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Health Effects for Boron and Borates

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Health Effects for Boron and Borates

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PRODUCT DESCRIPTION

Boron occurs in varying concentrations in coal fly ash and is typically found in fly ash leachates. The U.S. Environmental Protection Agency (EPA) is in the process of performing a risk assessment to determine safe levels of boron for human ingestion. This report describes existing information on the health effects of boron and how that information is being used to calculate a reference dose (RfD) and acceptable concentration in drinking water.

Results & Findings

Boron occurs as borates in natural systems, and its water-soluble forms are primarily boric acid $B(OH)_3$ and the monovalent anion $B(OH)^4$. It is widespread in the environment, serves as an essential nutrient for bacteria and plants, and is known to be beneficial to humans. Boron is not considered a carcinogen. The primary adverse health effects associated with boron ingestion in animal studies involved reproductive and developmental toxicity. Reproductive effects included reduced fertility and sterility, while the primary developmental effects were fetal rib malformations and decreased fetal body weight.

The U.S. EPA chose depressed fetal body weight in rats as the critical effect to calculate an RfD of 0.2 mg/kg-day. The RfD represents the human dose likely to be without appreciable risk of non-cancer effects. This RfD yields an acceptable intake of 14 mg B/day for an adult male (70 kg body weight) and 12 mg B/day for an adult female (60 kg body weight). Accounting for an average dietary intake of 1.5 mg B/day, and using the standard assumption for water intake of 2 L/day, yields an acceptable concentration in drinking water of 6.2 mg/L for an adult male and 5.2 mg/L for an adult female. Using an alternative method based on recommended dietary allowance applied to the most sensitive subpopulation (infants 0 to 0.5 yrs) yields an acceptable concentration of 0.5 mg/L.

This assessment is largely based on animal studies, with little available information on chemical mechanisms in humans (toxicodynamics). This is reflected in a high uncertainty factor for toxicodynamics in the calculation of acceptable daily intake. In addition, boron is believed to be essential to human health and little is known about the health effects of boron deficiency. More information in these areas would decrease uncertainty and could result in calculation of higher acceptable daily intake concentrations.

Challenges & Objective(s)

Boron is relatively soluble in fly ash and mobile in many groundwater environments. Understanding the potential health effects of boron in drinking water is an important component of assessing the actual risk associated with its environmental release from an ash management facility. This report summarizes the existing information on boron toxicity, describes how that information is being used to develop safe concentrations in drinking water, and identifies data gaps that increase uncertainty and may result in more conservative calculations.

Applications, Values & Use

The U.S. EPA is preparing a document entitled Toxicological Review of Boron and Compounds, based on the studies summarized in this report. The final version of the EPA document, now nearing completion, will likely use the newer risk assessment methods described here to calculate an RfD, which will serve as the basis for development of a drinking water standard for boron. The EPA report has not yet undergone the agency's Consensus Review Process. The information in this report can be used to critically evaluate the EPA approach to development of a drinking water standard as well as for site-specific risk assessments at ash management facilities.

EPRI Perspective

EPRI is preparing individual reports summarizing the occurrence, groundwater transport, treatment, and health effects of selected constituents found at ash management facilities. The first of these will be for boron, which is a unique indicator of leachate release from fly ash. Subsequent reports will include selenium, arsenic, and molybdenum. These reports will provide ash managers with a compilation of information needed to perform detailed and accurate risk assessments at their facilities.

Approach

The project team compiled and summarized existing information on the health effects of boron. Most of this work centered on dose-response studies in animals, primarily dogs and rats. They described use of the information to calculate no observed adverse effects levels (NOAELs), lowest observed adverse effects levels (LOAELs), and RfDs using traditional methods. They also described new EPA assessment methodologies using bench mark dose levels (BMDLs) to calculate the RfD and to determine allowable daily intake by sensitive subpopulations. Finally, they made recommendations for further research to decrease uncertainty with respect to the RfD.

Keywords

Coal Ash
Boron
Health Effects
Drinking Water
Borates
Toxicological Review

EXECUTIVE SUMMARY

Boron (B) is the fifth element in the periodic table and is assigned to Group IIIA. It has an atomic weight of 10.81 and exists as a mixture of stable isotopes ^{10}B and ^{11}B with respective abundances of 19.8% and 80.2% in the natural environment. Three (trigonal) covalent bonds with oxygen form boric acid and four (tetrahedral) borates. Most boron in nature is present in the form of borates because of the high affinity of boron for oxygen. Water-soluble forms of boron include boric acid $B(OH)_3$ and the monovalent anion $B(OH)_4^-$, with the predominant form depending on the pH of the solvent. Boric acid is a weak Lewis acid with a pK_a of 9.2 and is the dominant form of the element in physiological solutions. Boron is widely distributed in the environment, with a large amount in the ocean (4.6 mg/L), mineral deposits of old sea beds, and volcanic regions. The average concentration in the earth's crust is 10 mg/kg. Boron is an essential nutrient for bacteria and plants and is known to be beneficial to humans. The most important sources of human exposure are plant foods—particularly vegetables, nuts, fruits and their by-products where it is present as a structural component—and water. Minor sources of exposure include air, cosmetics, medicines and insecticides.

Boric acid and borates are readily absorbed from the gastrointestinal tract. They are not absorbed across skin, but occupational and consumer product exposures from inhaled dust can contribute a small amount to the overall total exposure. In blood and other body fluid boron exists as boric acid. Boric acid is not metabolized and is distributed throughout all tissues. Nearly 98% is eliminated in the urine of humans and rats, following first-order kinetics. The half-life of renal clearance is 21 hours. Boron does accumulate in bone, reaching steady-state levels four-fold higher than plasma within four weeks of exposure.

Animal studies identified reproductive and developmental toxicity as the most sensitive adverse effects. The primary reproductive effect is degeneration of the spermatogenic epithelium of the testes resulting in impaired spermatogenesis, reduced fertility and sterility. The toxic mechanism for the reproductive effects remains unknown. The primary toxicological adverse developmental effects are fetal rib malformations and decreased fetal weight at birth. The toxic developmental mechanisms remain unknown. Boric acid and borates are not considered carcinogens.

U.S. EPA assessment of dose-response relied on animal studies. The critical effect was chosen as depressed fetal body weight in rats. A reference dose (RfD) was derived using the bench-mark approach. A bench-mark dose level (BMDL) of 10.3 mg B/kg-day was calculated using the combined results of two dose-response rat studies that measured decreased fetal weight as an endpoint. The human dose likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime, the RfD, was determined to be 0.2 mg/kg-day.

The RfD was used to estimate an acceptable daily intake of 14 mg B/day for a 70 kg adult male and 12 mg B/day for a 60 kg adult female. Subtracting boron intake from food (1.5 mg B/day), left a safety margin of 6.2 mg B/day for an adult male and 5.2 mg B/day for an adult female. The mean U.S. drinking water boron concentrations are well below levels needed to achieve acceptable daily intakes using the EPA adult assumptions for water intake. The National Inorganics & Radionuclides Survey (U.S. EPA, 1987) surveyed 969 community water supplies and reported a mean of 0.1 mg B/L, an upper 99^{th} percentile of 1.0 mg B/L, and an upper range of 2 mg B/L. Applying the EPA assumption of a water intake of 2 L/day, and using the 99^{th} percentile for boron concentration, yields a margin of safety of 4.2 mg B/day for an adult male and 3.2 mg B/day for an adult female. Drinking water in the high range of 2.0 mg B/L would place infants and children above the acceptable daily intake when the Recommended Dietary Allowances are used as the predictor of water intake.

The acceptable daily intake could be increased if uncertainty regarding the toxicodynamics of boron were replaced by empirical data. This could occur if the chemical mechanism (toxicodynamics) underlying boron toxicity were elucidated. The acceptable daily intake would also be increased if boron was proven to be essential for human health and if the risk assessment process were forced to consider a safety factor to prevent boron deficiency. Given the state of boron research it is most likely that new knowledge in both of these areas will be derived from studies at the chemical and cellular level.

It is recommended that three areas of research be supported: (1) chemical mechanisms of toxicity at the cellular level, (2) control of boron contamination of water supplies, and (3) development of technologies to remove boron from contaminated drinking water sources.

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1
INTRODUCTION

Background on Risk Assessment

The Safe Drinking Water Act (SDWA), as amended in 1996, requires the Administrator of the U.S. Environmental Protection Agency (EPA) to establish a list of contaminants to aid priority-setting for the Agency's drinking water program. The Drinking Water Contaminant Candidate List (CCL) was published in 1998 and included contaminants, not subject to proposed or promulgated national primary drinking water regulation, but known to adversely affect public health, be present in public water systems, and in the future require regulation under the SDWA. EPA divided CCL contaminants into three groups: (1) those which were priorities for additional research, (2) those which needed additional occurrence data, and (3) those which were priorities for consideration for rulemaking. Boron was listed as one of thirty contaminants to be considered for regulatory priority in May 2000. It was not selected in the first group of nine to be evaluated for regulation.

Borates have a long history of use as pharmacological agents and most cases of human toxicity have occurred in clinical settings and through accidental poisoning in the treatment of disease (Gosselin et al., 1984; WHO (World Health Organization), 1988a). A review of acute boric acid poisoning reported an overall fatality rate of 55% with a rate of 70% in children under 1 year of age (Goldbloom and Goldbloom, 1953). Clinical symptoms of toxicity include gastrointestinal symptoms, dermal erythematous rash and exfoliation, depression and shock (Browning, 1969). The main route of entry is oral; dermal absorption is poor. Absorbed boron occurs in the blood in the form of boric acid and is distributed to all organ systems unchanged in structure. Kidneys are susceptible to boric acid toxicity because of their exposure to high concentrations of boric acid during excretion (Dreisbach, 1980).

The risk assessment process used by the EPA provides for the calculation of an oral reference dose (RfD), an inhalation reference concentration (RfC), and a carcinogenicity assessment. The RfD and RfC provide quantitative values for noncancer dose-response assessments. The RfD is an estimate of daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime, and is used in the estimation of risk for water contaminants. Both the RfD and RfC assume that thresholds exist for specific toxic adverse affects to health and are expressed in units of mg/kg-day and mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential and quantitative estimates of risk from oral and inhalation exposures. It includes a weight-of-evidence judgment of the likelihood that an agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are

presented in three ways. A slope factor is determined using 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 inhaled. The third form of presentation of risk in drinking water or air concentration gives risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000.

The risk assessment process begins with a literature search to identify what is known about an agent's physical and chemical characteristics, its occurrence in the environment, and the relationship between exposures to the agent and subsequent adverse effects.

Chemical and Physical Properties of Boron

Boron (B) is the fifth element in the periodic table and is assigned to Group IIIA. It has an atomic weight of 10.81 and exists as a mixture of stable isotopes ^{10}B and ^{11}B with respective abundances of 19.8% and 80.2% in the natural environment. Boron is a metalloid with an electronic structure of $1s^2 2s^2 p$ and oxidation state of +3. Three (trigonal) covalent bonds with oxygen form boric acid and four (tetrahedral) borates. Boron also has a strong tendency to form a fourth bond to complete the octet of valence electrons in molecules such as halides. Most boron in nature is present in the form of borates because of the high affinity of boron for oxygen. Soluble forms of boron include boric acid B(OH)3 and the monovalent anion $B(OH)4^-$, with the predominant form depending on the pH of the solvent. Boric acid is a weak Lewis acid with a pKa of 9.2 and is the dominant form of the element in physiological solutions. The structures of borate minerals contain trigonal BO_3, or tetrahedral BO_4 units forming large boron-oxygen anions. The geological forms of borate include: Tincal (borax) ($Na_2B_4O_7 \cdot 10H_2O$), Kernite (borax pentahydrate), $Na_2[B_4O_5(OH)_4] \cdot 2H_2O$; Colemanite, $Ca[B_3O_4(OH)_3] \cdot H_2O$; and Ulexite, $NaCa[B_5O_6(OH)] \cdot 5H_2O$. Elemental boron does not occur naturally (Wood, 1994).

Occurrences and Uses of Boron

The largest deposits of borate ores are found in Turkey and in the U.S. Mojave Desert. The world production of boron ores is approximately three million tons/year (Lyday, 1992). Of this, 750,000 tons of sodium borates and 195,000 tons of boric acid are produced in the United States. The principal uses are given in the Table 1-1. About 300,000 tons per year of boron are used in commerce (Table 1-2).

Table 1-1
Use of Boron Minerals in the United States

Use	Percent
Glass and ceramics	28
Insulation fiberglass	12
Textile fiberglass	9
Glass	3
Enamels and glazes	3
Detergents and bleaches	12
Alloys and metals	6
Fire retardants	5
Agriculture fertilizers	4
Adhesives	2
Other chemicals	19

*(adapted from Wood 1994)

Table 1-2
Global Industrial Boron/Borates Uses (1996)

Product	Total Sales (tons)
Insulation fiberglass/texile fiberglass/borosilicate glass	120,000
Detergents	60,000
Ceramics	40,000
Fertilizers	15,000
Cellulose Insulation	5,000
Other	70,000
Total	**310,000**

*Argust (1998)

Environmental Compartmentalization and Movement

Natural global movements of boron are associated with tectonic activity of the mantle and boron's ability to dissociate boric oxide (B_2O_3) to form boric acid ($B(OH)_3$) in aqueous solution. The boron concentration in the earth's crust is 10 mg/kg. Soil concentrations range from 10 to 20 mg/kg and rocks range from 5 mg/kg in basalts to 100 mg/kg in shales and 8,000 mg/kg in neosilicates. Boron concentrations in seawater range from 9.57 mg/L in the Mediterranean Sea to 0.52 mg/L in the Baltic Sea, but average 4.6 mg/L in the oceans world-wide (Argust, 1998).

Boric acid is volatile, and it is estimated that 1.3 to 4 million metric tons of boron move across the water-air interface at the ocean's surface into the atmosphere. Fresh surface water concentrations range from 0.01 to 0.1 mg/L, with some exceptions such as the Firehole River in Wyoming and rivers in Chile and Argentina that contain 1 mg/L and higher. Groundwater concentrations are highly site specific, but generally range between 0.01 and 1.9 mg/L boron (Meyer et al., 1998).

Biomass contains a significant amount of boron since boron atoms are essential components of plant cell walls. The total biomass of the earth is about 4×10^{15} kg, and plants make up about 99% of this. Some seaweeds contain concentrations as high as 248 mg/kg B, but the average boron content of organic matter ranges from 30 to 50 mg/kg B. Biomass B is in equilibrium with other compartment of the hydrological cycle through decay, agricultural burning and forest fires. Biomass burning is thought to contribute to the transfer of 156,500 tons of boron to the atmosphere each year.

Fossilized organic material varies in boron content. Oil has very low levels, whereas coal concentrations range between 12 and 136 mg/kg (Argust, 1998). When coal is burned, approximately 50% of the B is volatilized into boric acid and enters the atmosphere and 50% is retained in the ash (Argust, 1998). Argust estimates that 5 to 10% of the ash is transferred to the atmosphere and the rest enters soil or landfill sites. The 4.5 billion tons of coal burned per year contains between 54,000 and 605,000 tons of B. Thus, the yearly burning of coal transfers between 28,000 and 330,000 tons of B to the atmosphere and 24,000 to 287,000 tons to soil and landfills.

2
TOXICOLOGY OF BORON

Toxicokinetics

Absorption

Gastrointestinal

Boron is rapidly absorbed by oral exposure. Four human studies demonstrate that approximately 90% of boron as boric acid is absorbed by the gastrointestinal tract. Kent and McCance (1941) measured the amount of urinary boron excreted by two women following ingestion of 62 mg boric acid and food containing 80-140 mg B. More than 90% was excreted in their urine during the week following ingestion. Schou et al. (1984) compared urinary excretion in six people following ingestion of 131 mg B as boric acid or 130-258 mg B provided in a water-emulsifying ointment. Boron excretion was delayed by the ointment, but 92-94% of both preparations appeared in excreted urine within 96 hrs. A third study by Job (1973) measured urinary excretion in ten people that consumed 100 mg B/day in mineral water for two weeks. Over 90% of the ingested boron was excreted during this time. In another study, 84% of a 10 mg B/day supplement was recovered in the urine of men participating in the four week trial (Naghii et al., 1977).

Absorption studies using rats (Ku et al., 1991; Usuda et al., 1998; Vanderpool et al., 1994), rabbits (Draize and Kelley, 1959), sheep (Brown et al., 1989) and cattle (Owen, 1944, Weth et al., 1981) have all reported that boron is rapidly absorbed through the gastrointestinal tract. A recent study by Vanderpool found that fasted rats fed 20 μg ^{10}B excreted 95% of the isotope in the urine and 4% in the feces within 3 days. The liver concentration of ^{10}B peaked in three hours and returned to normal within 24 hours.

Respiratory Tract

Boron is readily absorbed following inhalation exposure. In an occupational study, Culver et al. (1994) measured boron levels in the blood and urine of workers exposed to dusts of borax, borax pentahydrate and anhydrous borax at the U.S. Borax production facility. They reported that blood and urine concentrations increased only the first day of the work week and did not increase further during the work week. Following a weekend off, pre-shift blood concentrations were 0.1 μg/g and end-of-shift levels rose to 0.25 μg/g. Pre-shift urinary levels were 2 μg/mg creatinine and post-shift levels were 12 μg/mg creatinine, showing significant absorption. The study controlled for dietary intake by providing the same food to all workers and monitoring air

concentrations of boron. The authors inferred that the large size of the dust particles (> 10 μm) results in borate deposition in the upper respiratory tract, where it was either absorbed directly through the mucous membranes or transported by mucociliary action to the gastrointestinal tract and absorbed.

Widing et al. (1959) evaluated the absorption of airborne boron oxide in rats. Urinary boron averaged 11.90 mg B/kg-day in animals exposed to 77 mg/m^3 versus 0.24 mg B/kg-day in controls. These data show that boron oxide is absorbed, but suggest less so than boric acid. No toxic end-points were observed.

Dermal

Boron is not absorbed through dermal exposure. Four human studies have examined preparations of boric acid provided as a powder, ointment, or aqueous solution. No increases in blood or urine boron were observed by Vignec and Ellis (1954) in 1-10 month old infants (n=12) exposed to talcum powder containing 5% boric acid applied 7-10 times per day over the period of one month. The presence of diaper rashes did not affect absorption. Draize and Kelley (1959) studied the effect of direct contact with powdered boric acid (15 g) for four hours in adult volunteers and observed no increase in urinary boron. Friis-Hansen et al. (1982) applied ointments containing 3% boric acid for 4-5 days to 22 newborn infants. Blood plasma boron declines after birth. Breakage of the dermal layer of the skin has been shown to increase boron absorption. Stuttgen et al. (1982) reported increased blood and urinary boron after aqueous jelly containing boric acid was applied to males with severe dermatitis. Dermal absorption in rabbits (Draize and Kelly, 1959) and rats (Nielsen, 1970) produced results consistent with those observed in humans.

Distribution

The major chemical form of boron in the body is undissociated boric acid; however, there is reason to suspect that other chemical structures containing one or more boron atoms will be identified in the future that serve unique biological roles in animals. Reports to date, however, assume all tissue boron concentrations are in the form of boric acid. Locksley and Sweet (1954) conducted a dose-response mouse study using intraperitoneal injections of borax. Tissue boron concentrations increased proportionally over a range of 1.8-71 mg B/kg. Ku et al. (1991) evaluated the tissue concentrations of male rats fed a 1575 mg B/kg diet that provided 93-96 mg B/kg-day for seven days. Boron tissue concentrations are given in Table 2-1. After treatment, bone had the highest concentration and percent increase of all tissues tested, indicating it is the major depository of boron. The seminal vesicles had the next highest concentration and are known to be a target of toxic exposure levels. The tissue with the highest concentration in the control was the adrenal gland. This ranked third highest in the treated group, but following treatment had the second lowest percent increase in concentration of all tissues analyzed, suggesting it saturated its mechanism for retaining the element.

Table 2-1
Tissue Levels (µg B/g) in Rats Following 7 Days Exposure to 1575 mg B/kg Diet

Tissue	Control	Day 7	Difference %
Bone	1.17 ± 0.19	47.40 ± 1.14	3951
Seminal vesicles	1.64 ± 0.23	23.70 ± 6.56	1345
Adrenals	7.99	21.90	174
Kidney	1.55 ± 0.03	19.80 ± 1.65	1177
Seminal vesicle fluid	2.05	19.20	836
Epididymis	0.81 ± 0.15	16.81 ± 3.7	1975
Plasma	1.94 ± 0.17	16.00 ± 0.71	725
Testis	0.97 ± 0.10	16.00 ± 1,19	1549
Large Intestine	3.08 ± 0.17	14.90 ± 0.7	384
Prostate	1.20	14.80	1133
Hypothalmus	0.91	14.30	1471
Muscle	3.69 ± 0.54	14.23 ± 0.19	286
Brain	0.76 ± 0.02	13.50 ± 0.86	1676
Liver	0.66 ± 0.10	13.13 ± 0.54	1889
Adipose	1.71 ± 0.17	3.78 ± 0.13	121

Values are mean ± sem (standard error of the mean), n=3 samples pooled from two animals or if given without sem, one sample pooled from six animals. Data modified from Ku et al., 1991.

A dose-response study of drinking water was conducted by Naghii and Samman (1996) in rats. Plasma and soft tissue concentrations increased proportionally with dose. Chapin et al. (1997) conducted a dose-response dietary study in rats over 9-12 weeks using diets ranging from 200 mg/kg to 9,000 mg/kg. Concentrations of bone B increased proportionally up to 6,000 mg/kg. Tissue saturation occurred within the first week at dietary concentrations up to 3,000 mg/kg, but took 4 weeks at higher doses.

The World Health Organization conducted a cross-species comparison and concluded that rats and humans exposed to 0.01-100 mg B-kg body weight had similar blood concentrations (WHO, 1998a).

Excretion

Urine

In humans and rats, more than 90% of orally administered boric acid is excreted in the urine as boric acid. Kent and McCance (1941) reported that 92-93% of an oral dose of boron (59.8 mg) as boric acid (352 mg) was eliminated in urine within one week of administration. In 1984, Jansen et al. (1984a) and Schou et al. (1984) both reported that the primary route of boric acid elimination was urine, and approximately 93% of an oral dose was eliminated in 96 hours.

Jansen also showed that 98.7% of an intravenous injection of 5-5.6 mg B per minute, a total dose of 91-108.5 mg B, was eliminated in urine with the remainder in saliva, sweat, and feces. Aster et al. (1988) reported on a case of acute intoxication of 45 g boric acid (7.9 g B) where >50% was eliminated during the first day.

Rat studies have shown that boron is essentially totally bioavailable and excretable. Vanderpool et al. (1994) administered 20 µg B/kg to rats and found that 95% was eliminated in the urine and 4% in the feces over three days. Usuda et al. (1998) used male rats to investigate the clearance of doses from 0 to 4 mg B/kg given orally as sodium tetraborate. Twenty-four hour urines accounted for 99.6% of the administered dose.

A recent rat study was designed to afford a comparison of rat and human boron toxicokinetics (U.S. Borax, 2000). The study evaluated groups of pregnant and non-pregnant rats. They were adjusted to a diet for 7 days, and on gestation day 17 were switched to a low casein diet containing 0.2 mg B/kg for 24 hrs. The next day rats were divided into groups of 10 and intubated by gavage 0.052, 0.52, and 5.2 mg B/kg. The low dose represented an estimate of the high end of the human dietary intake and the highest dose was approximately half of the NOAEL (no observed adverse effect level) reported for a rat developmental toxicity study by Price et al. (1996).

Pregnant rats receiving the high dose excreted higher total and urinary B concentrations. The concentration of urinary boron increased with dose and at high doses, the values were 32-37% higher in pregnant rats when expressed as mg B/ml and mg B/creatinine. The percent of administered dose recovered was greater in rats receiving low doses compared to mid- and high-dose groups in both pregnant and non-pregnant rats. The rate of boron clearance was independent of dose, suggesting boron clearance from blood is regulated by the kidney.

In a human study, blood and urine samples were taken from 16 pregnant and 16 non-pregnant women consuming their regular diets. Boron intake was estimated from 24-hr renal excretion to be 1.3 mg B/day or 0.02 mg B/day. The calculated boron clearance rate indicated the pregnant women cleared more effectively (0.92 ± 0.59 ml blood cleared of B/min/kg body weight) than non-pregnant women (0.64 ± 0.34 ml/min/kg).

The EPA used an empirical distribution function to represent boron clearance as a function of body mass for rats and humans. Clearance (mL/min/kg body mass) was assumed to be distributed as percentiles (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 95^{th}). The clearance at each percentile was calculated by linear interpolation assuming observations *i* were distributed as $(i - 0.5)/n$. The percentile clearance was 100 x $(i - 0.5)/n$, where *i* represents the rank order of the observations and n is the number of observations (Wilk and Gnanedisikan, 1967). Data presented in this way showed that pregnant rats clear boron an average of 3.6 times faster than pregnant women. The difference between species was greater at lower percentiles, for example it was 8.9% at the 5^{th} percentile. These data suggest that the toxicokinetics of boron elimination differs between rats and humans.

Plasma

There are three human studies reported on plasma clearance of boron. Jansen et al. (1984a) calculated the mean half-life of boric acid to be 21.0 hours, with a range from 12.5 to 26.6 hours in volunteers receiving 91-108.5 mg B (570 – 620 mg boric acid). The Jansen study also showed that clearance was biphasic, suggesting homeostatic control. Half-lives from victims of acute poisoning were calculated to range from 4.0 hrs (Litovitz et al., 1988) to 28.7 hrs (Astier, 1988) following ingestion of 7.9 g B. In a study reported to the EPA by U.S. Borax, pregnant women eliminated more boron from their plasma in 24 hours than non-pregnant women.

The U.S. Borax rat study discussed previously was designed to estimate the plasma half-life of boric acid. The results showed that plasma boron concentrations decreased in a monophasic manner expected of a one compartment model. There was no difference in the half life of plasma clearance between pregnant and non-pregnant rats, and neither group showed evidence of saturation kinetics.

Hazard Identification

Human Effects

Case Reports

Vomiting, abdominal pain and diarrhea are the most frequent symptoms of boric acid poisoning (Craan et al., 1997; WHO, 1998a; Culver and Hubbard, 1996; and Ishii et al., 1993). The minimum lethal oral dose was approximately 15-20 g for adults, 5-6 g for children and 2-3 g for infants. Two sibling infants ingested 30.4 and 94.7 mg B/kg-day by consuming infant formulas prepared with a boric acid eyewash (Baker et al. 1986). One infant ingested 30.4 mg/kg-day and had a serum level of 9.79 mg B/mL and developed face and neck rash. The other infant ingested 94.7 mg/kg-day, had serum values of 25.7 mg B/mL, and developed diarrhea, diaper rash and vomiting.

Between the mid-1800's and 1900, boron compounds were used for the treatment of epilepsy, malaria, urinary tract infections, and exudative pluritis. Culver and Hubbard (1996) reviewed literature cases of patients receiving 2.5 to 24.8 mg B-day for many years. Treatments above 5 mg B/kg-day resulted in indigestion, dermatitis, alopecia, and anorexia. Seizures occurred in five of seven infants 6 to 16 weeks old that received a honey-borax mixture for 4 to 10 weeks. The seizures ceased after the honey-borax treatment was discontinued.

Reproductive

Low sperm motility and low sperm counts, and elevated semen fructose were reported in twenty-eight laborers working for 10 or more years in a Russian boric acid production plant. Exposure via vapors and aerosols was 22-80 mg B/m^3 (Tarasenko et al., 1972). This report spurred an epidemiology investigation into the effects of sodium borates in workers in the U.S. Workers in the U.S. Borax mine in California were asked to complete a questionnaire. The response rate

was 72%, the exposure was 0.31 mg B/m^3 or 2.23 mg sodium borate/m^3, with an average employment at the plant of 15.8 years. The number of live births and sex of children born to wives of the workers during the 9 months after starting work at the plant were compared to the national fertility tables for U.S. women (unexposed control group). Wives and controls were matched for maternal and calendar age, parity, and race to develop a standardized birth ratio (SBR). The SBR is defined as the observed number of births divided by the expected number.

The boron workers fathered significantly more children than the controls, 529 versus 466.6 expected (SBR=113, $p<0.01$). The rate of vasectomies in the workers was also 5 times higher than the national average (36% vs 7%). No trend was observed when the workers were stratified according to 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) and then put into 5 groups of equal sizes of 108-109. The SBR in a high exposure group, 23.2 mg sodium borate/m^3 over an average of 4.9 years, was close to the expected 102 despite a vasectomy rate of 48%. There was, however, a small non-significant increase in the proportion of females born (52.7% vs 48.4%) (Whorton et al., 1994a, 1994b, 1992), but this was not correlated with sodium borate exposure. Sayli et al. (1998) also reported a non-statistically significant excess of female births in a region in Turkey where the drinking water contained 2.05-29 mg B/L drinking water compared to a region with 0.03-04 mg B/L. Exposure to boron did not impact the rate of spontaneous abortion (Swan et al., 1995).

Pulmonary Effects

Several studies have been designed to evaluate the impact of airborne boron compounds on the respiratory system (Whorton et al., 1994a, 1994b, 1992; Birmingham and Key, 1963; Ury, 1966; Garabrant et al., 1984, 1985; Wegman et al., 1994). Health surveys of workers at the U.S. Borax plant in Boron, CA found complaints of dermatitis, cough, nasal irritation, nose bleeds and shortness of breath (Birmingham and Key, 1963) under working conditions where the airborne dust impaired visibility. Following this finding, a cross-sectional study, in 1981, was designed employing questionnaires, spirometric tests, and roentgenograms on 629 workers (Gabrant et al., 1984, 1985). The analysis of forced expiratory volume (FEV) and respiratory illness in 82 men working for at least one year at the calcining and fusing processes suggested that they were more at risk than 547 who never worked at these processes (Ury, 1966). An additional study categorized 629 workers employed for 5 or more years into four groups according to borax exposure (1.2, 4.0, 8.4 and 14.6 mg/m^3 borax). There was a statistically significant dose related trend in the frequency of each of the following complaints: dryness of mouth, nose or throat; eye irritation; dry cough; nose bleeds; sore throat; productive cough; shortness of breath; and chest tightness. Symptoms in the high exposure group ranged from 33% to 5% and neither chest x-rays nor pulmonary function tests were affected by borax exposure. The results showed that borax was a simple respiratory irritant that could cause chronic bronchitis with non-impairment of respiratory function. Irritation occurred at concentrations of 4.4 mg/m^3. A subgroup of workers exposed to boron oxide or boric acid showed significantly higher rates of eye irritation, dryness of mouth, nose or throat, sore throat and cough at a mean exposure of 4.1 mg/m^3. These results demonstrated that boron oxide and boric acid produce upper respiratory and eye irritation at less than 10 mg/m^3.

In 1988, a longitudinal study of respiratory function in workers with chronic exposure to sodium borate dusts was conducted using 303 workers who participated in the 1981 study (Gabrant et al., 1984, 1985). A time-weighted sum of exposure was estimated for each worker for the 1981-1988 period. Pulmonary functions tests (FEV_1, Forced Expiratory Volume in 1 sec and FVC, Forced Vital Capacity) declined at a rate expected of U.S. populations (Wegman, 1994). Cumulative exposure to borate did not alter the age related decline that occurs in pulmonary function. The study found a positive dose-related increase in eye, nasal and throat irritation, cough and breathlessness with borate exposure (6-hr time-weighted average or 15-min time-weighted average). No differences were apparent between the chemical forms of borate (decahydrate, pentahydrate, anhydrous).

Animal Studies

Oral Exposure

Dogs: Beagles were given diets containing borax to deliver doses of 0.33, 3.9, and 30.l4 mg B/kg-day to males and 0.24, 2.5 and 21.8 mg B/kg-day for females (Weir and Fisher, 1972; U.S. Borax Research Corp., 1963, 1966, 1967). One high-dose male died as a result of diarrhea on day 68 of the study, with congestion of the mucosa of the small and large intestines and kidneys. No evidence of toxicity was observed in other dogs except for the testes. Testes weight decreased 44% in males fed borax and 39% in those fed boric acid compared to controls. Pathological examinations showed severe testicular atrophy in all high-dose dogs, with complete degeneration of the spermatogenic epithelium in 4 out of 5 cases. No testicular lesions were observed in low-dosed animals.

Both males and females given borax exhibited decreases in hematocrit (15% and 6% respectively) and hemoglobin (11%). Hemosiderin pigment accumulated in the liver, spleen, and kidney, an indication of hemoglobin breakdown, in dogs dosed with borax or boric acid. Other effects were decreased thyroid:body weight ratios and thyroid:brain weight ratios. There was an increase in the proportion of solid epithelial nests and minute follicules in the thyroid gland of males receiving borax and in females given boric acid lymphoid infiltration, and there was atrophy of the thyroid and increased width of the zona reticularis in both sexes given borax and in boric acid-dosed females and zona glomerulosa of the adrenal gland in boric acid-dosed females. The study identified a LOAEL (lowest observed adverse effect level) of 1750 ppm boron (male: 30.4 mg B/kg-day; female 211.8 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) (Weir and Fisher, 1972; U.S. Borax Research Corp., 1963, 1966, 1967).

In a study of the chronic effects in dogs, groups of four Beagles of each sex were given diets that provided 9, 58, 117 and 350 mg boron/kg (0, 1.4, 2.9 and 8.8 mg B/kg-day) for 104 weeks, followed by 13 weeks of recovery (Weir and Fisher, 1972; U.S. Borax Research Corp., 1966). One male control dog sacrificed after the 13-week recovery period demonstrated testicular atrophy. One dog provided 8.8 mg B/kg-day as boric acid had testicular atrophy at the end of the 104 weeks. After 24 weeks of treatment, two semen samples from the 8.8 mg/kg-day group were azoospermic with no motility. The pathologist considered the histopathological findings as "not compound induced". The small numbers of animals used in the study and conclusion from the pathologist render these studies of limited value for risk assessment.

Rats: Rats of the Sprague-Dawley strain were provided diets for 90 days containing 0, 52.5, 175, 525, 1750 and 5250 ppm boron as boric acid or borate (Weir and Fisher, 1972). The highest dose (5250 ppm) killed 100% of the animals, and 1750 ppm caused testicular atrophy. Other signs of toxicity included rapid respiration, eye inflammation, paw swelling, and desquamation of the skin on paws and tails. The NOAEL and LOAEL doses for the study were 8.8 and 26.3 mg B/kg-day, respectively. In a chronic 2-year study, the same authors exposed male and female rats to 0, 5.9, 17.5, and 58.5 mg B/kg-day. The highest level decreased food intake, suppressed growth and caused swollen paws with desquamation, scaly tails, and inflammation of the eyelids with bloody discharge from the eyes. After six months of exposure, all males exhibited atrophy of the seminiferous epithelium and testes. In contrast to testes, brain and thyroid:body weight ratios increased in the groups with the highest boron intake. The study identified a NOAEL and LOAEL of 17.5 and 58.5 mg B/kg-day, respectively. The National Toxicology Program (1987) concluded from this study that boric acid was not a carcinogen in rats.

A subchronic study in rats administered borax to male Long Evans rats (15/group) at 0, 150 and 300 mg B/L in drinking water for 70 days. The rats consumed a diet containing 54 ug B/g (Seal and Weeth, 1980). The total intake was estimated as 23.7 and 44.7 mg B/kg-day. Both doses significantly ($p<0.05$) decreased body weight, testis, seminal vesicle, spleen and right femur weight, and plasma triglyceride levels. Spermatogenesis was impaired and hematocrit decreased at the highest dose. The LOAEL for the study was 23.7 mg B/kg-day. No NOAEL could be identified.

Mice: The National Toxicology Program studied boric acid chronic and subchronic toxicity in mice (NTP 1987; Dieter, 1994). A subchronic 13-week study using B6C3F1 mice used diets that provided 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. At the highest dose >60% of the mice died and hyperkeratosis and acanthosis of the stomach was observed. Atrophy of the seminiferous tubules occurred in males at doses of 281 and 563 mg B/kg-day, and both sexes exhibited depressed weight gain at these levels. The study LOAEL was 34 mg B/kg-day for male mice with a NOAEL (no toxicity in absence of body weight loss) determined to be at or below 34 and 47 mg B/kg-day for male and female mice, respectively.

In a chronic study, B6C3F1 mice (50/sex/group) were given diet containing 0, 2500 or 5000 ppm boric acid for 103 weeks (NTP, 1987; Dieter, 1994). These provided doses of 48 and 96 mg B/kg-day. No treatment-related clinical signs were observed, but the body weights were 10-17% lower. The survival rates at termination were 82, 60 and 44% for the control, low and high dose males, respectively, and 66, 66 and 74% for the females. Testicular atrophy and interstitial cell hyperplasia occurred in the high-dosed mice. A stress-related dose-dependent increase of splenic lymphoid depletion also occurred in males. Although some mice developed hepatocellular carcinoma and several subcutaneous cancers, they were within the range expected for the mice in the study laboratory and the NTP concluded they were not due to boric acid.

Sodium metaborate was added to drinking water given to 54 male and 54 female mice providing 0 or 0.95 mg B/kg-day (Schroeder and Mitchener, 1975). No differences were detected in life spans, body weight or tumor incidence at the end of the study.

Animal Inhalation Exposure

Wilding and colleagues (1959) evaluated boron oxide aerosol exposure in rats and dogs. Rats (70) were exposed to 24 mg B/m^3 for 6 h/d, 5 d/wk over 24 wks or 54 mg B/m^3 for 12 weeks, or 146 mg B/m^3 for 10 weeks. Dogs were exposed to 18 mg B/m^3 for 23 weeks. No clinical signs from exposure occurred, except for a reddish nasal exudate from the dust in rats and a 9% reduction in the rate of growth. At the low dose in rats there was a decrease in urine pH and an increase in creatinine.

Developmental Studies

Pregnant Sprague-Dawley rats (29/group) were given boric acid supplemented diets that provided 0, 13.6, 28.5 or 57.7 mg B/kg-day. Two additional groups (15 rats/group) received 0 or 94.2 mg B/kg-day from gestational ages 6 to 15, the major period of organogenesis, in order to by-pass potential problems with preimplantation loss or early embryolethality. No maternal mortality occurred, and food intake increased 5-7% from 12 days gestation in dams receiving 28.5 and 57.7 mg B/kg-day. At a level of 94.2 mg B/kg-day, the intake of food and water decreased on days 6-9 and increased on days 15-18, relative to controls. Pregnancy rates were unaffected by treatment and ranged from 90 to 100%. Maternal effects included dose-dependent increases in liver and kidney weights at 28.5 mg B/kg-day and higher, and a decrease in body weight gain at 57.7 mg B/kg-day.

The impact on the developing fetus was more dramatic. The body weights of male and female fetuses were reduced in a dose-related manner. The percent malformed fetuses/litter, percent of litters with at least one malformed fetus, and percent with skeletal malformations were all significantly increased at doses of 28.5 mg B/kg-day and higher. Malformations consisted of anomalies of the eyes, central nervous system, cardiovascular system and axial skeleton. In the 28.5 and 57.7 mg B/kg-day groups the most common malformations were enlarged lateral ventricles of the brain and agenesis or shortening of rib XIII. Based on changes in organ weights the maternal LOAEL was 28.5 mg B/kg-day and the NOAEL 13.6 mg B/kg-day. Based on a decrease in fetal body weight/litter the LOAEL was established at 13.6 mg B/kg-day.

A follow-up study (Price et al., 1996a, 1994) provided pregnant dams 3.3, 6.3, 9.6, 13.3 and 25 mg B/kg-day. No clinical symptoms occurred in the mothers, but a significant trend of decreasing body weight occurred. There was no impact of the treatment on ovarian corpora lutea or uterine implantation sites. However, body weights of offspring were lower in the 13.3 and 25 mg B/kg-day group at gestational day 20. The only malformation was skeletal. There was a dose-related increase in short rib XIII, and wavy rib or wavy rib cartilage variation. Both increased at 13.3 and 25 mg B/kg-day. The LOAEL was considered to be 13.3 mg B/kg-day based on decreased fetal body weight. The NOAEL was 9.6 mg B/kg-day. Maternal boron concentrations of 1.27 and 1.53 µg B/g blood were associated with the NOAEL and LOAEL.

A second trial was conducted using 3.2, 6.5, 9.7, 12.9 and 25.3 mg B/kg-day to allow the mothers to deliver and rear their litters until they were 21 days old. There was no treatment impact on the body weights of newborns or at 21 days of age. The percentage of pups/litter with short rib XIII was still elevated at day 21 in the 25.3 mg B/kg-day group but wavy rib variations were not elevated. The NOAEL and LOAEL were 12.9 and 25.3 mg B/kg-day.

The same experimental design was used to investigate the impact of boric acid on the development of mice and rabbits (Heindel et al. 1994, 1992; Field et al., 1989). The mouse study fed diets to provide 0, 43.4, 79.0 and 175.3 mg B/kg-day during gestational days 0-17. A dose-related increase was observed in maternal renal tubular dilation. The 175.5 mg B/kg-day treatment increased the percent of resorptions/litter, the percent of litters with one or more resorptions, the average fetal weight, and the percent malformed fetuses, with the most frequent malformation being a short rib XIII. The 79.0 mg B/kg-day dose decreased average fetal weight. The maternal NOAEL was 43.4 mg B/kg-day and the LOAEL 79 mg B/kg-day.

The rabbit study provided 0, 10.9, 21.9 and 43.7 mg B/kg-day in an aqueous gavage on gestational days 6 – 19 (Price et al., 1996b, 1991; Heidel et al., 1994). The only treatment-related clinical signs of toxicity in the mothers were vaginal bleeding and a higher relative kidney weight at 43.7 mg B/kg-day. Fetal developmental effects at 43.7 mg B/kg-day compared to controls included 90%/6% resorption; pregnant females with no fetuses 73%/0%; day 30 live fetuses per litter 2.3/8.8. The high dose also significantly increased cardiovascular malformation, from 11% in controls to 64%. The NOAEL based on maternal and developmental effects was 21.9 mg B/kg-day and the LOAEL 43.7 mg B/kg-day.

Reproductive Studies

Male-Only Exposure

Fertility was accessed in male rats following a single dose of borax to provide 0, 45, 150 and 450 mg B/kg (Dixon et al., 1976). There was no impact on fertility or evidence of testicular lesions, thus identifying a NOAEL of 450 mg B/kg for an acute or single oral dose.

Water containing borax at 0, 0.3, 1.0 or 6.0 mg B/L provided respective doses of 0, 0.42, 0.14 and 0.84 mg B/kg-day to male rats for 30, 60 and 90 days (Dixon et al., 1976). There were no adverse effects observed at any dose, thus setting a NOAEL of 0.84 mg B/kg-day for the study.

A dietary study (Dixon et al., 1979; Lee et al., 1978) using borax provided 0, 25, 50, or 100 mg B/kg. The diameter of the seminiferous tubules was decreased in a dose-dependent manner, and doses of 100 and 50 mg B/kg caused significant loss of germinal cell with, aplasia complete at 100 mg B/kg. The level of follicle stimulating hormone (FSH) increased in a dose dependent manner, but luteinizing hormone (LH) and testosterone levels were not affected. There was a lower fertility at 50 and 100 mg B/kg, without changes in copulatory behavior. Based on the dose-related tubular germinal aplasis, which was reversible at low doses, the NOAEL of the study was 25 mg B/kg and the LOAEL 50 mg B/kg.

The effect of boric acid given by gavage to male Sprague-Dawley rats to provide 0 or 350 mg B/kg was examined over a 57-day period (Linder et al., 1990) or 0, 44, 87, 175 or 350 mg B/kg was examined after two weeks. No significant clinical toxicity was observed. Histopathological examination revealed adverse effects on epididymal sperm morphology and abnormal spermatids in seminiferous tubules at 175 and 350 mg B/kg and an increase in sperm head count per testis and per g testis in the 350 mg B/kg group at 14 days. Abnormal sperm morphology was also observed in the epididymis at day 14. Recovery occurred by day 57, but the LOAEL for male reproductive effects was 175 mg B/kg and the NOAEL 87 mg B/kg. The diets of Fisher rats (strain F344), were supplemented with boric acid to provide 60.9 mg B/kg-day for 4 to 28 days. (Treinen and Chapin, 1991). At 7 days half the rats exhibited spermiation in the 10-30% stage-IX tubules, by 10 days spermiation was observed in all stage-IX and X tubules and by 28 days there was advanced epithelia disorganization with cell exfoliation, luminal occlusion and cell death with loss of spermatocytes and spermatids. Boric acid had no effect on kidney or liver histology, but serum testosterone decreased from day 4 on. Tissue boron concentrations reached steady state by 4 days and no selective accumulation was observed in blood, epididymis, liver, or kidney. In a subsequent study (Ku et al., 1993b), the authors compared dose with the pathological endpoints. Spermiation was inhibited at 26 mg B/Kg-day and atrophy began at 52 mg B/kg-day. Testis B concentrations of 5.6 ug B/g tissue inhibited spermiation and 11.9 ug B/g caused atrophy. Effects of doses of 38 mg B/kg-day were reversible after 16 weeks, but effects of doses of 52 and 68 mg B/kg-day were not. The LOAEL for the study was 26 mg B/kg-day. In vitro studies determined that boric acid did not alter steroidogenesis in Lydig cells, suggesting that changes in hormones occurred through the central nervous system (Ku et al., 1994). DNA metabolism was the most sensitive indicator of boric acid toxicity in the cell culture studies. Significant elevations of 1,25-dihydroxyvitamin D concentrations and decreases in plasma triacyglycerol and total HDL-cholesterol after four weeks were observed in rats provided 2 mg B/day in their drinking water (Naghii et al. 1996b).

Male and Female Studies

A multigenerational study using doses of borax and boric acid of 0, 5, 17.5, and 58.5 mg B/kg reported no adverse effects at or below 17.5 mg B/kg through the F3 generation. Doses of 58.5 mg B/kg of both borax and boric acid resulted in sterile males and females with decreased ovulation. The NOAEL was therefore 17.5 and the LOAEL was 58.5 mg B/kg-day.

Mice colonies were provided 0, 26.6, 111, and 220 mg B/kg to males and 0, 31.8, 152, and 257 mg B/kg to females. Treatment decreased body weight and impaired fertility. There was lowered sperm motility in all exposed males. Seminiferous tubular atrophy occurred at 111 and 220 mg B/kg. The fertility of the 26.6 mg B/kg group was not impacted during the first generation, although the body weights of the F2 pups were decreased. The LOAEL was 26.6 mg B/kg for males and 31.8 mg B/kg for females.

Other Studies

Genotoxicity

Short-term mutagenicity studies indicated that boron is not genotoxic in E. coli (Iyer and Szybalski, 1958; Szybalski, 1958), *S. typhimurium* (Demerec et al., 1951), or rat or hamster liver S-9 activating systems (Benson et al., 1984; Haworth et al., 1983; NTP, 1987). Similarly the results were negative in the microsome assay (Stewart, 1991), but did show a response in a short test of DNA lesions (Odunola, 1997).

Mammalian mutagenicity tests have also been negative. This includes using hepatocytes (Bakke, 1991), lymphoma cells (NTP, 1987; Rudd, 1991), Chinese hamster cells, mouse embryo fibroblasts, and human foreskin fibroblasts (Landolph, 1985). Also negative were sister chromatid exchanged tests (NTP, 1987), and micronucleus assays (O'Loughlin, 1991).

Neurological Studies

Rats provided 20.8 mg B/kg-day in their drinking water showed an increase in cerebral succinate dehydrogenase activity and increases in acid proteinase and RNA. In humans, doses of 500 mg B/kg resulted in headaches, tremors, restlessness and convulsions. Histological examination revealed degeneration of neurons, and congestion and edema of the brain and meninges, with perivascular hemorrhage and intravascular thrombosis. Infants exposed to 16-48 mg B/day in honey-borax mixture for 4-10 weeks had convulsions and seizures (O'Sullivan and Taylor, 1983).

Toxicodynamics

Toxicodynamics describe the chemical and biological mechanisms responsible for how toxins target specific sites and the magnitude of their adverse effects. The adverse effects are influenced by the dose, toxicokinetics of the agent, varying response magnitude of tissue sites, dose-dependent repair mechanisms, and additive and synergistic effects with other chemicals. Toxicodynamic processes may influence the physiological processes that govern the toxicokinetics. For example, a respiratory irritant may influence the mucociliary clearance or dilation of the airways. This in turn changes the toxicokinetics of absorption and excretion in subsequent exposures.

Oral exposure to boron as boric acid and borax leads to a specific toxicity to the testes, but the mechanism of action is unknown. The data suggest an effect on the Sertoli cell that disrupts sperm maturation and release (Fail et al., 1998). The most sensitive adverse effects from boron on developing rodents are decreased fetal body weight and, at slightly higher doses, malformations and variations of the fetal ribs. It has been proposed that decreased body weight results from a general inhibition of mitosis, while the rib malformations result from direct binding of boron to bone tissue (Fail et al., 1998). This has yet to be proven. Toxicodynamics remains the area of greatest uncertainty in boron toxicity.

Nutritional and Biological Roles for Boron

First identified as an essential plant nutrient in 1923 (Warington, 1923), it took 73 years to understand boron's role in stabilizing the architecture of plant cells. Evidence of a vertebrate requirement was first observed in growth-retarded rainbow trout embryos (*Oncorhynchus mykiss*) (Eckhert, 1997; 1998). Further investigation showed boron was essential for the formation of viable blastula in zebrafish (*Danio rerio*) (Rowe and Eckhert, 1999) and the survivability and normal morphogenesis of frog (*Xenopus*) embryos (Fort et al., 1998). Boron's essentiality has not been proven in humans, but it has been shown to modulate several important biological processes. Three human clinical trials have been performed to deplete body boron levels. Subjects showed changes in neuropsychological function, steroid metabolism, and blood cell indicators (Penland, 1994; Nielsen, 1994).

New studies suggest boron is involved in fundamental mechanisms of cell biology. Bacteria and plants use boric acid as a precursor in the synthesis of several different compounds. Cyanobacteria require boron for organelle synthesis (Bonilla, (1995). Bacteria also synthesize three antibiotics containing a single boron atom (Chen et al., 1979; Dunitz et al., 1971; Dunitz et al., 1995). In addition, they synthesize a pheromone called autoinducer (AI-2) that contains a single boron atom (Chen et al. 2002). AI-2 coordinates gene expression between bacterial species and regulates biofilm formation. In plants, boron is essential for growth. Plant cells elongate to hundreds of times their length and utilize boron to stabilize their cell structure. Polysaccharide chains of rhamnoglacturonan II, a complex carbohydrate, provide the scaffolding to maintain plant cell architecture during growth (Pellerin et al., 1996; Kobayashi et al., 1996; O'Neill et al., 2001). Dimers of rhamnoglacturonan II are held together using a borate ester linkage. A boron transporter has also been identified that moves borate anions from plant roots to the shoots. It is not known if boron anion transporters are present in animals, but homology studies with the plant transporter suggest one may exist in human kidneys (Takano et al. 2002; Frommer and von Wirén, 2002).

Boric acid is the major form of boron in physiological fluids, but until recently little was known about its interaction with other biomolecules in mammalian cells. Boric acid and borate form complexes with nucleotides by binding to the cis-diol groups of ribose (Woods, 1994; Kim et al., 2003a, 2003b). Recently, this property has been shown to stabilize ribose under the primitive atmospheric conditions of early Earth (Ricardo et al., 2004). This discovery solved a long standing puzzle concerning the origin of life. Ribose was thought to be unstable under Earth's primitive conditions. The fact that plenty of boron exists in the nebula, which form in stars and planets, makes it possible for ribose to have been present in the mix of prebiotic organic molecules at the time life emerged on Earth.

Boron may have a beneficial role in retarding human prostate cancer. Boric acid has been shown to inhibit dehydrogenases by complexing with their coenzyme NAD+. Boric acid has also been shown to inhibit prostate serum antigen, a serine protease, and inhibit the growth of prostate tumors (Gallardo-Williams et al., 2002) and cancer cell lines (Barranco, 2003). Epidemiological evidence suggests that dietary boron lowers the risk of prostate cancer (Cui et al., 2004).

3
RISK ASSESSMENT FOR BORON

Dose-Response Assessment

Background

The risk assessment process evaluates empirically derived toxicological data that describe the relationship between dose and harm to estimate safe levels of exposure for the most sensitive populations. It uses this information to set politically mandated regulatory standards that define safe levels for different environmental media. The risk assessment process is often broken down into four steps. The first three steps in the process determine if an agent represents a hazard to human health. The fourth step uses experts to finish the risk characterization process by assigning a quantitative estimate of risk.

1. Hazard identification: A determination is made as to whether human exposure to an agent has the potential to increase the incidence of an adverse injury or disease (adverse health effect). This step identifies the qualitative relationship between an environmental agent and a specific adverse health effect.

2. Dose-response assessment: The relationship between the quantity of a toxin and an adverse health effect is given quantitatively in the form of dose-response curves. The curves describe the quantitative relationship between the dose, or exposure, and the probability of induction of injury or disease. The primary terms used to define the relationship in the risk assessment process are dose, no observed adverse effect level (NOAEL) and benchmark dose level (BMDL).

   Dose refers to the amount of a chemical administered, expressed as a ratio of surface area (cm^3) or weight (kg) of the recipient. NOAEL and BMDL refer to the highest dose of a chemical that does not produce an adverse biological effect and are derived from dose-response curves. The NOAEL relies on one data point from one experiment, whereas the BMDL is derived statistically and is not limited to one experiment or data point.

   A literature search covering a specific toxin may be large, but only a small portion is usually useful for predicting risk to human populations. The list below illustrates the type of information that is compiled for evaluation in the risk assessment process.

- Generic toxicity data (structure-activity relationships and results of other correlational analyses)
- Data on acute toxicity (on lethality in microorganisms or effects on mammalian cells in vitro)
- Acute mammalian lethality data (usually rodent)
- Toxicokinetics data (absorption, distribution, retention, and excretion)
- Genotoxicity data (results of short-term in vitro tests in microorganisms, genetic models [e.g. Drosophila], and mammalian cells)
- Data on subchronic toxicity (on 14-day or 28-day toxicity in rodents)
- Toxicodynamic data (metabolic pathways and metabolic fate in rodents and other mammalian species, with special attention given to exposure from specific media, e.g. air)
- Data on chronic toxicity (on carcinogenicity, neurobehavioral toxicity, reproductive and developmental toxicity, and immunotoxicity in two rodent species of both sexes, with special attention given to the exposure from specific media)
- Human toxicity data (clinical, biomonitoring, and epidemiological data)
- Data on toxic mechanisms, dose-effect relationships, influence of modifying factors (age, sex, and other variables) on susceptibility, and interactive effects of mixtures of chemical and physical agents

(*Ref. Science and Judgment in Risk Assessment, National Research Council, 1994)

3. Exposure assessment: Exposure assessments identify the exposed population, describe its composition and size, and present the type, magnitude, frequency, and duration of exposure. The terms estimated exposure dose (EED) and margin of exposure (MOE) are used to define the exposure. Information relating to the absorption, distribution, biotransformation and excretion of chemicals is classified under the terms toxicokinetics and toxicodynamics.

Sound risk assessment depends on a strong database. In the absence of data there is uncertainty. The uncertainty, or gap in knowledge, is factored into the risk assessment. Uncertainty factors (UF) are divided into the NOAEL or BMDL to derive safe levels of exposure from experimental data. The NOAEL and BMDL represent the largest experimental dose that does not cause a significant adverse effect. They usually occur at the dose level, on the dose-response curve, below which a statistically significant trend in dose-response becomes apparent (Allen et al., 1994).

Uncertainty Subfactors

Toxicokinetic (TK) data deals with what the body does to a chemical. The goal is to determine the internal dose of the ultimate toxic form of the compound on toxic tissue. It describes what is known about the delivery of a toxin to the site of toxicity and its removal.

Toxicodynamics (TD) deals with what a toxic dose of a chemical does to the body. Its goal is to determine how a toxic chemical targets specific sites and how it disrupts normal biological processes at those sites to cause harm. A "pure" toxicodynamic factor must be independent of the toxicokinetics. Since it is unlikely that in vivo responses will be free of kinetic variability, toxicodynamic data are obtained primarily from in vitro cellular level studies.

Ideally, the TK/TD model is a sophisticated multi-compartment, highly non-linear, biologically-based toxicokinetic model linked to a mathematical dose-response model relating molecular/cellular response to whole-organism response. In reality, the models used to assess risk to toxins are extrapolations using a simple multiplicative combination of uncertainty factors for TK and TD. Often there are no data for TD, so a default value is used. The approach is often to find one or more kinetic variables related to internal dose for which an animal-to-human ratio can be estimated to scale human exposure of external dose relative to test animals. Additional factors such as absorption and distribution constants are often required to relate the internal kinetics to external dose.

Boron Risk Assessment

Regulatory agencies have typically used reference doses (RfDs) or reference concentrations (RfCs) using the NOAEL approach. An alternative is to use the entire dose-response database to define a BMD, the statistical lower bound on a dose corresponding to a relatively low level of response (Crump, 1984). Unlike a NOAEL, a BMD incorporates all of the dose-response information, is sensitive to sample size and can be applied consistently to different studies since it does not depend on specific dose levels used by investigators. Allen et al., (1996) applied the BMD approach to boron toxicity. They relied on dose-response developmental toxicity data on short or missing ribs XIII and reduced body weight on fetuses of exposed female rats (Heindel et al., 1992; Price et al., 1994, 1995).

World Health Organization

Tolerable Intake Calculation

The International Programme on Chemical Safety (IPCS) characterizes the relationship between exposure to environmental agents and human health for the World Health Organization (WHO, 1998). The term "tolerable intake" is used by the IPCS to characterize risk. Tolerable intake (TI) is the lifetime intake of a substance that can occur without appreciable health risks. TI = NOAEL / UF. The UF is a composite of interspecies and intraspecies uncertainty. The general formula for the TI is the following:

$$TI = \frac{NOAEL}{[\text{toxicodynamic x toxicokinetics}]_{\textit{interspecies uncertainty}} \times [\text{toxicodynamic x toxicokinetics}]_{\textit{intraspecies uncertainty}}}$$

WHO and IPCS maintain default values for interspecies and the intraspecies uncertainty, and each are assigned a value of $10^{1.0}$. The value of $10^{1.0}$ is the product of the uncertainty in knowledge of the toxicodynamic and toxicokinetic properties of a chemical. The relative weight of uncertainty differs depending on whether gaps in knowledge relate to interspecies or intraspecies information.

The TI is calculated as:

$$TI = \frac{NOAEL}{[10^{0.4} \times 10^{0.6}]_{\textit{interspecies uncertainty}} \times [10^{0.5} \times 10^{0.5}]_{\textit{intraspecies uncertainty}}}$$

The default for uncertainty is 100 and is used in the absence of available data on interspecies and intraspecies variation.

$$TI = \frac{NOAEL}{10 \times 10} = \frac{NOAEL}{100}$$

To set the TI, the WHO Task Group on Environmental Health Criteria for Boron first compiled all the published data concerning dose-response, toxicodynamics and toxicokinetics.

Determination of Critical Effect From the Boron Toxicity Literature

The most sensitive tissues to toxic levels of boron were identified from laboratory studies. The sites manifesting adverse effects at the lowest doses were in the reproductive system, particularly the testis, and in the developing fetus, fetal weight and rib structure. The **critical effect** is the most sensitive toxic endpoint and is the first adverse effect to appear at the lower end of the dose-response studies. For boron toxicity, the critical effect was identified as depressed fetal body weight at 20 days gestation in rat mothers fed 13.3 mg boron/kg body weight/day from the Price et al. (1996a, 1994) study. No adverse effects were observed from the next lowest dose in the study, 9.6 mg/kg-day. The impact on rat fetal weight was used to identify the no observed adverse effect level (NOAEL) as 9.6 mg B/kg-day. The lowest observed adverse effect level (LOAEL) was 13.6 mg B/kg-day. That is, when pregnant mother rats were fed 9.6 mg B/kg/day their offspring were of normal weight, but if they consumed 13.6 mg B/kg their offspring were statistically slightly smaller.

Evaluation of Literature for Interspecies Uncertainty

Toxicodynamics: The mechanism for differences between species remains unsubstantiated. Although there are hypotheses, no mechanistic data are available to explain differences in toxicity between humans and other species. Thus, the default value of $10^{0.4}$ was not reduced.

Toxicokinetics: The oral absorption of boric acid for rats was 94% and for humans 95%. Since there appeared to be no difference in the rate of metabolism or excretion between species, the default value of $10^{0.6}$ was reduced to $10^{0.1}$.

Evaluation of Literature for Intraspecies Uncertainty

Toxicodynamics: Animal data suggested intraspecies variability does exist, but data do not exist for humans. In the absence of this information the default value of $10^{0.5}$ was not reduced.

Toxicokinetics: There were no data on boron metabolism in humans, but some data existed in animals. Thus, some reduction from default values were justified. The reduction was small since the available data indicated some variation exists in the kinetics of metabolism in humans. The default value of $10^{0.5}$ was dropped to $10^{0.4}$. The final TI was calculated as 0.4 mg B/ kg body weight.

$$\text{TI} = \frac{9.6 \text{ mg/kg}}{[10^{0.4} \times 10^{0.6}]_{\textit{interspecies}} \times [10^{0.5} \times 10^{0.5}]_{\textit{intraspecies}}} = 0.4 \text{ mg B/kg}$$

U.S. Environmental Protection Agency

The U.S. EPA traditionally has taken the NOAEL and divided it by uncertainty factors and a modifying factor to estimate a reference dose (RfD).

$$\text{RfD} = \text{NOAEL}/ \text{UF} \times \text{MF}$$

However, the use of NOAELs has been criticized because they rely on one data point from one experiment. The EPA does not use the NOAEL for carcinogens and is now moving toward using a benchmark dose level (BMDL) to calculate reference doses for systemic toxins. The newer BMD approach uses all the experimental data in an experiment or multiple experiments to fit model dose-response curves (Allen et al., 1994). The process identifies a curve that best fits the data to estimate a benchmark dose defined as the statistical lower bound on a dose corresponding to a specified level of risk. That is, the models estimate a statistical lower bound on dose associated with a predefined level of risk, typically in the range of 1 to 10%. The level of risk selected is within or slightly below the range of experimentally derived data. The lower bound on dose, estimated in this manner, is referred to as the BMD.

The first step in the process is to determine if the most critical effect, the sensitive toxic indicator in the critical study, is discrete or continuous. This affects the choice of dose-response models appropriated for the data. Discrete or quanta data such as "number of malformed fetuses" or "number of litters with a malformed fetus" require the use of a quantal model such as the Weibull model whose equation is given below:

$$P(d) = 1 - exp(-(\alpha + \beta * d^{\gamma}))$$

Where $P(d)$ is the probability of a response at dose level d and α, β and γ are estimated from the dose-response data in an iterative manner.

If the data are continuous, such as "body weight" (e.g. 134 g) or in the form of a frequency, such as " % malformed fetuses", a continuous power model such as the Mantel-Haensel test is used.

$$M(d) = (\alpha + \beta * d^{\gamma})$$

Where $M(d)$ is the mean proportion affected in the group at a given dose d, and α, β and γ are estimated from the dose-response data in an iterative manner.

Figure 3-1 (Kavlock et al., 1994) illustrates a curve showing a normal distribution of mean litter weights. In examinations of data on many different toxins Allen (1994, 1995) and Kavlock (1994) determined that a dose which causes a critical effect in a small percentages of test animals (e.g. 5%, referred to as the 5% lower bound on dose) yields results similar to the NOAEL. It was also a more consistent indicator of NOAEL levels than others obtained by subtracting from the mean: percents, standard deviations, and standard errors of the mean (see Figure 4-1 below).

The calculated dose is called the BMDL and has advantages over empirically derived NOAEL in that it is based on more data points from the dose-response curve, is less influenced by background incidence rates, is less influenced by the spacing of doses used in the animal experiments, and can incorporate the data from more than one experiment.

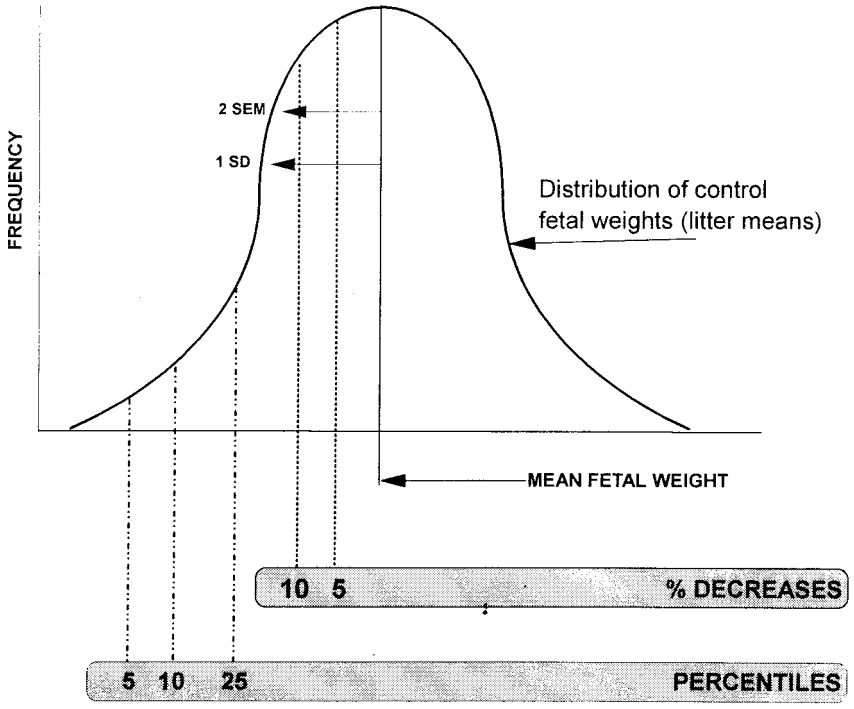

Figure 3-1
Normal distribution of mean litter weights

The vertical lines on the curve indicate several quantitative approaches for describing reductions from the mean fetal weight. Shown are reductions in magnitude of: one standard deviation and one standard error of the mean; 5% and 10% lower than the mean fetal weight; and the points where the frequency of fetal weights is at the 5^{th}, 10^{th} and 25^{th} lower percentiles of the weight distribution.

Derivation of BMDL for Boron Toxicity

The BMDL for boric acid was determined by Allen and colleagues (Allen et al., 1996) using fetal weight as the critical effect from data in both the Heindel et al. (1992) study and the Price et al. (1994, 1995) study. Adversely low birth weight was considered to be any weight less than the 5^{th} percentile of the fetal weights in the concurrent control group. The value obtained was 56 mg boric acid/kg-day for the Heidel study and 47 mg boric acid/kg-day for the Price study. The Hiedel study result of 56 mg boric acid/kg/day gives a value of 10.3 mg B/kg-day which is very close to the empirically determined NOAEL of 9.6 mg B/kg-day in the Price study. The EPA used the Allen value of 10.3 mg B/kg-day as the BMDL for calculating the RfD.

EPA Approach for Deriving RfDs

Uncertainty factors are applied in the RfD methodology to account for recognized uncertainties in extrapolation from experimental conditions to lifetime exposure for humans. The EPA uses an animal-to-human (interspecies; UF_A) extrapolation and a "sensitive human" (interindividual:

UF_H) extrapolation. Both UF_A and UF_H are calculated based on uncertainties in toxicokinetics (TK) and toxicodynamics (TD). If the TK and TD factors are derived from data they no longer represent uncertainty, but variability factors.

Determination of Values for Uncertainty Factors and Variability Factors

The U.S. EPA assumes an equal contribution ($10^{0.5}$) for both interspecies animal-to-human uncertainty (UF_A) and intraspecies within-human uncertainty (UF_H) split into toxicokinetic and toxicodynamic subfactors. These subfactors are by default assigned a value of $10^{0.5}$ (3.16) each.

$$\mathbf{RfD} = \frac{\mathbf{BMDL}}{[10^{0.5} \times 10^{0.5}] \times [10^{0.5} \times 10^{0.5}] \quad \mathbf{x} \quad [10^{0.5} \times 10^{0.5}] \times [10^{0.5} \times 10^{0.5}]}$$

$$(UF_A) = TD \times TK \qquad\qquad (UF_H) = TD \times TK$$

Where:

BMDL = benchmark dose lower bound

UF_A = interspecies toxicodynamics (TD) and toxicokinetic (TK) uncertainty factors (default $10^{0.5} \times 10^{0.5}$) each.

UF_H = human interindividual toxicodynamic and toxicokinetic uncertainty factors (default $10^{0.5} \times 10^{0.5}$) each.

Compounds Justifying Uneven Default Values

The use of UF_{AK} and UF_{AD} defaults of $10^{0.5}$ is based on the absence of evidence that they are unequal. For some compounds, in which the absorption and distribution are nearly the same in animals and humans, and no metabolism occurs, it is justifiable to use physiological rate to scale interspecies differences in toxicokinetics. In this case, UF_{AK} and UF_{AD} have been assigned default values of 4.0 and 2.5, respectively. The U.S. EPA bases these modified defaults on a comparison of toxicokinetic and toxicodynamic factors between animals and humans by Renwick (Renwick, 1993). The Renwick study compared toxicokinetic factors: blood flow (renal and hepatic), live weight and plasma kinetics (absorption and 1st pass metabolism) in animals (mouse, rat, rabbit, dog, and monkey) with human values. The toxicodynamic endpoints were physiological (hematological) responses that were both constitutive and chemically stimulated. The comparison found animal to human ratios 2.1 for toxicokinetic endpoints and 1.2 for toxicodynamic endpoints. Partitioning these relative differences within the UF 10-fold interspecies subfactors TK and TD defaults gave values of 4 and 2.5 respectively.

In both rats and humans, approximately 98% of administered boron is eliminated in urine. The differences between the species are in renal clearance rates. Much of the difference in kinetics between species can be accounted for by differences in basal metabolic rate which is related to body weight $(BW)^{0.75}$. Using the allometric exponent of 0.75 and reference body weights of

70 kg for humans and 0.35 kg for rats, a rat:human allometric scaling factor calculates to 3.8. The EPA rounds this up to 4.0 to account for minor species differences in absorption and distribution.

EPA Determination of an RfD for Boron

If the TK and TD factors are derived from data they no longer represent uncertainty, but variability factors. Therefore the interspecies uncertainty factors (UF) have been changed to variability factors (VF) in the formula below.

$$\mathbf{RfD} = \frac{\mathbf{BMDL}}{(\mathbf{VF_{AK} \times VF_{AD} \times VF_{HK} \times VF_{HD}}) \times (\mathbf{UF_{AK} \times UF_{AD} \times UF_{HK} \times UF_{HD}}) \times \mathbf{MF}}$$

Interspecies Variability **Intraspecies Uncertainty**

Derivation of Values for Variability and Uncertainty Factors

The toxic effects of boron occur in the fetus so the pregnant female is considered the "sensitive population". The relationship that describes an equivalent toxic dose across two species (rat and human) was determined in the EPA risk assessment. The toxicokinetics of boron are first order and the fetus is a compartment of the pregnant female toxicokinetic model. Maternal toxicokinetic variability can therefore be used as a surrogate for fetal dose variability.

The rat:human renal boron clearance ratio provides an inverse estimate of relative internal dose and is a scalar of ingested boron with a dose rate given in mg/kg-day. In order to tie an internal dose to an external dose an additional factor must be considered. A convenient appropriate estimator for internal dose is the average steady-state circulating boron concentration (Css).

$$Css = k_0/Cl$$

Where:

k_0 = constant infusion rate (mass/time)

Cl = clearance rate (vol/time)

The infusion rate k_0 is actually the bioavailability of the ingestion rate. k_0 can be calculated from the ingestion rate (D_e), absorption (f_a), absorbed fraction distributed to plasma compartment (f_p) and body mass (M_b).

$$k_0 = D_e f_a f_p M_b$$

therefore:

$$Css = D_e f_a f_p M_b/Cl \quad \text{and De} = CssCl/f_a f_p M_b$$

VF_{AK} is an interspecies kinetic adjustment factor used to scale an external animal dose to an equivalent human dose at the target tissue.

$$VF_{AK} = D_{erat}/D_{ehuman} = \frac{Css_{rat} \times Cl_{rat} \times f_{ah} \times f_{ph}}{Css_{h} \times Cl_{human} \times f_{arat} \times f_{prat}}$$

Simplify:

Css_{rat}/Css_{h} cancel, since the target tissues are the same $Css_{rat}/Css_{h} = 1$

M_{bh} and M_{brat} can be eliminated since the scalar unit is to be expressed relative to mass (ml/min-kg)

$$VF_{AK} = D_{erat}/D_{ehuman} = \frac{Cl_{rat} \times f_{ah} \times f_{ph}}{Cl_{human} \times f_{arat} \times f_{pratt}}$$

The mean boron clearance for pregnant rats and humans is known

Cl_{rat} = 3.3 ml/min-kg and Cl_{h} = 1.02 ml/min-kg

Intestinal absorption in adult rats and humans is about 95% and 90% respectively. The EPA considers them the same and sets the f_s for both at 0.95.

So f_{arat} = 0.95 and f_{pratt} = 0.95

The absorbed fraction of boron distributed to the plasma compartment was determined by a comparison of plasma volume to total body mass ratio. The values were: f_{ph} = 0.0911 and f_{prat} = 0.0723.

$$VF_{AK} = \frac{3.3 \times 0.95 \times 0.0911}{1.02 \times 0.95 \times 0.0723} = 4.08$$

Kidney glomerular filtration rate (GFR) is a surrogate for boron clearance. The intra-individual or intra-human variability VF_{HK} was calculated by using a ratio of the mean glomerular filtration rate (GFR_{AVE}) to the "lower bound" for a population of healthy pregnant women, averaged across the entire gestational period. The lower bound was taken as the 0.1 percentile of the lognormal distribution of GFR for pregnant women (Dunlop (1981). This gave 99.0% coverage of the population variability.

$$VF_{HK} = \frac{GFR_{AVE}}{GFR_{LOW}} = \frac{2.281 \text{ mL/min-kg}}{1.427 \text{ mL/min-kg}} = 1.60$$

The UF_{HK} was assigned a value of 1.2, rather than 1, because there was still some uncertainty in the estimation of population variance from the Dunlop (1981) study.

There were no data pertaining to boron toxicodynamics, so all of the dynamic factors were assigned their default values ($VF_{AD} = VF_{HD} = 1.0$, $UF_{AD} = 2.5$, $UF_{HD} = 3.16$. The modifying factor MF was assigned a value of 1.

Going back to the equation:

$$\mathbf{RfD = \frac{BMDL}{(VF_{AK} \times VF_{AD} \times VF_{HK} \times VF_{HD}) \times (UF_{AK} \times UF_{AD} \times UF_{HK} \times UF_{HD}) \times MF}}$$

Interspecies Variability **Intraspecies Uncertainty**

Where:

BMDL = 10.3 mg B/kg/day

$VF_{AK} = 4.08$	$UF_{AK} = 1$ toxicokinetic data adequate to reduce from $10^{0.5}$ to 10^{0} or 1
$VF_{AD} = 1$	$UF_{AD} = 2.5$ unchanged default
$VF_{HK} = 1.60$	$UF_{HK} = 1.2$
$VF_{HD} = 1$	$UF_{HD} = 10^{0.5}$ unchanged default or 3.16
	MF = 1

Therefore:

$$\text{RfD} = \frac{\text{10.3 mg B/kg-day}}{(4.08 \times 1 \times 1.60 \times 1) \times (1 \times 2.5 \times 1.2 \times 3.16) \times 1}$$

RfD = 0.2 mg/kg-day

(10.3/61.9 = 0.166, rounded to one digit of precision = 0.2)

4
BORON IN DRINKING WATER

Risk Determination

The Food and Nutrition Board (National Research Council, 1989) has recommended a water intake of 1.5 ml/kcal. The average energy allowance was used to estimate the total water intake for different subpopulations, as shown in Table 4-1.

Table 4-1
Estimation of Human Water Intake

Subpopulation*	Weight (kg)	Water Requirement (ml/kcal)	Average Energy Allowance kcal/kg x kg = kcal	Total Water Intake/day (ml)
Infant (0-6 m)	6	1.5	95 x 6 =570	855
Infant (0.5 -1 y)	9	1.5	85 x 9 = 765	1,148
Children 7-10 y	28	1.5	2,000	3,000
Male 25-50 y	79	1.5	2,900	4,350
Female 25-50 y	63	1.5	2,200	3,300
Pregnant	76	1.5	2,500	3,750
Lactating	72	1.5	2,700	4,050

*****Values for weight and water requirement from Food and Nutrition Board data (National Research Council, 1989)

A safe reference dose (RfD) of 0.2 mg/kg-day was used to estimate an acceptable daily intake (ADI) of boron in different subpopulations based on body weight. The relative source contribution of boron to total human exposure is well understood. The primary sources are diet and drinking water, with very small contributions from air and personal care products. For the purposes of estimating total boron, only food intake was subtracted from the ADI to determine the amount of boron exposure that could come from water intake and remain at the level of the ADI for each subpopulation. Table 4-2 shows the values for the current EPA adult male and female and also provides values when water intake has been revised upward to levels recommended by the National Research Council's Food and Nutrition Board (Recommended Dietary Allowances, National Research Council, 1989).

Table 4-2
Estimation of Maximum Safe Drinking Water Concentration

Subpopulation	Weight (kg)	Boron ADI (mg/day)	Food Intake (mg B/day)	ADI minus Food (mg/day)	Total Water Intake (ml/day)	Concentrations of Drinking Water B to achieve ADI (mg/L)
EPA adult male	**70**	**14.0**	**1.5**	**12.5**	**2000**	**6.2**
EPA adult female	**60**	**12.0**	**1.5**	**10.5**	**2000**	**5.2**
*Infant (0-0.5 y) (most sensitive)	6	1.2	0.21 breast milk	0.4	855	0.5
*Infant (0.5 -1 y)	9	1.8	0.8	1.0	1,148	0.8
*Children 7-10 y	28	3.6	0.86	2.7	3,000	0.9
*Male 25-50 y	79	15.8	1.5	14.3	4,350	3.2
*Female 25-50 y	63	12.6	1.0	11.6	3,300	3.5
*Pregnant	76	15.3	1.05	14.2	3,750	3.8
*Lactating	72	14.4	1.27	13.1	4,050	3.2

*****Values calculated from Recommended Dietary Allowance, National Research Council, 1989.

The bottom of the table illustrates the magnitude of decrease in safety should the EPA revise its adult water intake from 2 L/day to 1.5 ml/kcal to account for activity level, sweating, solute load and infants and children (Recommended Dietary Allowances, National Research Council, 1989).

Table 4-3 lists boron concentrations in drinking water and surface water. The mean U.S. drinking water B concentrations are well below levels needed to achieve acceptable daily intakes using the EPA adult assumptions for water intake. The National Inorganics & Radionuclides Survey (U.S. EPA, 1987) surveyed 969 community water supplies and reported a mean of 0.1 mg B/L, an upper 99th percentile of 1.0 mg B/L, and an upper range of 2 mg B/L. Applying the EPA assumption of a water intake of 2 L/day, and using the 99th percentile for boron concentration yields a margin of safety of 4.2 mg B/day for an adult male and 3.2 mg B/day for an adult female. Drinking water in the high range of 2.0 mg B/L would place infants and children above the acceptable daily intake when the Recommended Dietary Allowances are used as the predictor of water intake.

Table 4-3
Boron Levels in Water

Source	Boron mg B/L
Ocean	4.6
U.S. surface	0.01 > 2
50th percentile	0.76
90th percentile	0.387
U.S. drinking water	< 0.1; median 0.076
Mean 989 public water supplies	0.15
Range	0.05 – 2.0
90th percentile	0.4
99th percentile	1.0
Maximum (National Inorganics & Radionuclides Survey (1987)**	4.0
Bottled water 37 brands	0.75
Canada surface	0.16
United Kingdom freshwater	0.5 to 0.82

*Source Coughlin (1998); **U.S. EPA (1987)

Recommendations

The acceptable daily intake could be increased if uncertainty regarding the toxicodynamics of boron were replaced by empirical data. This could occur if the chemical mechanism (toxicodynamics) underlying boron toxicity were elucidated. The acceptable daily intake would also be increased if boron was proven to be essential for human health and if the risk assessment process were forced to consider a safety factor to prevent boron deficiency. Given the state of boron research it is most likely that new knowledge in both of these areas will be derived from studies at the chemical and cellular level.

It is recommended that three areas of research be supported: (1) chemical mechanisms of toxicity at the cellular level, (2) control of boron contamination of water supplies, and (3) development of technologies to remove boron from contaminated drinking water sources.

5
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