose- and duration-related manner at all dose levels, while plasma LH and testosterone levels were not affected significantly. Serial mating studies revealed reduced fertility without change in copulatory behavior at the two higher dose levels. Based on dose-related tubular germinal aplasia, which is reversible at low doses, this study defines a LOAEL of 50 mg B/kg-day and a NOAEL of 25 mg B/kg-day.

Linder et al. (1990) examined the time- and dose-response of male rat reproductive endpoints after acute administration of boric acid. In the time-response experiment, Sprague-Dawley rats (6/group) were given 0 or 2000 mg boric acid/kg bw (0 or 350 mg B/kg, respectively) by gavage and were sacrificed at 2, 14, 28 and 57 days after dosing. In the dose-response experiment, groups of eight male rats were administered 0, 250, 500, 1000 or 2000 mg boric acid/kg (0, 44, 87, 175 or 350 mg B/kg) by gavage and were killed 14 days later. In both the time-response and the dose-response studies, the above doses are the total of 2 doses administered at 0900 and 1600 hours on the same day. No significant clinical signs of toxicity were observed during the study. Histopathologic examinations of the testes and epididymis revealed adverse effects on spermiation, epididymal sperm morphology and caput sperm reserves. The testicular effects, apparent at 14 days, included enlarged irregular cytoplasmic lobes of Step 19 spermatids in stage VIII seminiferous tubules and retention of Step 19 spermatids in stage IX-XIII tubules at the 175 and 350 mg B/kg dose levels, and a substantial increase ($p<0.05$) in the testicular sperm head count per testis and per g testis in the 350 mg/kg time-response group. Epididymal effects, also apparent at 14 days, included an increase in abnormal caput epididymal sperm morphology (percent with head or tail defects, $p<0.05$) and reduced caput epididymal sperm reserves ($p<0.05$). In the day 28 time-response group (350 mg B/kg), significant effects ($p<0.05$) included an increase in abnormal caput and cauda epididymal sperm morphology and a decreased percentage of motile cauda spermatozoa with reduced straight-line swimming velocities. Substantial recovery had occurred by day 57. This study described a LOAEL for male reproductive effects of 175 mg B/kg bw and a NOAEL of 87 mg B/kg bw following acute oral exposure in rats.

Treinen and Chapin (1991) examined the development and progression of reproductive lesions in 36 mature male F344 rats treated with boric acid in the diet for 4-28 days. Thirty animals served as controls. Boric acid was added to the feed at a level of 9000 ppm. Based on food consumption and body weight data, the investigators estimated that over the 28-day period the mean intake of boric acid was 348.3 mg/kg-day, or 60.9 mg B/kg-day. Sacrifices were conducted at 4, 7, 10, 14, 21 and 28 days on six treated and four control animals per time point. Liver, kidney and testicular histology, serum testosterone and androgen binding protein (ABP) levels and tissue boron levels were assessed. In half of the treated rats there was inhibition of

spermiation in 10-30% of stage-IX tubules at 7 days. Inhibited spermiation was observed in all stage-IX and stage-X tubules of exposed rats at 10 days. Advanced epithelial disorganization, cell exfoliation, luminal occlusion and cell death were observed after 28 days, causing significant loss of spermatocytes and spermatids from all tubules in exposed rats. Throughout the study, specific lesions became more severe with increasing duration of exposure. Treatment with boric acid had no effect on kidney and liver histology. In treated rats, basal serum testosterone levels were significantly decreased ($p<0.05$) from 4 days on, but serum testosterone levels stimulated by human chorionic gonadotropin or luteinizing hormone releasing factor were not affected. Steady-state levels of boron were reached in tissues by 4 days of treatment, and there was no selective accumulation of boron in blood, epididymis, liver or kidney. After 4 days of treatment with boric acid, serum ABP levels were significantly reduced relative to controls; however, this difference disappeared by day 7.

Ku et al. (1993a) and Chapin et al. (1994) compared testis boron dosimetry to lesion development. Rats were fed 0, 3000, 4500, 6000 or 9000 ppm boric acid (0, 545, 788, 1050 or 1575 ppm boron) for up to 9 weeks and examined. Based on food intake and body weight data, the researchers estimated the daily intake of boron as <0.2, 26, 38, 52 or 68 mg B/kg-day. At 32 weeks post-treatment, recovery was assessed. Inhibited spermiation occurred at 3000 and 4500 ppm, and atrophy at 6000 and 9000 ppm. A mean testis boron level of 5.6 µg B/g of tissue was associated with inhibited spermiation, whereas 11.9 µg B/g was associated with atrophy, with no boron accumulation during the 9-week exposure. This suggests that separate mechanisms may be operating for these effects based on testis boron concentration. Severely inhibited spermiation at 4500 ppm was resolved by 16 weeks post-treatment but some areas of focal atrophy did not recover post-treatment. Atrophy in the 6000 and 9000 ppm dose groups did not recover post-treatment. The low dose of 26 mg B/kg-day was a LOAEL in this study.

Following *in vitro* boric acid exposure, Ku et al. (1993b) evaluated endpoints in the cell culture system that suggest that boric acid has an effect on DNA synthesis that occurred at concentrations associated with atrophy *in vivo*, and suggests that boric acid interferes with the production and maturation of early germ cells.

Ku et al. (1994) showed that testicular atrophy and central nervous systems (CNS) hormonal effects were not due to selective accumulation in testis or brain/hypothalamus with boron testis concentrations of 1-2 mM. *In vitro* studies addressed boric acid testicular toxicity: mild hormone effect, the initial inhibited spermiation and atrophy. No effect of boric acid on the steroidogenic function of isolated Leydig cells was observed supporting the suggestion of a CNS mediated hormonal effect. The authors found that inhibited spermiation was not due to increased testicular cyclic adenosine monophosphate (cAMP) or reduced serine proteases plasminogen activators (PA). Boric acid effects were evaluated in Sertoli-germ cell co-cultures on Sertoli cell energy metabolism (lactate secreted by Sertoli cells is a preferred energy source for germ cells) and DNA/RNA syntheses (germ cells synthesize DNA/RNA and boric acid impairs this nucleic acid in the liver). The most sensitive *in vitro* endpoint was DNA synthesis of mitotic/meiotic germ cells, with energy metabolism in germ cells affected to a lesser extent, which was manifested *in vivo* as a decrease in early germ cell/Sertoli cell ratio prior to atrophy in the testes.

Naghii et al. (1996b) studied the specificity of the effect of boron on steroid hormones and the impact of plasma lipids in rats. After 2 weeks on boron addition to the drinking water (2 mg B/rat/day) significant elevations occurred in the plasma 1,25-dihydroxyvitamin D concentration and a significant decrease in the plasma triacyglycerol and total HDL-cholesterol concentrations compared to controls. At 4 weeks the plasma testosterone concentration was significantly elevated and the HDL-cholesterol was significantly lower.

4.3.2.2. *Male and Female Exposure*

In a multigeneration study, Weir and Fisher (1972) administered 0, 117, 350 or 1170 ppm boron (approximately 0, 5.9, 17.5 or 58.5 mg B/kg-day) as borax or boric acid in the diet to groups of 8 male and 16 female Sprague-Dawley rats. No adverse effects on reproduction or gross pathology were observed in the rats dosed with 5.9 or 17.5 mg B/kg-day, which were examined to the F3 generation. Litter size, weights of progeny and appearance were normal when compared with controls. The test groups receiving 58.5 mg B/kg-day boron from either compound were found to be sterile. In these groups, males showed lack of spermatozoa in atrophied testes, and females showed decreased ovulation in the majority of the ovaries examined. An attempt to obtain litters by mating the treated females with the males fed only the control diet was not successful. A LOAEL of 58.5 mg B/kg-day and a NOAEL of 17.5 mg B/kg-day were identified from this study.

Fail et al. (1990, 1991) examined the effects of boric acid in Swiss CD-1 mice in a reproductive study using a continuous breeding protocol. Male and female F_0 mice (11 weeks old) were fed a diet containing 0, 1000, 4500 or 9000 ppm boric acid for up to 27 weeks. There were 40 pairs in the control group and 20 pairs per treatment group. Based on an average food consumption of 5 g/mouse and on body weights, the diet was predicted by the authors to provide boric acid at 152 mg/kg-day (26.6 mg B/kg-day) to males and 182 mg/kg-day (31.8 mg B/kg-day) to females in the 1000 ppm group, 636 mg/kg-day (111 mg B/kg-day) to males and 868 mg/kg-day (152 mg B/kg-day) to females in the 4500 ppm group and 1260 mg/kg-day (220 mg B/kg-day) to males and 1470 mg/kg-day (257 mg B/kg-day) to females in the 9000 ppm group. According to the authors, actual boric acid consumption during the study did not differ from the predicted consumption by more than 12%. Following 1 week of treatment, the F_0 mice were caged as breeding pairs for 14 weeks. During weeks 2-18, the average body-weight gain of high-dose males and females was significantly reduced relative to controls. Mortality rates in the treated groups over the 27 weeks were not significantly different from controls. Treatment with boric acid significantly impaired fertility. None of the 9000 ppm pairs were fertile. The number of litters per pair, number of live pups per litter, proportion of pups born alive, live pup weight and adjusted pup weight (adjusted for litter size) were significantly ($p<0.05$) decreased at the 4500 ppm level. The initial fertility index (percentage of cohabited pairs having at least one litter) was not significantly altered in the 1000 and 4500 ppm groups, but the progressive fertility index (percentage of fertile pairs that produced four litters) was decreased relative to controls in the 4500 ppm group. The trend toward a lower fertility index at 4500 ppm started with the first mating and progressed in severity with subsequent matings.

To determine the affected sex, the control and 4500 ppm F_0 mice were then assigned to three crossover mating groups: control male x control female, 4500 ppm male x control female, and control male x 4500 ppm female. Each group was composed of 19-20 pairs that were mated for 7 days or until a copulatory plug was detected, whichever occurred first; control feed was provided for all mice during this week, followed by a resumption of the same diets they had received previously. Mating and fertility indices were significantly depressed in the 4500 ppm male x control female group and only one pair in that group produced a live litter; these indices were not affected in the control male x 4500 ppm female group. Dosed females mated to control males had a lower body weight on pnd 0, had a longer gestational period than control groups and gave birth to pups with decreased litter-adjusted weight. After completion of the crossover mating trial (total of 27 weeks on test), a necropsy was performed on control and 4500 ppm F_0 males and females and on 1000 and 9000 ppm F_0 males, which had been maintained on their respective diets to allow a comparison of semen parameters and testicular histology among all four treatment groups. Males treated with 9000 ppm boric acid had significantly reduced body, testis and epididymal weights. In the 4500 ppm males, body weight was not affected, but testis, epididymal and prostate weights were reduced; these parameters were not altered in the 1000 ppm males. Significant reductions in sperm motility were observed in the 1000 and 4500 ppm groups and in sperm concentration in the 4500 and 9000 ppm groups. The percentage of abnormal sperm was significantly increased in the 4500 ppm group. Sperm motility and morphology could not be fully evaluated in the 9000 ppm group due to absence of sperm (in 12 of 15 observed males) or severe reduction in sperm counts (in the other 3 males) of this group. Seminiferous tubular atrophy occurred in mid- and high-dose males; the severity was dose-related. Tissues of low-dose males exhibited no significant changes. Other indices of testicular morphology (spermatogenic index, seminiferous tubule diameter, spermatids per testis) were also altered at 4500 ppm or more. Effects observed at necropsy in 4500 ppm females (1000 and 9000 ppm females were not examined) were limited to a reduction in both relative and absolute liver weights and absolute kidney plus adrenal weights in comparison with controls.

The final F_1 litters (exposed during gestation and lactation) from the continuous breeding experiment were fed the same dosage of boric acid in the diet as their parents had received. Since there were no litters at 9000 ppm and few of the mice born alive in the final litters at 4500 ppm survived through weaning, only the 0 and 1000 ppm F_1 mice were included in a fertility trial. The F_1 mice were cohabited in nonsibling pairs (40 pairs of 0 ppm and 20 pairs of 1000 ppm mice) for 7 days or until a copulatory plug was observed, whichever occurred first. They were maintained on their respective diets during mating and until the F_2 litters were delivered, and then were necropsied. The fertility of the 1000 ppm F_1 mice was not affected, but the litter-adjusted body weights of the F_2 pups (females and combined males and females) were significantly decreased relative to controls. Effects in 1000 ppm F_1 females were significant increases in uterine and kidney plus adrenal weights, significantly shorter estrous cycles and fewer ambiguous vaginal smears. A reduction in epididymal sperm concentration in the 1000 ppm F_1 males approached significance ($p=0.053$); sperm motility and morphology were not affected. Histopathologic examination was unremarkable. The lowest dose tested, 1000 ppm, decreased sperm motility in the F_0 males, marginally decreased epididymal sperm concentration in F_1 males, increased uterine and kidney/adrenal weights and shortened estrus cycles in F_1 females, and reduced litter-adjusted

birth weights in the F_2 pups. Hence, the LOAEL for this study is 1000 ppm boric acid (26.6 and 31.8 mg B/kg-day for males and females, respectively). A NOAEL was not identified.

4.4. OTHER STUDIES

4.4.1. Genotoxicity Studies

Results of most short-term mutagenicity 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 either a 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 for mutagenicity in the *Salmonella* microsome assay using strains TA1535, TA1537, TA1538, TA98 and TA100 in both 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 mutagenicity test 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 either the presence or absence of a 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.

4.4.2. Neurological Studies

Sodium tetraborate was administered in the drinking water to 2-month-old Wistar rats for up to 14 weeks. Exposure to approximately 20.8 mg B/kg/day caused an increase in cerebral succinate dehydrogenase activity after 10-14 weeks of exposure (Settimi et al., 1982). Increased acid proteinase activity and increased RNA were also noted at the end of the 14-week experiment.

ATSDR (1992) reported on case reports of neurological effects after accidental ingestion of high levels of boron as boric acid. Doses of about 500 mg B/kg/day showed CNS involvement with headaches, tremors, restlessness and convulsions followed by weakness, coma and death. Histological examination revealed degenerative changes in brain neurons, congestion, and edema of brain and meninges with perivascular hemorrhage and intravascular thrombosis.

O'Sullivan and Taylor (1983) reported convulsions and seizures on seven infants exposed to a honey-borax mixture for 4-10 weeks, where the estimated ingestion was 16-48 mg B/day (see Section 4.1.1.).

4.4.3. Mechanistic Studies - Testicular Effects

The occurrence of testicular effects in the absence of overt systemic toxicity (see Section 4.2.1) suggests a testicular-specific mechanism of action for boron. Many studies have been conducted to elucidate the mechanism by which boron produces testicular effects (see Section 4.3.2.1 for descriptions of some of these studies). Recent reviews of this work have been published by Fail et al. (1998) and ECETOC (1994). Despite the number of studies that have been done, the mechanism of boron testicular toxicity remains unknown. The available data suggest an effect on the Sertoli cell, resulting in altered physiological control of sperm maturation and release (Fail et al., 1998).

4.4.4. Mechanistic Studies - Developmental Effects

Studies regarding the mechanism of developmental toxicity produced by boron were reviewed by Fail et al. (1998). The two most sensitive effects of boron on developing rodents are decreased fetal body weight and malformations and variations of the ribs. Fail et al. (1998) concluded that reduced fetal growth probably results from a general inhibition of mitosis produced by boric acid, as documented in studies on the mammalian testis, insects, yeast, fungi, bacteria and viruses (Beyer et al., 1983; Ku et al., 1993b), while the rib malformations probably result from direct binding of boron to the bone tissue.

4.4.5. Nutrition Studies

Boron has been known since the 1920s to be an essential micronutrient for the growth of all plants. In humans boron is a trace element for which essentiality is suspected but has not been directly proven (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). Experimental boron nutrition research data indicate that boron can affect the metabolism or utilization of a number of substances involved in life processes including calcium, copper, magnesium, nitrogen, glucose, triglyceride, reactive oxygen, and estrogen. These effects can affect the composition of several body systems including blood, brain and skeleton (Nielson, 1996). It is suggested that boron may prevent inflammatory disease as several key regulatory enzymes in the inflammatory response are inhibited by physiological amounts of supplemental dietary boron (Hunt, 1996). New boron nutrition research should better characterize the mechanisms through which boron modulates immune function, insulin release and vitamin D metabolism (Hunt, 1996). 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; Penland, 1994). Data from three human studies of potential boron essentiality demonstrate 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 additional 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). 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 than in the U.S. and Canada 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.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION (IF KNOWN) — ORAL AND INHALATION

4.5.1. Oral Exposure

Studies in laboratory animals conducted by oral exposure have identified the developing fetus and the testes as the two most sensitive targets of boron toxicity in multiple species (Weir and Fisher, 1972; Seal and Weeth, 1980; NTP, 1987; Fail et al., 1991; Price et al., 1996a,b; Field et al., 1989). 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., 1993a). The mechanism for boron's effect on the testes is not known, but the available data suggest an effect on the Sertoli cell, resulting in altered physiological control of sperm maturation and release (Fail et al., 1998). Developmental effects have been reported in mice, rabbits and rats (Heindel et al., 1994, 1992; Field et al., 1989; Price et al., 1996a,b, 1991). The developmental effects that have been reported following boron exposure include high prenatal mortality, reduced fetal body weight and malformations and variations of the eyes, central nervous system, cardiovascular system, and axial skeleton (Price et al., 1996a,b; Field et al., 1989). Increased incidences of short rib XIII (a malformation) and wavy rib (a variation), and decreased incidence of rudimentary extra rib on lumbar I (a variation), were the most common anomalies in both rats and mice. Cardiovascular malformations, especially interventricular septal defect, and variations were the frequent anomalies in rabbits. Fail et al. (1998) attributed reduced fetal growth, the most sensitive developmental endpoint, to a general inhibition of mitosis by boric acid, as documented in studies on the mammalian testis, insects, yeast, fungi, bacteria and viruses (Beyer et al., 1983; Ku et al., 1993b).

4.5.2. Inhalation Exposure

Studies in humans and animals have shown that borates are absorbed following inhalation exposure (Culver et al.,1994; Wilding et al., 1959). It is not clear what percentage of the absorbed material in these studies was absorbed via the respiratory tract directly; transport of deposited material from the upper respiratory tract to the gastrointestinal tract may have played an important role (Culver et al.,1994). However, because borates in the body all exist as boric acid, are distributed evenly throughout the soft tissues in the body water and are not metabolized (Ku et al., 1991; Naghii and Samman, 1996b; WHO, 1998a), there is no reason to expect route-specific differences in systemic targets. Therefore, systemic target tissues identified in oral studies comprise the potential systemic targets following inhalation exposure. There may, however, be route-specific differences in ability to deliver toxic doses to the targets, so that for example, very high exposure concentrations may be required to produce effects by inhalation exposure. Portal-of-entry effects may also differ with exposure route.

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 (boric acid) 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 far 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 chronic exposure (Wegman et al., 1994). These data are inadequate to support derivation of an RfC for boron compounds.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION — SYNTHESIS OF HUMAN, ANIMAL, AND OTHER SUPPORTING EVIDENCE, CONCLUSIONS ABOUT HUMAN CARCINOGENICITY, AND LIKELY MODE OF ACTION

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 mention any 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 40%, 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 data were located. Studies of boron compounds for genotoxicity were overwhelmingly negative, including studies in bacteria, mammalian cells and mice *in vivo*.

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

4.7. SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

The developing fetus is the most sensitive target of boron toxicity that has been identified. An oral dose of 13.3 mg B/kg-day on days 0-20 of gestation produced decreased fetal body weight in rats (Price et al., 1996a). The NOAEL was 9.6 mg B/kg-day. Maternal effects were not seen in the same study, even at doses of 25 mg B/kg-day. Fetal body weight deficits did not

continue into the postnatal period, suggesting that the effect is specific to the fetal period. Based on data from poisoning case reports, the lethal oral dose of boric acid in infants (2-3 g) and children (5-6 g) is similar to that in adults (15-20 g) on a mg/kg basis (≈200 mg/kg). Based on acute human data, infant doses of 30.4-94 mg B/kg were at the upper end of the adult dose response curve of 35-90 mg B/kg. Acute infant and adult human response to boron is similar quantitatively and qualitatively (Culver and Hubbard, 1996) (see Section 4.1.1.). No additional information was available to assess childhood susceptibility.

4.7.2. Possible Gender Differences

The two most sensitive targets of boron that have been identified are the developing fetus (rats, mice and rabbits) carried by the pregnant female, and the testes of the male. The developing fetus (LOAEL = 13.3 mg B/kg-day, NOAEL = 9.6 mg B/kg-day) appears to be slightly more sensitive than the male testis (LOAEL = 29 mg B/kg-day, NOAEL = 8.8 mg B/kg-day) (Price et al., 1996a; Weir and Fisher, 1972).

Effects on the pregnant females themselves are seen only at considerably higher doses (no clearly adverse maternal effects even at 94.2 mg B/kg-day in the same study used to derive the NOAEL and LOAEL values for the developing fetus reported above). We don't see that either can be shown to be more sensitive (male vs. female) based on the data shown here. A specific target of boron toxicity has not been identified in non-pregnant females, who are markedly less susceptible to boron than males. Data are inadequate to assess differences in gender susceptibility with regard to non-reproductive, non-developmental effects.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect — with Rationale and Justification

Developmental effects (decreased fetal weights) are considered the critical effect. The studies by Price et al. (1996a, 1994, 1990) and Heindel et al. (1992) in rats were chosen as critical developmental studies because they were well conducted studies of a sensitive endpoint that identified both a NOAEL and LOAEL. Rats were more sensitive than mice and rabbits, which were also studied for developmental toxicity (Price et al., 1996b; Heindel et al., 1994). The dog study by Weir and Fisher (1972) identified a NOAEL and LOAEL for testicular effects. Testicular effects were found at higher doses in rats and mice in this and other studies (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).

The Institute for Evaluating Health Risks 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 (IEHR, 1997). 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.

5.1.2. Methods of Analysis — Including Models (PBPK, BMD, etc.)

The RfD was derived by the benchmark dose (BMD) approach. Several BMD analyses were conducted by Allen et al. (1996) using all relevant endpoints in the Heindel et al. (1992) and Price et al. (1996a, 1994) studies. The earlier study by Heindel et al. (1992) did not define a NOAEL while the later study by Price et al. (1996a) was designed as a follow up study to the Heindel study to examine fetal body weight at lower doses to define a NOAEL. The results of the Allen et al. (1996) benchmark dose analysis for decreased fetal body weight for the Price study alone gave a BMDL of 47 mg BA/kg-day (8.2 mg B/kg/day) and for the Heindel study alone, the BMDL reported by Allen et al. (1996) was 56 mg BA/kg/day (9.8 mg B/kg/day). The combined data from Heindel et al. (1992) and Price et al. (1996a, 1994) gave a BMDL of 59 mg BA/kg/day (10.3 mg B/kg/day). 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 response, 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 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. The BMDL of 10.3 mg B/kg-day from the combined studies was chosen to derive the RfD because they were similarly designed studies conducted in the same laboratory and all the dose response data could be used in the BMDL estimation, thereby increasing the confidence that the dose response pattern has been estimated satisfactorily.

5.1.3. RfD Derivation — Including Application of Uncertainty Factors (UF) and Modifying Factors (MF)

Uncertainty factors (UFs) have been traditionally applied to account for recognized uncertainties in extrapolation from experimental conditions to the assumed human scenario (chronic exposure over a lifetime). However, recently there has been an emphasis to incorporate more of the data into the choice of the uncertainty factor. The U.S. EPA has not yet established guidance for the use of data for derivation of uncertainty factors, but the division of uncertainty factors into toxicodynamic (TD) and toxicokinetic (TK) components has been used in the Reference Concentration methodology (U.S. EPA, 1994b). Additionally, this concept has been examined by the World Health Organization and other national regulatory institutions. The WHO (1994) has maintained 10 as a default UF for both the UF_A (interspecies uncertainty) and UF_H (intraspecies uncertainty) components of uncertainty factor. For the UF_A, they have apportioned the factor of 10 between the TD and TK components so that the default value for the TD component is 2.5 ($10^{0.4}$) and the default value for the TK component is 4.0 ($10^{0.6}$) in the absence of data describing toxicodynamic or toxicokinetic differences. Similarly, WHO (1994) divided UF_H into TD and TK components with assigned default values of 3.16 ($10^{0.5}$) each. However, U.S. EPA's assessments to date assume a division of both UF_A and UF_H into TD and TK components assigned default values of 3.16 ($10^{0.5}$) each.

Prior to the development of the U.S. Borax-sponsored studies, boron had already been the subject of several projects through which "data-derived" uncertainty factors were developed (see Section 5.1.4.). Boron is not metabolized in rats or humans and is similiar in absorption and distribution between these two species. Boron has shown to be eliminated in rats and humans approximately 98% in the urine. The difference in elimination between rats and humans for boron is the clearance rate. While no data presently exist by which the default uncertainty factors for boron's toxicodynamic component of UF_A or UF_H can be refined, the application of presently available data describing animal to human differences and differences among humans in the urinary elimination (clearance) of boron can be used to develop uncertainty factors for the toxicokinetic component of the the UF_A and UF_H, respectively.

The uncertainty factors for animal-to-human variability (UF_A) and within-human variability (UF_H) are each split into toxicokinetic and toxicodynamic components (sub-factors). These sub-factors are 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 can be reduced to 1.0 by a dose-

adjustment factor equal to the appropriate pregnant rat:pregnant human ratio of boron clearance. The RfD "model" for boron is now represented by Equation 1.

$$RfD = \frac{BMDL}{AF_K \times {}_D U_A \times {}_D U_H} \quad (1)$$

where:

BMDL = benchmark dose lower bound
AF_K = aggregate toxicokinetic dose-adjustment factor (data-derived)
${}_DU_A$ = interspecies toxicodynamics uncertainty factor (default = $10^{0.5}$)
${}_DU_H$ = human interindividual toxicodynamics uncertainty factor (default = $10^{0.5}$)

The toxicokinetic adjustment factor is no longer an uncertainty, but a known dose-scaling factor. In the general application, the magnitude of AF_K is represented by Equation 2.

$$AF_K = \frac{\theta_{KA}}{\theta_{KH}} \quad (2)$$

where:

θ_{KA} = animal toxicokinetic value
θ_{KH} = human toxicokinetic value

For boron, θ_{KH} represents the toxicokinetic value in the sensitive subpopulation or, at least, the surrogate for the sensitive subpopulation. Therefore, AF_K comprises both the interspecies and intrahuman values for toxicokinetics.

The animal toxicokinetic value, θ_{KA}, is meant to represent the toxicokinetics of the test animals in the critical study, specifically the most sensitive animals in that study. This representation is based on the concept that interspecies uncertainty factor (UF_A) represents the extrapolation of a NOAEL (or BMDL) or, rather, the residual risk at the NOAEL (or BMDL), between species (Swartout et al., 1998). Therefore, the appropriate θ_{KA} value for boron is one toward the lower end of the clearance distribution, as lower clearance equates with higher internal dose and greater susceptibility to boron toxicity. The 5th percentile of the pregnant rat boron clearance distribution is chosen as representative of the sensitive test animals. Likewise, as pregnant women represent the sensitive human subpopulation, the 5th percentile of the boron clearance distribution is selected for θ_{KH}.

An empirical distribution function is chosen to represent both rat and human boron clearance, as no mathematical function well fits the rat boron clearance data. The boron clearance observations (i) are assumed to be distributed as the percentiles 100 x (i - 0.5)/n, where i is the

rank order of the observation and *n* is the number of observations (Wilk and Gnanedisikan, 1968). As an example, for a sample size (n) of 10, the first and last observations are assumed to be the 5^{th} (100 x 0.5/10) and 95^{th} (100 x 9.5/10) percentiles, respectively. Values at percentiles not directly observed are estimated by linear interpolation. The cumulative distributions of boron clearance for pregnant rats and pregnant women are shown in Figure 1. Linear interpolation is shown by the lines connecting the data points. The toxicokinetic extrapolation used in the derivation of the RfD is also shown (AF_K). Table 9 (Section 3.4.1) shows selected percentiles of the same distributions for this empirical distribution function. The respective 5^{th} percentile values for θ_{KA} and θ_{KH} are 2.53 and 0.286 mL/min/kg yielding an AF_K of 8.85. The combined interspecies and intrahuman toxicokinetic uncertainty factor component is reduced to 1. The remaining uncertainty factor of 10 is the product of the default values for the interspecies and intrahuman toxicodynamic components. The boron RfD is calculated as follows:

BMDL	=	10.3 mg/kg-day
Scaling factor (AF_K	=	8.85
BMDL(adj)	=	1.16 mg/kg-day (10.3 ÷ 8.85)
UF	=	10
RfD	=	0.1 mg/kg-day

Confidence in the principal developmental studies is high; they are well-designed rat studies that examined relevant developmental endpoints using a large number of animals. Developmental effects were also observed in mice and rabbits. 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.

1

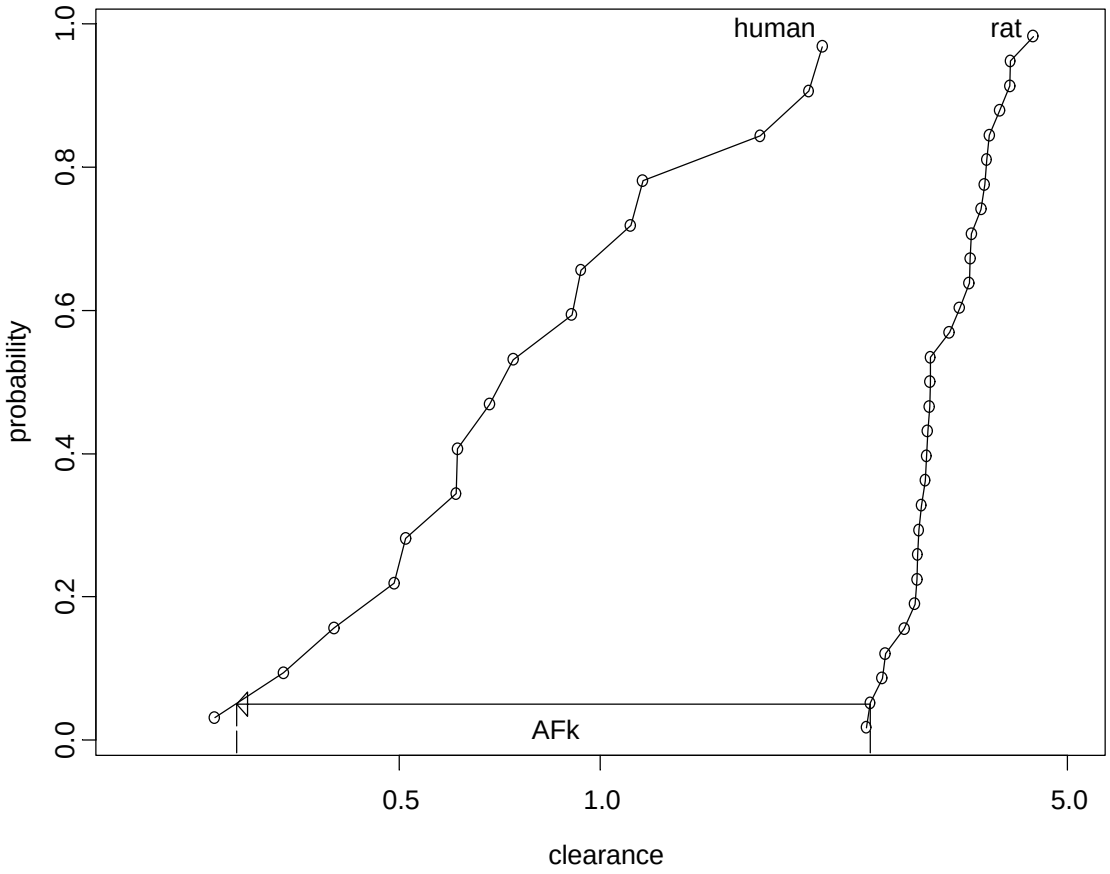

Figure 1. Cumulative empirical distribution of pregnant rat and human boron clearance values showing toxicokinetic extrapolation

5.1.4. Other Approaches

An alternative toxicokinetic extrapolation approach was published by Dourson et al. (1998). Most of the fundamental assumptions remain the same as for the approach on which the boron RfD is based. However, the focus is on the mean values of the toxicokinetic parameters, rather than on the distribution of those values. Using the boron kinetic data of U.S. Borax, 2000 and the Dourson et al. (1998) approach the UF_A toxicokinetic factor, then, is calculated as the ratio of the mean boron clearance in pregnant rats to the mean boron clearance in pregnant women. The mean boron clearance (in ml/min-kg) for pregnant rats and pregnant women is 3.3 and 0.92, respectively. The value of UF_A toxicokinetic factor is, thus, 3.59. For UF_H, the toxicokinetic factor is calculated as the ratio of the mean boron clearance in pregnant women to the boron clearance value at 2 standard errors (standard error of the mean) below the mean (for pregnant women). The standard error of the mean (SE) is estimated as the sample standard deviation divided by the square root of the sample size. The sample standard deviation for the boron clearance data for pregnant women is 0.5896 ml/min-kg, with a sample size of 16. The resulting SE is 0.1474 ml/min-kg. The boron clearance for pregnant women at 2 standard deviations below the mean is 0.625 ml/min-kg ($0.92 - 2 \times 0.1474$). Thus, the toxicokinetic factor for UF_H would be 1.47 [$0.92 \div 0.625$]. The combined toxicokinetic factor for UF_A and UF_H would be 5.28 (3.59×1.47). The remaining uncertainy is the toxicodynamic uncertainty in both UF_A and UF_H. Each of these factors are set to the default value of $10^{0.5}$ (usually rounded to 3). As no other areas of uncertainty apply, the aggregate UF is reduced to a value of 10. Based on the BMDL of 10.3 mg/kg-day, an RfD 0.2 mg/kg-day would result ($10.3 \div 5.28 \div 10$). A more limited application of this model would use just the UF_A toxicokinetic factor, if it was felt that the intrahuman extrapolation was unwarranted. In this case, the overall remaining aggregate UF would be 30, which is the product of the entire default factor (10) for UF_H and the default toxicodynamic uncertainty (3) remaining for UF_A. The resulting RfD would be 0.1 mg/kg-day ($10.3 \div 3.59 \div 30$).

The U.S. EPA chose not to use the mean-value approach for two reasons. First, data on the entire distribution were available. Second and more fundamentally, the mean-value approach addresses the group as a whole and does not directly address individuals in the population, with which the RfD is concerned. The mean-value approach focuses on the confidence interval of the group mean, which, depending on the sample size, could be a relatively high percentile (the 30^{th} in this example) of the distribution of individual values.

Others have used different methods to derive uncertainty factors. The U.S. EPA has not yet endorsed any of these approaches, as there are a number of critical unresolved scientific and methodological issues.

The International Program on Chemical Safety (IPCS) uses “data-derived” uncertainty factors to estimate Tolerable Intake Values (WHO, 1994; Renwick, 1993). This method allows for subdivision of each of the interspecies and intraspecies default uncertainty factors to incorporate data on toxicokinetics (pharmacokinetics) or toxicodynamics (pharmacodynamics). For interspecies uncertainty, the 10-fold factor is divided into a default factor of $10^{0.6}$ (4.0) for

toxicokinetics and $10^{0.4}$ (2.5) for toxicodynamics in the absence of toxicokinetic and toxicodynamic data. For intraspecies uncertainty, the 10-fold factor is subdivided into a default of $10^{0.5}$ (3.2) each for toxicokinetics and toxicodynamics in the absence of toxicokinetic and toxicodynamic data.

Several risk assessments have recently been completed for boron using an uncertainty factor less than 100. A description of the critical effect chosen and the uncertainty factors used follows.

The European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1994) developed a Tolerable Daily Intake for developmental effects of boron. Decreased fetal body weight in rats was chosen as the critical effect (Price et al., 1994) with a NOAEL of 9.6 mg B/kg/day. A factor of $10^{0.5}$ was chosen for interspecies uncertainty factor due to the similarity in pharmacokinetics (metabolism and distribution were cited) between animals and humans. A default factor of 10 was chosen for the intraspecies uncertainty factor. The composite uncertainty factor was 30.

Murray (1995, 1996) used the Price et al. (1994) study choosing decreased fetal body weight in rats as the critical effect with a NOAEL of 9.6 mg B/kg/day. The interspecies uncertainty factor chosen was 4 (2 for pharmacokinetics and 2 for pharmacodynamics, 2x2=4). The reasons cited for the reduced interspecies uncertainty factor for pharmacokinetics were as follows: boron is not metabolized in animals or humans, eliminating a major potential source of pharmacokinetic variation; is rapidly distributed throughout body water and does not accumulate; the toxicity profile of boron is similar across species; and parameters of elimination were considered by the author to be similar in humans and other animals. The reasons cited for the reduced interspecies uncertainty factor for pharmacodynamics were as follows: the sensitivity of the target tissue receptor appears, to the author, to be similar across species based on the similarity of symptoms of acute toxicity in animals and humans, and because developmental and reproductive toxicity appear to be the most sensitive endpoint of toxicity in all animal species tested. The intraspecies uncertainty factor chosen was 8 (2.5 for pharmacokinetics and 3.2 for pharmacodynamics). The intraspecies pharmacokinetic factor was decreased because metabolism is normally the major source of pharmacokinetic variance in humans and borates are not metabolized. The composite uncertainty factor chosen was 4x8=32.

The Institute for Evaluating Health Risks (IEHR, 1997) determined an Unlikely Effect Level for Developmental Toxicity for Boron based on the benchmark dose for decreased fetal body weight by Allen (1996). The interspecies uncertainty factor chosen for boron was $10^{0.5}$, which includes $10^{0.25}$ each for pharmacokinetics and pharmacodynamics. The justification for these other than default values was stated as the variability in the intrinsic sensitivity of the target site (embryo, testis, ovary) to the chemical's toxic effects in humans versus that in the experimental animal and metabolic and pharmacokinetic differences among species The intraspecies uncertainty factor chosen for boron was a default value of 10. The composite human sensitivity factor was 30.

In their Environmental Health Criteria Document, WHO (1998a) developed a Tolerable Daily Intake for boron where decreased fetal body weight in rats was chosen as the critical effect (Price et al., 1994) with a NOAEL of 9.6 mg B/kg/day. The interspecies uncertainty factor chosen was $10^{0.5}$ ($10^{0.1}$x$10^{0.4}$= $10^{0.5}$) which used a $10^{0.1}$ for pharmacokinetics due to the similarity of absorption, distribution, metabolism and elimination of boron in rats and humans and a $10^{0.4}$ (default) for pharmacodynamics. The intraspecies uncertainty factor chosen was $10^{0.9}$ ($10^{0.4}$x$10^{0.5}$ =$10^{0.9}$), $10^{0.4}$ for pharmacokinetics due to lack of metabolism in humans and $10^{0.5}$ (default) for pharmacodynamics. The composite uncertainty factor was 32.

In their Guidelines for Drinking-Water Quality, WHO (1998b) developed a Tolerable Daily Intake for boron to set a guidance value for drinking water. Decreased fetal body weight in rats was chosen as the critical effect (Price et al., 1994) with a NOAEL of 9.6 mg B/kg/day. A default value of 10 was chosen for the interspecies factor due to a reported lack of data to support reduction in the pharmacokinetic and pharmacodynamic factors. For intraspecies extrapolation a default value of 3.2 for pharmacokinetic data was reduced to 1.8 and a default value of 3.2 was retained for pharmacodynamic data. Thus the uncertainty factor for intraspecies uncertainty was 1.8x3.2=5.7 rounded to 6. The composite uncertainty factor was considered to be 10x6=60.

Dourson et al. (1998), as part of the development of WHO (1998b), developed a Tolerable Daily Intake for boron. Although the authors agreed to the lack of metabolism and the similarity in absorption and elimination of boron in animals and humans, interspecies variation in kinetics for boron was considered to relate to renal clearance rates. A 3-fold clearance rate difference between rats and humans for boron was estimated, after eliminating studies with little confidence from an earlier projected 4-fold difference. The calculated renal clearance rate difference (3-fold) between rats and humans for boron was considered by the authors to be similar to a 4-fold difference that would be expected of other chemicals (Renwick, 1993). Based on this difference in clearance rates, the authors (Dourson et al., 1998) chose not to reduce the interspecies uncertainty factor for pharmacokinetics or pharmacodynamics. Therefore, a default value of 10 was chosen for the interspecies factor. For intraspecies uncertainty the pharmacokinetic factor was reduced from a default of 3.2 to 1.8. The authors proposed that the likely difference for humans in boron kinetics occurs during pregnancy and is based on an increase in the GFR (Glomerular Filtration Rate), a recognized physiological adaption during pregnancy. The estimation of the 1.8 factor for intraspecies variation in pharmacokinetics was based on a ratio of the mean GFR of 144 mL/min +/- 32(SD) from pooled data of healthy humans in late pregnancy (number of subjects not mentioned) and this mean GFR minus two standard deviations from the mean to account for variation in the average to the susceptible human 32(SD) x2=64; 144(GFR)-64(2SDs)=80; the ratio of 1.8 was calculated as 144 mL/min divided by 80=1.8. The intraspecies pharmacodynamic factor used was a factor of 3.1, which the authors considered as a default factor, although previous methodology considered it to be 3.2. The intraspecies uncertainty factor was 1.8x3.1=5.58 rounded to 6. The composite uncertainty factor was 10x6=60.

Murray and Anderson (2000) detailed the use of reduced uncertainty factors for boron risk assessments in recent years and noted the use of factors in the range of 25-60 using the NOAEL

from the Price et al. (1996) rat developmental study. The authors recommended using data derived uncertainty factors in a range of 22-44 using new rat clearance data from U.S. Borax. The authors detailed a method where they estimated the human dose expected to provide the same boric acid area under the curve in target tissues as the NOAEL in rats and then applying reduced uncertainty factors for pharmacokinetic and pharmacodynamic uncertainty to this estimated human NOAEL. Interspecies pharmacokinetic value was estimated at 3.1, while interspecies pharmacodynamic uncertainty was estimated at 1.25-2.5. Intraspecies factors for pharmacokinetics was 1.8-2.0 and intraspecies pharmacodynamics was 3.2.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

The available inhalation data are inadequate to support derivation of an RfC for boron compounds.

5.3. CANCER ASSESSMENT

The available data are inadequate for evaluation of the human carcinogenic potential of boron. Derivation of slope factors and unit risks is, therefore, precluded.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

Boron is a naturally-occurring element that is widespread in nature; the average concentration in the earth's crust has been estimated to be 10 ppm (Woods, 1994). Boron in the environment is always found chemically bound to oxygen, usually as alkali or alkaline earth borates, or as boric acid (IEHR, 1997; U.S. EPA, 1987). Boric acid and sodium borates are widely used for a variety of industrial purposes. Boron is not transformed or degraded in the environment, but depending on environmental conditions (e.g., pH, moisture level), changes in the specific form of boron and its transport can occur (ATSDR, 1992). The most important source of exposure for human populations is ingestion of boron from food (primarily fruits and vegetables) (Naghii and Samman, 1996a). Occupational exposure to boron dust and exposure to boron in consumer products (e.g., cosmetics, medicines, insecticides) are other potentially significant sources (ATSDR, 1992).

Boron is readily absorbed from the gastrointestinal tract following oral exposure (Schou et al., 1984; Vanderpool et al., 1994). Boron is also absorbed following inhalation exposure, although it is not clear how much is absorbed directly through the mucous membranes of the respiratory tract and how much is cleared by mucociliary activity and swallowed (Culver et al., 1994). Boron is not absorbed across intact skin, but is readily absorbed across damaged skin (Draize and Kelley, 1959). Boric acid and borate compounds in the body exist primarily as

undissociated boric acid, which distributes evenly throughout the soft tissues of the body (Ku et al., 1991; Naghii and Samman, 1996b). Although it does not accumulate in the soft tissues, boron does accumulate in bone, reaching steady-state levels approximately 4-fold higher than plasma levels after 1-4 weeks, depending on dose (Ku et al., 1991; Chapin et al., 1997). Boric acid is not degraded in the body, but can form complexes with various biomolecules by mechanisms that appear to be concentration dependent and reversible (IEHR 1997; WHO, 1998a). Boric acid is excreted primarily in the urine. It is cleared from the plasma with a half-life of approximately 21 hours (Jansen et al., 1984a), but eliminated very slowly from bone (Chapin et al., 1997).

Studies in laboratory animals conducted by oral exposure have identified the developing fetus and the testes as the two most sensitive targets of boron toxicity in multiple species (Weir and Fisher, 1972; Seal and Weeth, 1980; NTP, 1987; Fail et al., 1991; Price et al., 1996a,b; Field et al., 1989). 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). The mechanism for boron's effect on the testes is not known, but the available data (as reviewed by Fail et al., 1998) suggest an effect on the Sertoli cell, resulting in altered physiological control of sperm maturation and release. The developmental effects that have been reported following boron exposure include high prenatal mortality, reduced fetal body weight and malformations and variations of the eyes, central nervous system, cardiovascular system, and axial skeleton (Price et al., 1996a,b; Field et al., 1989). Increased incidences of short rib XIII (a malformation) and wavy rib (a variation), and decreased incidence of rudimentary extra rib on lumbar I (a variation), were the most common anomalies in both rats and mice. Cardiovascular malformations, especially interventricular septal defect, and variations were the frequent anomalies in rabbits. Fail et al. (1998) attributed reduced fetal growth, the most sensitive developmental endpoint, to a general inhibition of mitosis by boric acid, as documented in studies on the mammalian testis, insects, yeast, fungi, bacteria and viruses (Beyer et al., 1983; Ku et al., 1993b).

Because boron is absorbed following inhalation exposure, is distributed evenly throughout the soft tissues of the body as boric acid, and is not metabolized, there is no reason to expect route-specific differences in systemic targets. Therefore, systemic target tissues identified in oral studies comprise the potential systemic targets following inhalation exposure. There may, however, be route-specific differences in ability to deliver toxic doses to the targets, so that for example, very high exposure concentrations may be required to produce effects by inhalation exposure. Portal-of-entry effects may also differ with exposure route. The literature regarding toxicity of boron by inhalation exposure is sparse. There is a report of testicular effects in Russian workers exposed to very high concentrations (Tarasenko et al., 1972), but no evidence of an effect on fertility in a controlled epidemiology study in U.S. borate production workers (Whorton et al., 1994a,b, 1992). Only irritant effects have been associated with borate exposure in U.S. workers, with no evidence of an effect on pulmonary function (Wegman et al., 1994; Garabrant et al., 1984, 1985). Irritant effects and reduced growth were the only effects reported in the lone

animal study (Wilding et al., 1959). These data are inadequate to support derivation of an RfC for boron compounds.

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 40%, 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. Overwhelmingly, studies of boron compounds for genotoxicity were negative, including studies in bacteria, mammalian cells and mice *in vivo*. Under EPA's current guidelines for carcinogen risk assessment (U.S. EPA, 1986a), boron is classified as Group D; not classifiable as to human carcinogenicity. Under the new proposed guidelines (U.S. EPA, 1996a), the data are considered to be inadequate for evaluation of the human carcinogenic potential of boron.

6.2. DOSE RESPONSE

The studies by Price et al. (1996a, 1994, 1990) and Heindel et al. (1992) in rats were chosen as the critical developmental studies because they were well conducted studies of a sensitive endpoint that identified both a NOAEL and LOAEL. Rats were more sensitive than mice and rabbits, which were also studied for developmental toxicity (Price et al., 1996b; Heindel et al., 1994). The dog study by Weir and Fisher (1972) identified the most sensitive NOAEL and LOAEL for testicular effects. This study was not used to calculate the RfD due to several limitations as stated in Section 4.2.1. Testicular effects were found at higher doses in rats and mice in this and other studies (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).

The quantitative estimates of human risk as a result of exposure to boron are based on animal experiments because no human data exist. The human dose that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime (RfD) is .1 mg/kg-day. This RfD was derived by the benchmark dose approach. Several BMD analyses were conducted (Allen et al., 1996) using all relevant endpoints to analyze data from the Heindel et al. (1992) and Price et al. (1996a, 1994) studies alone and the combined data from both 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. For mean fetal weight analysis, the BMDL was defined as the 95% lower bound on dose corresponding to a 5% decrease in the mean. 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 chosen for development of the RfD 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. Because the difference in toxicokinetics between animals and humans are primarily represented by the clearance of boron (Section 5.1.3.), the BMDL was adjusted to1.16 mg/kg-day by muliplying by a toxicokinetic adjustment factor of 8.85, which accounted for the difference in boron clearance between pregnant women and pregnant rats. This factor was calculated from boron clearance data provided by U.S. Borax (2000). The aggregate uncertainty factor was reduced to10 as a result. The remaining aggregate uncertainty factor of 10 represents the combined interpsecies and intra-human toxicodynamic uncertainty.

Confidence in the principal developmental studies is high; they are well-designed studies that examined relevant developmental endpoints using a large number of animals. Similar developmental effects were noted in rats, mice and rabbits. 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.

The available data are inadequate to support derivation of an RfC, slope factor or unit risk for boron compounds.

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APPENDIX A. EXTERNAL PEER REVIEW - SUMMARY OF COMMENTS AND DISPOSITION

The toxicological review for Boron and the individual boron assessments have undergone both internal peer review performed by scientists within EPA and a more formal external peer review performed by scientists according to U.S. EPA (1998). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. Public comments were read and considered. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. All three external peer reviewers recommended that this document and the accompanying assessments were acceptable with minor revisions.

(1) General Questions for Peer Reviewers

General Question For the RfD, has the most appropriate critical effect been chosen (i.e., that adverse effect appearing first in a dose-response continuum)? For the cancer assessment, are the tumors observed biologically significant? relevant to human health? Points relevant to this determination include whether or not the choice follows from the dose-response assessment, whether the effect is considered adverse, and if the effect (including tumors observed in the cancer assessment) and the species in which it is observed is a valid model for humans.

A. Comment All three reviewers agreed that developmental effects are considered the most appropriate critical effect for development of an RfD. However, one reviewer suggested looking at the references of Beyer et al. (1983) and Dixon et al.(1979) where more sensitive endpoints are reported.

Response to Comment The sensitive endpoint referenced in Beyer (1983, a review article) is a reduced sperm count reported from a USSR study, which was poorly reported without experimental details. The general toxic effect of boron in a 21-35 day study was noted as the reduced activity of the aldolase of blood serum at 6 mg/kg boron while another study of 6 month duration reports reduced aldolase and sperm motility at 0.3 mg/kg. There are very little details given for this study which makes it unacceptable for use in determination of an RfD. The studies by Dixon et al. (1979) are reported as a US and USSR cooperative laboratory effort to improve and validate experimental techniques to assess reproductive effects in laboratory animals. The studies by Dixon et al. (1979) reported in the toxicological review are acute and subchronic studies that do not observe toxic effects below the level chosen as the NOAEL in the Price et al. (1996a, 1994) studies.

General Question Have the noncancer and cancer assessments been based on the most appropriate studies? These studies should present the critical effect/cancer (tumors or appropriate

precursor) in the clearest dose-response relationship. If not, what other study (or studies) should be chosen and why?

B. Comment All reviewers agreed that the studies chosen were the most appropriate.

General Question Studies included in the RfD and RfC under the heading "Supporting/Additional Studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, any evidence corroborative of the critical effect, or to establish the comprehensiveness of the data base with respect to various endpoints (such as reproductive/developmental toxicity studies). Should other studies be included under the "Supporting/Additional" category? Should some studies be removed?

C. Comment All reviewers agreed with what appeared in the document. One reviewer commented that no studies needed to be removed.

General Question For the noncancer assessments, are there other data that should be considered in developing the uncertainty factors or the modifying factor? Do you consider that the data support use of different (default) values than those proposed?

D. Comment Two reviewers agreed that there was no reason to support use of uncertainty factors other than those proposed in the document but one of these reviewers questions what the Agency is going to do about the FQPA. One reviewer objected to the write up of the pharmacokinetic section of the document and did not think that the write up of that section supported the reduced uncertainty factor for interspecies variation. This reviewer suggested a revision to the pharmacokinetic section.

Response to Comment The comments in response to this question are addressed in the following Boron Specific Questions. (Question #4)

General Question Do the confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the studies chosen, the relevancy of the effects (cancer and noncancer) to humans, and the comprehensiveness of the data base? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

E. Comments All reviewers agreed with the confidence statements.

(2) Comments on Boron Specific Questions

Question 1 Do you agree with the developmental effect, decreased fetal body weight in rats, as being the most appropriate critical effect? If not, why not?

Comments All three external reviewers agreed that decreased fetal body weight in rats was the critical effect.

Question 2 Do you agree that in light of new developmental data in three species (rats, mice and rabbits) that use of the dog study (Weir and Fisher, 1972) for development of an RfD is unacceptable based on the low number of animals used, the testicular atrophy noted in the control animals and the NOAEL and the LOAEL were taken from two different studies of different duration?

Comments All three reviewers agreed that the dog study should not be used for development of an RfD for the reasons stated in the text and the new developmental data should be used.

Question 3 Do you agree that use of the benchmark dose (Allen et al., 1996) is appropriate for use in calculating an RfD based on developmental toxicity?

Comments All three reviewers agreed that the use of the benchmark dose from Allen et al. (1996) was appropriate for calculating the RfD. One reviewer also added that proper statistical methods were applied.

Question 4 Do you agree with the use of an other than default uncertainty factor for inter-species extrapolation based on the reasons given in the Toxicological Review? If not, what do you think it should be and why? Do you agree with the default uncertainty factor chosen for intra-species extrapolation? If not, what do you think is appropriate and why?

Comments Two reviewers agree with the less than default uncertainty factor for interspecies extrapolation. Although one of these two reviewers had a question about how the agency was going to handle additional 10x uncertainty factor for the (FQPA) Food Quality Protection Act. A third reviewer questioned the write up of the physiologically based pharmocokinetic section. This reviewer recommended a rewrite of the pharmacokinetic section especially the Excretion and Elimination Section with more data added.. This reviewer could not support the proposed reduced uncertainty factor for interspecies extrapolation without a rewrite of the excretion and elimination section showing the data.

Response to Comment At this time the agency has not come to agreement on the 10x uncertainty factor for the FQPA. Based on the high confidence of the toxicity data base, the

assessment for boron and that the critical effect is decreased fetal body weight (developmental toxicity) in the most sensitive species, the author does not think that an extra 10x uncertainty factor is needed to protect for children's risk to boron. Parts of the Toxicokinetic section including Section 3.2 (Distribution) were revised to include more information on the tissues examined and relative amounts of boron in those tissues. More information was included concerning volumes of distribution in a human study and a rat study. Section 3.4 (Elimination and excretion) was completely rewritten to include a comparison between animals and humans for excretion and elimination in the urine and blood. A new pharmacokinetic section was added to emphasize the similarities between animals and humans to support the reduction of the interspecies uncertainty factor.

Question 5 For the RfC, do you agree with the NOT VERIFIABLE status that indicates the data do not meet the minimum requirements according to the current Agency methods document for Inhalation Reference Doses? If not, what effect and data would you use to develop an RfC?

Comments All three reviewers agree that the inhalation data are sparse and insufficient to determine an RfC.

Question 6 Do you agree with the Cancer Classification of Group D using the old guidelines, and under the new proposed guidelines that data are insufficient for evaluation of the human carcinogenic potential for boron?

Comments All three reviewers agreed with the cancer classification under current guidelines and new proposed guidelines.

Question 7 Do you agree with the confidence statements on the RfD? (High confidence in the study, high confidence in the data base and high confidence in the RfD). If you do not agree, what would you change it to and why?

Comments All three reviewers agree with the high confidence in the study, data base and in the RfD.

APPENDIX B. BENCHMARK DOSE FOR RfD

A. COMPUTATIONAL MODELS - CONTINUOUS DATA

The continuous power model was fit by Allen et al. (1996) to the data by the maximum likelihood method. The model is expressed as:

$$m(d) = \alpha - \beta \times d^{\gamma},$$

where m(d) is the average litter mean at dose d (expressed in mg/kg-day) and α, β and γ are the parameters to be estimated.

B. DATA

Dose of Boric Acid (mg/kg-day)	Fetal Weight (litter mean ± std dev, in g)	
	Heindel et al., 1992	Price et al., 1996a, 1994
0	3.70 ± 0.32	3.61 ± 0.24
19		3.56 ± 0.23
36		3.53 ± 0.28
55		3.50 ± 0.38
76		3.38 ± 0.26
78	3.45 ± 0.25	
143		3.16 ± 0.31
163	3.21 ± 0.26	
330	2.34 ± 0.25	

C. MODEL FIT

The model was examined for fit to the data by an F test that compared the lack of model fit to an estimate of pure error. A likelihood ratio test was performed to determine if a single function could adequately describe the dose-response in both the Heindel et al. (1992) and Price et al. (1996a, 1994) studies.

D. RESULTS

Study	Significant Trend?[a]	Max LL[b]	Goodness-of-fit p-value[c]	Dose corresponding to BMR[d]	
				MLE[e] (mg/kg-day)	BMDL[f] (mg/kg-day)
Heindel et al., 1992	Yes	141.74	0.24	80	56
Price et al., 1996a, 1994	Yes	215.87	0.89	68	47
Combined	--	353.43	0.58	78	59

[a] Tested for trend by Mantel-Haenszel trend test. A significant trend corresponds to a p-value less than 0.05. Combined study results were not tested for trend.

[b] Maximum value of the log-likelihoods of the models fit to the data, ignoring constant terms not related to parameter estimates. The Max LL for the studies combined is not significantly different (p=0.01) from the sum of the Max LL values for the studies individually, indicating that the data are consistent with a single dose-response curve.

[c] Significant fit of the model to the data is indicated by p-value > 0.05

[d] BMR = benchmark response, in this case a 5% decrease in mean fetal weight per litter

[e] MLE = maximum likelihood estimate of dose corresponding to BMR

[f] BMDL = benchmark dose, the 95% lower confidence limit on the MLE

E. DISCUSSION

Results of the likelihood ratio test showed that data from the two studies are consistent with a common dose-response curve. The BMDL of 59 mg/kg-day boric acid (10.3 mg B/kg-day) obtained from the combined data is used for calculation of the RfD. This BMDL is based on combined results of two similiarly designed studies conducted in the same laboratory. The BMDL selected is not much less than the lowest dose tested (78 mg/kg-day, 13 mg B/kg-day) in Heindel et al. (1992) which was a LOAEL, and is very close to the NOAEL of 55 mg/kg-day (9.6 mg B/kg-day) (Price et al., 1994).

F. U.S. EPA BENCHMARK DOSE SOFTWARE

Similiar results were obtained when the combined data from the Heindel et al. (1992) and Price et al. (1996a, 1994) studies were fit to the Agency Draft Benchmark Dose Software power model revision:1.6. The following output shows those results.

BMDS MODEL RUN

The form of the response function is:

Y[dose] = control + slope * dose^power

Dependent variable = MEAN
Independent variable = D
rho is set to 0
The power is not restricted
A constant variance model is fit

Total number of dose groups = 10
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 2.22045e-016
Parameter Convergence has been set to: 1.49012e-008

Default Initial Parameter Values

alpha	=	0.0794435
control	=	3.7
slope	=	-0.252147
power	=	0.0658232

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho
have been estimated at a boundary point, or have been specified by
the **MISSING TEXT** and do not appear in the correlation matrix)

	alpha	control	slope	power
alpha	1	-1.4e-007	-6.2e-008	-0.00024
control	-1.4e-007	1	0.61	-0.024
slope	-6.2e-008	0.61	1	-0.041
power	-0.00024	-0.024	-0.041	1

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	0.0787966	0.00664767
control	3.62363	0.0210371
slope	-0.000628061	2.86511e-005
power	1.31242	0.266498

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev
0	29	3.7	0.32	3.62	
0.281					
1e-008	26	3.61	0.24	3.62	
0.281					
19	29	3.56	0.23	3.59	
0.281					
36	27	3.53	0.28	3.55	
0.281					
55	29	3.5	0.38	3.5	0.281
76	29	3.38	0.26	3.44	
0.281					
78	28	3.45	0.25	3.43	
0.281					
143	27	3.16	0.31	3.2	0.281
163	29	3.21	0.26	3.12	
0.281					
330	28	2.34	0.25	2.35	
0.281					

Model Descriptions for likelihoods calculated

Model A1: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma^2$

Model A2: $Yij = Mu(i) + e(ij)$
$Var\{e(ij)\} = Sigma(i)^2$

Model R: $Yi = Mu + e(i)$
$Var\{e(i)\} = Sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
Al	220.937	11	209.937
A2	227.175	20	207.175
fitted	216.494	4	212.494
R	76.319	2	74.319

Test 1: Does response and/or variances differ among dose levels (A2 vs. R)
Test 2: Are variances homogeneous (Al vs A2)
Test 3: Does the model for the mean fit (Al vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	df	p-value
Test 1	289.235	18	<0.00001
Test 2	12.477	9	0.1877
Test 3	8.88462	7	0.261

The p-value for Test 1 is less than 0.05. There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data.

The p-value for Test 2 is greater than 0.05. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than 0.05. The model chosen appears to adequately describe the data.

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.950000

BMD = 74.9006

BMDL = 57.8307

CITATIONS FOR BENCHMARK DOSE

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.

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., 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.

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

0410
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).

_III. [reserved]

_IV. [reserved]

_V. [reserved]

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CASRN -- 7440-42-8
Last Revised -- 00/00/00

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___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
Last Revised -- 00/00/00