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Boron as a Medicinal Ingredient in Oral Natural Health Products

Natural Health Products Directorate
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EXECUTIVE SUMMARY

Boron is a mineral that occurs naturally in soil, water, and food. The average daily intake of boron from natural sources by Canadian adults is estimated to be approximately 0.86 mg from water and 2.5 mg from food for a total of 3.4 mg/day. Orally administered boron is readily and completely absorbed, passes through the body without metabolism, is excreted with a half-life of 21 hours, and is mostly eliminated with only a low level of accumulation in bone.

Boron is an essential nutrient element for the normal growth and development of plants, but while there is some evidence to support the essentiality of boron in animals, and the World Health Organization concluded that boron is “probably essential” in humans, that has not been proven conclusively since no specific biochemical function has been identified for boron in higher animals or humans. Studies in animals and humans have shown that boron interacts with magnesium, copper, vitamin D and estrogen to affect calcium metabolism, which suggest implications for reducing the risk of osteoporosis. However, beneficial effects of boron supplementation were seen mainly in animals and people deficient in boron, magnesium, copper, vitamin D, or a combination of these nutrients. Artificial boron deficiency also adversely affects embryonic development, brain function and cognitive performance, but natural boron deficiency is rare anywhere in the world and unknown in North America. Boron supplementation in people who are not deficient will not necessarily provide any benefits to the structures and functions affected by deprivation.

The acute lethal dose in animals is estimated to be in the range of 400-900 mg boron equivalents/kg body weight. Data from accidental poisonings indicate that the human acute, lethal dose of boric acid is 15-20 g for adults, 5-6 g for children, and 2-3 g in infants (equal to 2.6-3.5 g elemental boron for human adults). Boron’s acute toxicity may result in symptoms of dermatitis, alopecia, anorexia and indigestion at lower doses; high dose poisoning symptoms include nausea, vomiting, diarrhea, headache, skin rashes, desquamation, kidney damage, central nervous system stimulation followed by depression, ataxia, convulsions and possibly death as a result of circulatory failure.

Boron chronic toxicity evidence comes primarily from animal studies. The reproductive tract appears to be a consistent target for high dose boric acid/borax exposure in all species. Reproductive effects reported in dogs, rats, mice and rabbits include testicular atrophy, inhibition of sperm formation, loss of germ cells, and changes in epididymal sperm morphology. Developmental effects include decreased fetal body weight at doses not toxic to the mother, increased fetal cardiovascular malformations, skeletal malformations including cleft sternum, malformations of the central nervous system including enlarged lateral ventricles of the brain, hydrocephaly, and increased

resorptions. These effects are seen at doses exceeding 10 mg of boron/kg body weight/day.

The threshold for chronic boron toxicity in humans is not known. There is some epidemiological evidence to suggest that levels as high as 29 mg of boron/L in drinking water do not cause overt symptoms of toxicity. No difference was found in fertility rates between Turkish villages with normal versus high boron concentrations in the drinking water. In situations of industrial exposure to boron (mining, semiconductor industry), in men there was a significantly higher than expected standardized birth ratio; in women there was no significant difference in live births, nor was there a significant association between exposure to boron and spontaneous abortion risk. These measures are less sensitive than histopathological studies but they are clinically relevant. To date, there is no conclusive evidence that boron causes reproductive toxicity in humans.

Reference Doses or Tolerable Daily Intake values have been set by a number of agencies in Canada and internationally for boron either as a contaminant or as a dietary mineral. Most calculations are based on the No Observed Adverse Effect Level of 9.6 mg boron/kg bw/day for fetal effects in a study using Sprague Dawley rats, reduced by Uncertainty Factors (UF) that have varied from 22 to 1000. Reference Doses may differ with respect to setting limits for unintended or unavoidable intake from foods, beverages, pest management products, medicines, cosmetics, and consumer goods, or intended intake as a dietary mineral or medicinal ingredient. Thus, the Tolerable Daily Intake of boron from food in Canada is 0.4 mg/kg bw/day, while the Chronic Reference Dose for boron from pest management products in Canada is 0.01 mg/kg bw/day.

The Natural Health Products Directorate (NHPD) of Health Canada has set a Chronic Reference Dose for boron as follows:

> 9.6 mg/kg bw/day / 1000 UF = 0.01 mg/kg bw/day x 70 kg reference body weight = 0.7 mg/day.

This is for boron as a trace mineral without specific associated health claims but as one medicinal ingredient of “Adult only” multivitamin-multimineral natural health products consumed on a daily basis.

Since the Australian Therapeutic Goods Administration has authorized boron-containing health products (max. 3 mg boron/day) with specific health claims related to bone mineralization, the NHPD anticipates that product licence applicants will be submitting evidence in support of such claims to be on natural health products marketed in Canada. To set a safe dosage maximum for these therapeutic purposes, the NHPD has calculated a maximum Acceptable Daily Intake (ADI) value for all sources of boron exposure as follows:

9.6 mg/kg bw/day /100 = 0.096 mg/kg bw/day x 70 kg reference body weight = 6.72 mg/day.

This was further reduced to make allowance for boron intake from food and water by subtracting from the ADI the 95th percentile of the dietary intake of 2.5 mg/day and water exposure of 0.86 mg/day:

6.72 mg/day - 2.5 mg/day - 0.86 mg/day = 3.36 mg/day.

At the maximum permissible dose of 3.36 mg for boron in oral therapeutic natural health products, the following conditions of use will apply:

- No specific health claim associated with the boron content in the absence of specific supporting evidence for safety and efficacy;
- Adults only;
- Contraindicated in pregnancy and breastfeeding;
- Cautionary statement to consult with a health care practitioner prior to use in the case of an estrogen-dependent cancer.

INTRODUCTION

Boron is a non-metallic element that is ubiquitous in the environment, occurring naturally in over 80 minerals. Canadian consumers are exposed to boron naturally through food, water, air-borne particulate matter, consumer goods and health products.

The purpose of this document is to describe Health Canada's analysis of the potential risks and benefits of authorizing boron as a medicinal ingredient in oral natural health products, with specific requirements regarding the dose, conditions of use, and cautionary labelling.

Health Canada is the Federal department responsible for helping the people of Canada maintain and improve their health. Health Canada regulates the safety, efficacy and quality of a wide variety of products that contain boron, including foods, drinking water, medicines, cosmetics, consumer goods, and pesticides. Boron may be present either intentionally, as a medicinal ingredient, pest management agent, or preservative, or unintentionally, as a contaminant or as a natural trace mineral in foods, cosmetics, health products, or drinking water. Different regulatory approaches are appropriate depending on whether boron is present for a purpose or as a contaminant.

The mandate of the Natural Health Products Directorate is to ensure that all Canadians have ready access to natural health products that are safe, effective and of high quality, while respecting freedom of choice and philosophical and cultural diversity. The Natural Health Products Directorate applies the *Natural Health Products Regulations* to these ends.

This analysis is presented to illustrate in an open and transparent manner the careful deliberations undertaken by Health Canada to assess the safety, efficacy, and quality issues surrounding oral natural health products containing boron as a medicinal ingredient, in order to provide Canadian consumers access to safe products about which they can make informed choices for the maintenance and improvement of their health.

NATURAL EXPOSURE TO BORON

Boron (B, atomic number 5, atomic weight 10.811 g/mole) never occurs in nature by itself – it is always found chemically bound to oxygen as either boric acid (H_3BO_3) or its salts, called borates. For example, borax is hydrated sodium borate ($Na_2B_4O_7 \cdot 10\ H_2O$). However, for ease of comparison of the different sources of boron, all of the concentrations and dosages described in this document have been adjusted to give amounts of boron in its elemental form.

Rocks and soil contain quantities of boron varying from less than 10 mg/kg typically, to more than 100 mg/kg in shale and some soils, particularly in volcanic regions. In water, borates break down to usually undissociated boric acid (pK_a 9.2). Sea water contains from 0.5 to 9.6 mg of boron per litre (L) (USEPA-IRIS 2004), for example between 3.7 and 4.3 mg/L in Canadian coastal waters (Health Canada 1991).

Boron enters the body mainly through what we drink and eat (USEPA-IRIS 2004). Levels in well water have been reported to be more variable and often higher than those in surface waters, most likely owing to erosion from natural sources. In Canada, surface water concentrations of boron range from <0.01 mg/L to 2.9 mg/L, with an overall mean of 0.16 mg/L. In Canadian municipal treated and distributed water, the boron concentration ranges from 0.00004 mg/L to 0.6 mg/L, but most communities' drinking water has a boron concentration of 0.1 mg/L or less. In general, drinking water in Canada provides a maximum boron intake of 0.86 mg/day (Health Canada 1991). Other beverages are also sources of boron, e.g. milk contains 0.5-1 mg/L and wine contains up to 8.5 mg/L (Health Canada 1991).

The natural boron content of foods varies considerably, e.g. 0.05-0.6 mg/kg in meat, 1-5 mg/kg in grains, 2-20 mg/kg in green vegetables, 0.3-3 mg/kg in fresh fruits, up to 14 mg/kg dry weight in nuts, and 25-50 mg/kg in legumes (Health Canada 1991; EGVM 2003; USEPA-IRIS 2004). Moore (1997) estimated that dietary intake of boron in North Americans ranges from 0.26-7.1 mg/day, with a mean of 1.9 mg/day, but the upper value of 7.1 mg may be an extreme value. Health Canada (1991) estimated the dietary intake of a Canadian adult between 20-40 years of age to range from 1-3 mg of boron daily, with an average of 2.5 mg/day. Typical US population mean dietary intake values are 1.17 mg of boron per day for men (95^{th} percentile for males between 51-70 years of age was 2.53 mg boron/day) and 0.96 mg boron/day for women (95^{th} percentile 1.94 mg/day). Vegetarian male adults had a mean dietary intake value of 1.47 mg boron/day (95^{th} percentile 2.42 mg/day). Vegetarian female adults had a mean dietary intake value of 1.29 mg boron/day (95^{th} percentile 4.18 mg boron/day) (Rainey *et al.* 1999). These estimates are similar to others for US and UK populations (Hunt and Meacham 2001; NHANES III referenced in IOM 2001; Rainey *et al.* 1999; Hamilton and Minski 1973; Zook and Lehmann 1965).

Medicines (e.g. eye drops), pesticides, and consumer products that contain borates as preservatives and acidity adjusters (e.g. cosmetics, fabric softeners, detergents, soaps and shampoos, paints, adhesives, and insulation) could provide up to an additional 0.5 mg/day (EGVM 2003). Talcum powder may contain 5% boron but the boron is not absorbed across intact skin – inhalation, ingestion, and absorption across severely damaged skin are the only routes for boron exposure from topical products (USEPA-IRIS 2004). Boron may be present as a contaminant in some products, e.g. magnesium

oxide may contain from 1.5 to 850 mg/kg of boron (Mortier *et al.* 1986), magnesium chloride may contain from 10 to 100 mg/kg of boron (Rohm and Haas 2007), and even pharmacopoeial grade magnesium sulphate (Epsom Salt) may contain up to 15 mg/kg of boron (PQ Corporation 2007). However, not all products in these categories contain boron and these sources of exposure are not usually occurring on a daily basis.

In summary, the daily intake of boron from natural sources by Canadian adults is estimated to be up to 0.86 mg from water and 2.5 mg from food for a total of 3.4 mg/day, with a normal range from 1-4 mg daily depending on dietary habit (e.g. vegetarians ingest more), geographic location and other sources of exposure.

BORON ORAL ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

Orally administered boron is readily and completely absorbed (>90%) through the human gut as boric acid (Hunt 1996; Murray 1998). Boric acid is rapidly distributed through body water by passive diffusion with a blood/soft tissue ratio of 1:1 and blood/bone ratio of 1:4 (Hamilton and Minski 1973; Murray 1998). Boron does not accumulate in the soft tissues of animals including humans (0.05-0.6 mg boron/kg fresh weight; Samman *et al.* 1998; Nielsen 1986; Murray 1998). According to a rat study, boron at high doses of 3000 to 9000 ppm accumulates in bone, reaching a steady state within one week, but declines to 10% of the maximum after 8 weeks, and is only 3 times the levels of controls 32 weeks after cessation of exposure (Chapin *et al.* 1997). This accumulation may be related to boric acid's potentially beneficial interaction with the metabolism of calcium (reviewed in Devirian and Volpe 2003).

Boric acid is excreted from the body through urination with a high recovery rate of between 84% (Samman *et al.* 1998) and 92% in 96 hours (Schou *et al.* 1984). The half-life for elimination of boric acid is about 21 hours for both intravenously (Jansen *et al.* 1984a) and orally (Jansen *et al.* 1984b) administered boric acid. Individuals with kidney disease have been reported to have increased pre-dialysis plasma boron levels (Usuda *et al.* 1996).

Boron does not undergo biotransformation. Lack of metabolism of boron eliminates metabolic clearance as a potential source of interspecies variation. Therefore, renal clearance is expected to be the major determinant of interspecies variation in pharmacokinetics. The magnitude of the difference (rat vs. human) between average clearance values by surface area has been shown to be approximately 3.6-fold and 4.9-fold for pregnant and non-pregnant individuals, respectively. This is in close agreement with differences in kinetic parameters predicted by allometric scaling (approximately 4-fold) (USEPA-IRIS 2004). Renal clearance by body weight reveals a rat to human ratio of 0.43 (Pahl *et al.* 2001) Compared with relevant experimental species, the available pharmacokinetic data support a high degree of qualitative similarity, e.g. lack of metabolism, high clearance through renal filtration mechanisms, and apparently

consistent extravascular distribution characteristics (USEPA-IRIS 2004). In the rat, according to first-order kinetics, a half-life of 14-19 hours was calculated (Murray 1998), which is close to human data. Based on these similarities, some regulatory authorities reduced their interspecies Uncertainty Factor.

BORON'S POSSIBLE BENEFITS FOR HEALTH

Boron is an essential nutrient element for the normal growth and development of plants, where its functions include involvement with sugar transport, cell wall synthesis, and RNA metabolism (Nielsen 1986).

The European Food Safety Agency Scientific Panel on Dietetic Products, Nutrition and Allergies (EFSA 2004) stated, "There is also some evidence to support the essentiality of boron in animals." The USEPA-IRIS (2004) quoted Nielsen (1994) to state, "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." The United Kingdom Expert Group on Vitamins and Minerals (EGVM 2003) stated that boron "is presumed to be essential in animals, since boron deprivation in both experimental animals and humans causes changes in biological function which are reversible by restoration of boron." A World Health Organization Expert Committee on Trace Elements in Human Nutrition concluded that boron is "probably essential" (Coughlin and Nielsen 1999).

Natural boron deficiency in humans has never been reported in North America and is extremely rare anywhere in the world. Kashin-Beck disease is a musculoskeletal and myocardial disease which may cause severe joint deformity and heart failure. Kashin-Beck disease has not been reported in Canada, but it has been reported from certain regions in China and the former Soviet Union, usually mountainous regions far from the sea where there is evidence of soil boron deficiency. Dietary mineral supplementation (mainly with selenium 1 mg/day) can reverse the pathological status of this disease, although causes of Kashin-Beck disease are still being investigated. A cross-sectional survey in China found significantly lower boron levels in the hair of children with Kashin-Beck disease than in the hair of local controls; therefore, it has been suggested that boron deficiency could be a contributing factor to Kashin-Beck disease. Other trace elements, such as germanium and molybdenum, have also been implicated to play a role in this disease (Fang *et al.* 2003; Peng *et al.* 2000).

No specific biochemical function has been identified for boron in higher animals or humans, so its nutritional essentiality has not been firmly established. Nonetheless, dietary guidance should be formulated for boron, because of its demonstrated beneficial, if not essential, effects in both animals and humans (Nielsen 1998). Several

human experiments conducted by Nielsen and colleagues have shown that dietary boron manipulation may affect blood composition, copper, estrogen, thyroid hormone, testosterone, and most notably, calcium metabolism. Boron has been hypothesized to exert its effects on calcium and hormone metabolism by affecting cell membrane functions or stability. Another possibility is that boron acts as a metabolic regulator through forming esters or complexes with a variety of substrate or reactant compounds including enzymatic systems (Nielson 1998), but there is no solid evidence to support either hypothesis.

Boron and Calcium Metabolism

The first human study to suggest that boron affects calcium metabolism found that boron deprivation increased the urinary excretion of calcium and magnesium and decreased 17 β-estradiol and testosterone concentrations in postmenopausal women (Nielsen *et al.* 1987). A series of four boron deprivation studies involving postmenopausal women and men over the age of 45 was subsequently conducted to further investigate the relationship between boron and calcium metabolism, as well as to identify other possible effects of dietary boron manipulation. During the boron depletion period of the studies, subjects were fed a diet providing approximately 0.25 mg boron/2000 kcal for 63 days. The 49-day repletion period that followed required subjects to consume the same diet supplemented with 3 mg of boron as sodium borate. Two of the experiments provided diets low in magnesium (approximately 115 mg/2000 kcal) and marginally adequate in copper (about 1.6 mg/2000 kcal) (Nielsen 1989; Nielsen *et al.* 1990), whereas the other two experiments provided adequate magnesium throughout the study duration (about 300 mg/2000 kcal) and adequate copper from day 33 onward (2.4 mg/2000 kcal) (Nielsen *et al.* 1991 and 1992).

One of the studies providing a marginal copper and low magnesium diet found that boron manipulation affected several variables associated with calcium metabolism. Plasma ionized calcium and serum 25-hydroxycholecalciferol levels were significantly lower, and the serum calcitonin level was significantly higher during boron depletion compared to boron repletion (Nielsen *et al.* 1990). In a magnesium and copper adequate study only serum 25-hydroxycholecalciferol, which was decreased during boron depletion, was reported to be affected by boron manipulation (Nielsen *et al.* 1992). In a review of these studies, Nielson explained that serum calcitonin and serum osteocalcin levels were abnormally high in subjects consuming the magnesium and copper poor diets compared to those consuming the adequate diets, and these levels were even higher during boron depletion (Nielsen 1998). From this comparison, Nielson concluded that consumption of a diet deficient or marginal in magnesium and copper results in abnormal calcium metabolism, which is exacerbated by boron depletion. It is important to note that in contrast to these findings, a recent study in postmenopausal women found that dietary boron manipulation did not have an obvious effect on the

response to a magnesium deficient diet. While magnesium deficiency significantly decreased urinary calcium excretion, and increased 25-hydroxycholcalciferol, boron did not affect either of these variables. In addition, neither magnesium, nor boron affected serum calcitonin, osteocalcin, mid-molecule parathyroid hormone, or alkaline phosphatase. Nielson concluded that previous reports of magnesium status affecting the response to boron probably reflect an indirect, rather than a direct, relationship between the two elements (Nielson 2004b).

Boron and Osteoarthritis

The effects of boron on calcium metabolism, and 25-hydroxycholecalciferol specifically, noted above may have positive implications on bone metabolism including a reduced risk for osteoporosis and perhaps other maladies (Zitterman 2003). In further support of these findings, a study conducted in 13 subjects predetermined to be vitamin D deficient found that during a 60-day supplementation period with 6 mg boron/day, serum 25-hydroxyvitamin D levels rose by an average of 20% (reviewed in Miljkovic *et al.* 2004). Boron has also been shown to improve bone strength characteristics in rats (Nielsen 2004a) and pigs (Armstrong *et al.* 2000).

A comparison between countries found that the occurrence of arthritis is negatively correlated with the level of boron in the soil and food supply. The study found that in areas where daily boron intakes are typically 1.0 mg or less, the estimated incidence of arthritis ranges from 20-70% whereas, in areas where boron intakes are typically 3 to 10 mg daily, the estimated incidence of arthritis ranges from 0 to 10% (Newnham 1991). In further support, a double-blind study involving 20 subjects with osteoarthritis found beneficial results in those taking 6 mg boron/day. After 8 weeks of supplementation the average condition of all patients' joints was significantly better, and there was significantly less pain on passive movement, for those taking boron compared to those on placebo (Newnham 1994).

Boron and Menopause Symptoms

Also worthy of note are the findings regarding boron manipulation and serum 17 β-estradiol. As mentioned previously, one study found that boron deprivation significantly decreased 17 β-estradiol levels in postmenopausal women not on estrogen therapy (Nielsen *et al.* 1987). One of the studies providing a magnesium and copper adequate diet reported somewhat different results. Initially, women on estrogen therapy had higher levels of 17 β-estradiol and plasma copper concentrations compared to subjects not ingesting estrogen, and levels of these variables were significantly higher during boron supplementation, but only for subjects consuming estrogen. In addition, serum immunoreactive ceruloplasmin and triglyceride concentrations were higher in subjects ingesting estrogen, but boron repletion increased both variables in all subjects, not just

those ingesting estrogen. These findings suggest that boron both enhances and mimics some effects of estrogen. It was proposed that since boron has been shown to have estrogenic effects, and estrogen is known to affect calcium, perhaps boron affects calcium metabolism through similar processes (Nielsen *et al*. 1992). Naghii and Samman (1997) also demonstrated a significant increase in plasma estradiol concentrations as a result of boron supplementation at 10 mg/day over 4 weeks which they believed could imply a potential beneficial role for boron in atherosclerosis.

Since boron has been shown to have effects similar to estrogen, Nielson and Penland (1999) conducted a double-blind crossover trial in 43 peri-menopausal women to determine if supplementation with 2.5 mg boron could reduce symptoms of menopause including night sweats and hot flashes. However, this was not the case as a significant number of women (46%) reported more frequent and severe hot flashes and night sweats during boron supplementation compared to placebo, whereas some women (22%) reported less severe symptoms, and others (33%) reported no change. The study authors explained that boron may be acting in manner similar to selective estrogen receptor modulators, which can influence some changes of menopause, such as bone loss, but not others (Nielsen and Penland 1999).

Potential Protective Role Against Prostate Cancer

Preliminary cell culture, animal and human evidence suggests that boron may have a protective role in prostate cancer risk. A cross-sectional case-control analysis based on data from the third National Health and Nutrition Examination Survey (NHANES III) found that increased dietary boron intake was associated with a decreased risk of prostate cancer with a dose-response pattern. The adjusted odds ratio was 0.46 (95% CI: 0.21-0.98) for the highest quartile of boron intake compared to lowest quartile (P for trend = 0.0525) (Cui *et al.* 2004). In support of these findings, one study using nude mice implanted with human prostate adenocarcinoma (LNCaP) cells found that boron supplementation reduced serum prostate-specific antigen (PSA) levels, and reduced tumor size and expression of IGF-1, a tumor trophic factor (Gallardo-Williams *et al.* 2004). Another study showed that boric acid inhibits the proliferation of some human prostate cancer cell lines (Barranco and Eckhert 2004).

Potential Supportive Effects of Boron on Early Embryonic Development

Adverse embryonic effects related to boron depletion have been reported for frogs (Fort *et al.* 1998 and 1999) and zebra fish (Rowe and Eckhert 1999). Boron has been shown to stimulate embryonic and larval growth in trout (Eckhert 1998). Results from a series of *in vivo* and *in vitro* rodent studies suggest that boron deficiency impairs early embryonic development. In comparison to dams fed a boron adequate diet, dams fed a low boron diet had a significantly reduced number of implantation sites, reduced

blastocyst formation, reduced blastocyst cell numbers, and an increased number of degenerates. However, it should be noted that one of the studies found that high levels of boron (>2000 µM) consumption can impair embryonic differentiation and proliferation in mice (Lanoue *et al.* 1998).

These studies suggest that boron may be essential for proper reproduction and development but boron deprivation studies have not shown development effects consistently in rodent or higher animal models. Furthermore, these studies cannot be considered to provide evidence for potential benefits of boron supplementation where a deficiency does not exist.

Potential Supportive Effects on Brain Function and Cognitive Performance

A series of studies has consistently shown that boron deprivation in rats and humans leads to undesirable effects on brain electrophysiology (Penland 1998) and, in humans, results in significantly poorer performance on tasks involving eye-hand coordination, attention, and short-term memory (Penland 1994 and 1998). It has also been shown that boron depleted diets in humans may reduce performance on tasks measuring manual dexterity, perception, and long-term memory (Penland 1994). Again, it is important to note that boron supplementation in people who are not deficient will not necessarily provide any benefits to the structures and functions affected by deprivation.

TOXICITY OF BORON

Animal Data on Boron Toxicity

The acute lethal dose in animals is estimated to be in the range of 400-900 mg boron equivalents/kg body weight (EGVM 2003).

The reproductive tract appears to be a consistent target for high dose boric acid/borax exposure in all species. Reproductive effects reported in dogs, rats, mice and rabbits include testicular atrophy, inhibition of sperm formation, loss of germ cells, and changes in epididymal sperm morphology. Cross-over mating in the mouse indicated a predominantly male effect, but cross-over mating in the rat showed signs of a potential female/pup effect, in addition to a male effect. A lack of data on ovarian effects precludes a definitive assessment with respect to female sensitivity to boron exposure.

Developmental effects include decreased fetal body weight at doses not toxic to the mother, increased fetal cardiovascular malformations, skeletal malformations including cleft sternum, malformations of the central nervous system including enlarged lateral ventricles of the brain, hydrocephaly, and increased resorptions. Reviews of the

toxicology of boron have been published by the U.S. Environmental Protection Agency (USEPA-IRIS 2004), and previously by Health Canada (1991).

As described in Table 1, below, the Lowest Observed Adverse Effect Levels (LOAELs) and No Observed Adverse Effect Levels (NOAELs) for reproductive and developmental toxicity in rats, mice and rabbits range from 13-79 mg/kg bw/day and 9.6-58.5 mg/kg bw/day, respectively (Price *et al.* 1996a and 1996b; Ku *et al.* 1993; Heindel *et al.* 1992; Lee *et al.* 1978; Weir and Fisher 1972). In mice, 263-776 mg/kg bw/day intake increased their mortality (Heindel *et al.* 1992). Doses of 25.3 mg boron/kg bw/day or greater have resulted in renal effects including reduced or increased kidney size and tubular dilatation in rats, mice and dogs (reviewed in Pahl *et al.* 2005).

Table 1. Developmental and reproductive LOAEL and NOAEL values for boron.

Species	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)	Adverse Effects	Reference
Mouse	79	43	Developmental effects	Heindel *et al.* 1992
Rat	26	-	Mild inhibited sperm release	Ku *et al.* 1993
	52	26	Testicular atrophy	
Rat	50	25	Tubular germinal aplasia	Lee *et al.* 1979
Rat	13.3	9.6	Decreased fetal body weight	Price *et al.* 1996a
Rat	25	12.9	Developmental effects (short rib XIII)	Price *et al.* 1996a (phase II)
Rabbit	43.8	21.9	Fetal malformations	Price *et al.* 1996b
Rat	58.5	17.5	Decreased testes wt, testicular atrophy, increased brain/thyroid wt.	Weir and Fisher 1972
Dog	29.0	8.75	Testicular atrophy	Weir and Fisher 1972
		4.4		EGVM 2003 assessment of Weir and Fisher study
		3.6		PMRA 2003 analysis of unpublished data of Weir and Fisher

In a study using Sprague Dawley rats, Price *et al.* (1996a) concluded that the NOAEL was 9.6 mg boron/kg bw/day for fetal effects. Developmental toxicity was noted to be occurring at lower doses than maternal effects, which were limited to increased relative kidney weight with 0.2% boric acid (25.3 mg boron/kg bw/day) (Price *et al.* 1996a). This is a well-reported study and used by many international authorities (UK, WHO, IOM) as basis for their safe upper level calculations. In Phase II of the above study (Price *et al.* 1996a), dams were allowed to deliver and rear their litters until postnatal day 21. There were no offspring body weight effects observed through postnatal days 0-21, no treatment-related skeletal variations observed on postnatal day 21 and minor skeletal malformations of the ribs remained elevated only at the highest dose (25.3 mg/kg bw/day). The NOAEL and LOAEL for phase II of this study were 12.9 and 25.3 mg boron/kg bw/day, respectively; however, it should be noted that testicular development, a primary endpoint of concern, was not assessed.

A study by Weir and Fisher (1972) identified a NOAEL of 8.75 mg boron/kg bw/day and a LOAEL of 29 mg boron/kg bw/day for testicular effects in dogs. However, this study has many limitations, and it is not considered to be a critical study for reference dose derivation by most authorities because:

- the NOAEL and LOAEL were taken from two different studies of two different durations and the LOAEL was more than two times higher than the NOAEL
- the sample size was too small. There were only 4 test animals per group, and only two control animals
- testicular damage in one of four control animals was observed, and the histopathological findings were considered to be “non compound-induced.”

It is important to note that the Pest Management Regulatory Agency (PMRA) of Health Canada was able to conduct an analysis of the original boric acid and borax dog studies reviewed by Weir and Fisher. In contrast to what was reported by Weir and Fisher, PMRA stated that their analysis revealed that testicular effects were observed in dogs within the high-dose groups (8.8 mg boron/kg and 9.4 mg boron/kg boron) mid-dose groups (3.0 mg boron/kg and 3.6 mg boron/kg) and low-dose groups (1.4 mg boron/kg and 1.6 mg boron/kg). Moreover, the 90-day boric acid and borax dog studies, which were also included in the Weir and Fisher 1972 paper, reported occurrence of decreased absolute and testicular weights at 4.2 mg/kg and 0.4 mg/kg, respectively. There are some questions as to the statistical and clinical significance of these results since the studies involved irregular sacrifice schedules, dose level inconsistencies between studies, and variability in the actual intake of test compounds. The potential dose-effects within each of the two 2-year studies needed to be evaluated on an individual dog basis and treated groups could not be combined across the two 2-year dog studies. There were no apparent gross pathologic, organ weight or histopathologic treatment-related changes in testes in dogs administered low-, mid- or high-dose levels

of boric acid or borax for one year, although the low number of animals (1 male/group) evaluated pathologically limits the ability to arrive at definitive conclusions with regard to potential testicular or other toxicity of test boric acid and borax after 1 year of administration in dogs (sperm analysis was not done). Histologic artifacts from use of formalin confounded a number of the microscopic assessments, and some of the results were interpreted as spontaneous, incidental findings unrelated to the test article treatment.

The original studies' authors, Weir and Fisher (1972), reported that there did not appear to be any definitive test article effect on any parameter examined. PMRA assessment of the original unpublished data led to the conclusion that pathologic findings in 1 of 2 male dogs administered 9.4 mg/kg boric acid and 1 of 2 male dogs administered 8.0 mg/kg borax may constitute adverse effects of test article administration on testes of dogs. Since it is possible that the adverse effects observed were treatment-related, new studies are needed to clarify the effects of boron on male and female animals' reproductive organs.

In summary, high doses of boron have been associated with reproductive toxicity in laboratory animals, with characteristic effects being produced in the testes. A clear dose-response relationship has been demonstrated. According to the EGVM (2003), although the Weir and Fisher study resulted in a lower NOAEL of 4.4 mg/kg bw/day, the number of animals in this study was low and the differences between the dose levels tested were large, so the lowest dose at which adverse effects were observed was ten times this level. Considering the totality of the data, the EGVM concluded that the highest intake without significant adverse effects (the NOAEL) is 9.6 mg/kg bw/day, based on the study of Price *et al.* (1996a), a decision supported by most other authorities.

No evidence of carcinogenicity was observed from oral exposure to boron compounds in rats and mice (Dieter 1994). No evidence of genotoxicity was found in mammalian cell mutation *in vitro* assays (Weir and Fisher 1972; Benson *et al.* 1984; National Toxicology Program 1987). There is no evidence of an association between cancer and boron exposure in humans either, but nevertheless, the available data are considered inadequate for a proper evaluation of the human carcinogenic potential of boron (USEPA-IRIS 2004).

Human Acute Toxicity

Human data on the safety of boron are limited. Boron has been used in the treatment of malaria, urinary tract infections, exudative pleuritis, and more recently, in boron neutron capture therapy for brain tumors at doses of 25-35 mg boron/kg bw/day (USEPA-IRIS 2004). Boron has also been used in the treatment of epilepsy at doses of 2.5-24.8 mg

boron/kg bw/day for periods of many years. Symptoms including dermatitis, alopecia, anorexia and indigestion occurred in patients receiving doses of 5 mg boron/kg/day. Withdrawal of treatment resulted in recovery from these effects without sequelae (Culver and Hubbard 1996).

Data from accidental poisonings indicate that the human acute, lethal dose of boric acid is 2-3 g in infants, 5-6 g in children, and 15-20 g in adults (for example, this would be equivalent to 2.6-3.5 g elemental boron in adults) (Dixon *et al.* 1976; Siegel and Wason 1986; EGVM 2003; USEPA-IRIS 2004). However, in an examination of 748 cases of boric acid ingestion, Litovitz and coworkers (1988) found minimal to no acute toxicity at these intake levels and other authors have reported high inter-individual variability in human acute toxicity (EGVM 2003).

Evidence suggests that there is a linear relationship for acute toxicity in that similar boron intakes in infants (amounts per body weight) elicit similar effects as compared to adults (Culver and Hubbard 1996). Clinical symptoms in acute boron poisoning include nausea, vomiting, diarrhea, headache, skin rashes, desquamation and central nervous system stimulation followed by depression, ataxia and convulsions. Death is thought to result in approximately five days as a result of circulatory failure (Health Canada 1991; Ellenhorn 1997; EGVM 2003). Some acute boron poisonings have also resulted in renal symptoms which range from mild urinary changes including the presence of cellular sediment and tubular range proteinuria, to oliguria, anuria, and azotemia (Pahl *et al.* 2005).

Human Chronic Toxicity

A recent review of the literature found that while acute exposure to high quantities of boron (350-7000 mg) produces symptoms of renal toxicity, chronic exposure to non-lethal doses of boric acid in humans does not seem to be associated with renal symptoms (Pahl *et al.* 2005).

The threshold for chronic boron toxicity for humans is not known, but there is some evidence to suggest that it may be quite high. One study found that water boron levels in differing locations of the Kutahya Province of Turkey ranged from 2.05 to 29 mg boron/L, with a mean value of 10.20±4.08 mg boron/L. Despite such high levels of boron exposure, the authors stated that no remarkable findings of toxicity were observed in the residents. In their discussion, the authors concluded that “chronic boron exposure does not have important toxic effects because there is no established clear increase in disease among the people in the region” (Cöl and Cöl 2003). In addition, no difference was found in fertility rates in Turkish villagers living in two regions with boron concentrations of 2.05-29 mg/L and 0.03-0.4 mg/L in their drinking water (Sayli *et al.* 1998). Such epidemiological studies have their weaknesses in that they are

observational so there may be confounding factors, and laboratory analyses for non-overt pathologies were not done, but they do help to provide some information on whether or not chronic exposure to boron at these levels has clinically significant adverse effects on the parameters being studied.

With respect to the reproductive toxicity seen in animals, there is only limited evidence of overt symptoms of reproductive toxicity in humans with chronic industrial exposure (mainly by inhalation). A small study of Russian male workers exposed for 10 or more years to high levels of vapors and aerosols of boron salts (22-80 mg/m^3) involved in borax mining and the production of borates and boric acid suggested low sperm count, reduced sperm motility, changes in seminal fluid composition, and decreased sexual function. However, further studies triggered by this initial report found a significantly higher than expected standardized birth ratio in men who were exposed industrially. This suggests no clinically relevant reproductive toxicity, although the birth ratio is a less sensitive measure of reproductive toxicity than direct histopathologic testing for testicular effects. There was no correlation between high versus low boron exposure levels and a decrease in live birth rates among women who were exposed to boron in industrial settings, so exposure to borates did not appear to adversely affect fertility in these populations. Another study in women exposed to chemicals including boron used to manufacture semiconductors found no significant positive association between the level of exposure to boron and spontaneous abortion risk. However, given the limitations of these studies, the human data are insufficient to determine if boron may cause reproductive toxicity (USEPA-IRIS 2004).

With respect to adverse reaction reports in humans, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) contains nine case reports from the period January 1, 1997, to February 20, 2007, associated with a multivitamin-multimineral product, which contains only 160 µg/capsule of boron. The adverse reaction reports are not attributable to the boron itself but relate to worsening of symptoms in those patients who discontinued prescription medications or took the product in conjunction with prescribed medications without consulting a healthcare practitioner.

The CADRMP summary is based on information from adverse reaction reports submitted by health professionals and laypersons either directly to Health Canada or via market authorization holders. Each report represents the suspicion, opinion or observation of the individual reporter. The CADRMP is a spontaneous reporting system that is suitable to detect signals of potential health product safety issues during the post-market period. The data has been collected primarily by a spontaneous surveillance system in which adverse reactions to health products are reported on a voluntary basis. Under-reporting of adverse reactions is seen with both voluntary and mandatory spontaneous surveillance systems. Accumulated case reports should not be used as a basis for determining the incidence of a reaction or estimating risk for a particular

product as neither the total number of reactions occurring, nor the number of patients exposed to the health product is known. Because of the multiple factors that influence reporting, quantitative comparisons of health product safety cannot be made from the data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions. In some cases, the reported clinical data is incomplete and there is not certainty that these health products caused the reported reactions. A given reaction may be due to an underlying disease process or to another coincidental factor.

Due to the recognized under-reporting of adverse reactions and the potential nature of adverse effects associated with excessive exposure to boron, a lack of adverse reaction reports cannot in itself be used to state conclusively that boron is without risk.

DOSAGE LIMITATIONS FOR BORON IN ORALLY ADMINISTERED NATURAL HEALTH PRODUCTS

Reference Doses for Boron

Reference Doses (RfD) or Tolerable Daily Intake (TDI) values have been set by a number of agencies in Canada and internationally for boron either as a contaminant or as a dietary mineral. Most calculations are based on the NOAEL of 9.6 mg boron/kg bw/day for fetal effects in a study using Sprague Dawley rats but those of the USEPA-IRIS and IEHR are based on a benchmark dose of 10.3 mg boron/kg bw/day for decreased fetal body weight by Allen *et al.* (1996). The Uncertainty Factors (UF) used to account for interspecific, intraspecific, and other factors range from 22 to 1000. The results from various authorities are summarized in Table 2.

Table 2. Reference dose calculations for orally administered boron.

Authority	NOAEL (mg boron/kg bw/day)	UF	RfD (mg boron/kg bw/day)
WHO-IPCS (1998)	9.6	25	0.40
IOM-DRI (2001)	9.6	30	0.32
USEPA-IRIS (2004)	10.3	66	0.20
IEHR (1997)	10.3	30	0.34
ECETOC (1994)	9.6	30	0.32
EGVM (2003)	9.6	60	0.16
Murray (1995)	9.6	32	0.30
Murray and Anderson (2001)	9.6	22-44	0.44-0.22
PMRA (2003)	9.6	1000	0.01

The Canadian and United States Dietary Reference Intake for Boron

Health Canada worked with the Expert Advisory Committee on Dietary Reference Intakes and the U.S. Institute of Medicine's Food and Nutrition Board, overseen by the U.S. National Academies, to produce the Dietary Reference Intakes (DRIs). The resulting DRIs replace the former Canadian Recommended Nutrient Intakes and Nutrition Recommendations.

The DRIs reflect the current state of scientific knowledge with respect to nutrient requirements. The Office of Nutrition Policy and Promotion uses the DRIs to ensure that dietary guidance to Canadians, such as Canada's Food Guide to Healthy Eating, is scientifically sound. The DRIs are also used to assess the nutrient intakes of Canadians.

Even though boron is an essential element for plants, the biological function of boron in humans is not clear. Therefore the Institute of Medicine (2001) could not establish an Estimated Average Requirement, Recommended Dietary Allowance, or Adequate Intake.

Five expert groups that assessed the risk to humans from boron all used the NOAEL from Price and coworkers (1996a) of 9.6 mg/kg bw/day and UF values varying from 25 to 60. The Institute of Medicine (2001) concluded that there did not appear to be sufficient data to justify lowering the degree of uncertainty for extrapolating from experimental animals to humans from the 10 that is often used for nonessential chemicals. Based on expected similarities in pharmacokinetics among humans, a UF of 3 was chosen for intraspecies variability. The Reference Dose was calculated as follows:

9.6 mg/kg bw/day / 30 UF = 0.32 mg/kg bw/day.

The Tolerable Upper Intake Level (UL) for infants was judged not determinable due to insufficient data on adverse effects in this age group and concern about the infant's ability to handle excess amounts. Thus, it was decided that in order to prevent high levels of intake, the only source of intake for infants should be from food and formula. Due to the absence of reports of low dose boron toxicity in children and adolescents, the UL for children and adolescents, was extrapolated from the UL established for adults, and was adjusted on the basis of body weight.

DRI UL for Boron:

Adults (≥19 y)	20 mg/day
Adolescents (14-18 y)	17 mg/day
Children (9-13 y)	11 mg/day
Children (4-8 y)	6 mg/day
Children (1-3y)	3 mg/day

Since there are no reports of boron toxicity in lactating females, the UL for pregnant and lactating females is the same as that for non-pregnant and non-lactating females, i.e. 17 mg/day and 20 mg/day of boron for women 14-18 years and ≥ 19 years old, respectively.

Other Decisions from Health Canada with Respect to Boron Content

With respect to foods in Canada, Health Canada's Food Directorate Chemical Health Hazard Assessment Division considered the Tolerable Daily Intake (TDI) of 0.4 mg/kg bw/day established by the World Health Organization International Programme on Chemical Safety (WHO-IPCS) (1998) to be valid for the general population in relation to a food product contamination risk assessment.

For therapeutic products, currently there are three boron-containing oral mineral supplements for human use registered according to the Drug Product Database. Centrum 8401 (DIN 02254565) is a multivitamin-multimineral providing 150 mcg of boron from calcium borate, magnesium borate, and sodium borate, all in magnesium oxide, listed as being for non-prescription use. Centrum 8400 (DIN 02254530) providing 150 mcg of boron and Centrum 8285 (DIN 02243704) providing 70 mcg of boron, are both prescription multivitamin-multimineral products. These products were scheduled as prescription drugs because they contain vitamin K1.

In addition, there are 40 other boron-containing products in the Drug Product Database:

- 5 non-prescription ophthalmic anti-infectives (liquid and powder);
- 3 non-prescription topical anti-infective powders;
- 1 non-prescription topical antifungal solution;
- 1 professional use mouthwash/gargle (68.6% boric acid);
- 24 homeopathic medicines (oral 1X: 5 products, 2X (1C): 2 products, 3X: 4 products, 4X (4D): 2 products, 5CH: 1 product, 12X (6CH): 4 products, 8C: 1 product, 30X: 3 products, 6K: 1 product; topical 12X: 1 product);
- 1 intravenous prescription borate-derivative drug;
- 2 veterinary non-prescription ophthalmic anti-infective products;
- 1 veterinary prescription topical anti-infective product; and
- 2 surface disinfectants.

The dosage forms include solution, powder, drop, globule, granule, pellet, tablet, jelly, and aerosol. Routes of administration include topical, sublingual, oral, and ophthalmic.

Boric acid is also on the Health Canada List of Prohibited and Restricted Cosmetic Ingredients of May 2005. This indicates that boron is a restricted cosmetic ingredient. The qualifiers for boric acid and its salts are as follows:

- Permitted only at concentrations equal to or less than 5% provided the label of the cosmetic product contains a statement to the effect:
  "Do not use on broken or abraded skin. Not to be used by children under three years of age."
- Warning is not required when boric acid is used as a pH adjuster and the concentration is less than 0.1%.

If a cosmetic contains an ingredient which appears on the restricted list, the manufacturer may be advised to:

- Remove the substance from the formulation;
- Reduce the concentration of the ingredient to an acceptable level;
- Consider marketing the product as a drug, with appropriate claims and apply for a Drug Identification Number (DIN);
- Provide evidence that the product is safe for its intended use;
- Confirm that the product is labeled as required;
- Confirm that the product is sold in a child resistant package.

Dosage Limits for Boron in Oral Products in Other Jurisdictions

United States: In accordance with the Dietary Reference Intakes, boron products regulated as dietary supplements may provide up to 20 mg of elemental boron equivalents per day (IOM 2001). Under the Dietary Supplements Health and Education Act of 1994 (DSHEA), there is no mandatory pre-market review for these products, but they are not permitted to be labelled or advertised with claims to treat any disease.

The USEPA-IRIS RfD of 12 mg/day is calculated using an Uncertainty Factor of 66 and a benchmark level of 10.3 mg boron/kg bw/day (Allen *et al.* 1996, USEPA-IRIS 2004). This RfD is consistent with the recommendation that an intake of 10 mg/day is not too high, while 50 mg/day may be excessive. As boron appears to have some beneficial nutrient value, Nielsen (1992) also recommended a total daily boron intake of 1 mg to avoid boron deficiency. The RfD would appear to give an adequate margin of safety below, as well as above (USEPA-IRIS 2004). USEPA-IRIS commented that "Confidence in the principal development 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 database is high due to the existence of several subchronic studies, as well as an adequate reproductive and developmental toxicology data. High confidence in the RfD follows."

Australia: The Therapeutic Goods Administration (TGA) has licensed 14 oral boron-containing OTC supplements providing doses of less than or equal to 3 mg boron/day, primarily in combination with calcium, magnesium and vitamin D in products to help treat symptoms of osteoporosis, help bone remineralization, and help repair connective tissue. Authorized products have specific structure-function claims such as:

- "Boron is important for bone metabolism and the calcification of bones. It affects calcium, magnesium, and phosphorus levels";
- "Boron and vitamin D facilitate the utilisation of calcium";
- "Boron is a trace mineral involved with the efficient absorption of calcium in the body";
- "Calcium plus minerals such as boron and magnesium for optimum bone mineralization".

There was no cautionary labelling specific to boron other than that the products are for adults only (Australian Register of Therapeutic Goods URL: http://www.tga.gov.au/docs/html/artg.htm; Australian web site advertisements for authorized products cited in the Registry; personal communication from TGA to the NHPD, February 2007).

European Union: The European Food Safety Authority (2004) set a UL of 10 mg/person/day for adults and stated that on the basis of safety boric acid and sodium borate are suitable for use in foods for particular nutritional purposes, food supplements and foods intended for the general population providing UL is not exceeded.

United Kingdom: Boron is present in a number of multi-vitamin and mineral food supplements at levels up to 10 mg, but not in licensed medicines in the UK (EFSA 2004). The safe upper level for daily consumption for a lifetime was determined as 9.6 mg for a 60 kg adult based on a NOAEL of 9.6 mg/kg bw/day (Price *et al.* 1996a), with an inter-species variation (UF) factor x10 and inter-individual variation factor in humans x6 (EGVM 2003). Maximum estimated intake was 14 mg/day, including dietary 97.5 percentile 2.6 mg/day, water 0.6 mg/day (WHO-IPCS 1998), supplement 10 mg/day, cosmetic and consumer products 0.47 mg/day. Recently, the Scientific Panel on Dietetic Products, Nutrition and Allergies (2004) established Tolerable Upper Limit values for boron intake ranging from 3-10 mg/person/day, depending on age category (EFSA 2004). They state that although boron intake from food and water in the EU are below the UL, the consumption of some supplements containing boron (up to 10 mg/day) may

lead to intakes which exceed the UL. Therefore, intake values from food, water and consumer products (estimated to be up to 3.7 mg boron/day) were subtracted to provide a recommended limit of 6 mg/day for supplemental intake (EGVM 2003).

Singapore: The EGVM (2003) recommendation has been adopted (personal communication from the Singapore Health Authority to the NHPD, February 2007).

Switzerland: In 1994 the Swiss Authority questioned the risk/benefit ratio of boron and its salts. There are no approved OTC products including vitamin and mineral supplements registered in Switzerland which contain boron (personal communication from Swissmedic to the NHPD, February 2007).

World Health Organization: In its International Programme on Chemical Safety (1998), the WHO recommended a Tolerable Intake (TI) of 0.4 mg/kg bw/day for humans, which is equal to 28 mg/day for a 70 kg human adult. This TI was based on the NOAEL of 9.6 mg/kg bw/day from the rat developmental study (Price *et al.* 1996a), and a total UF of 25. The interspecies UF was reduced due to similarities in pharmacokinetics between rats and humans. Here are recommendations for applying this TI:

- Water and food guideline values should be based on the TI provided by this document;
- The TI should be applied with the understanding that boron may provide a physiological benefit for human health;
- It should be recognized in applying standards that boron is essential for some constituents of the environment (e.g. boron is an essential micronutrient for higher plants);
- Dietary supplements that exceed the TI should be avoided.

Setting Dosage Limits for Boron in Oral Natural Health Products

No new toxicity studies have been published since the DRI UL values were established, but the recent availability of unpublished toxicological evidence that may not have been available when Health Canada and the Institute of Medicine set the ULs provides a rationale for revisiting regulatory limitations on the dosage of boron permissible in oral natural health products.

The NHPD has employed an Uncertainty Factor approach to the risk assessment rather than a full benefit/risk approach due to the difficulties in establishing quantitatively levels at which specific benefits of boron can be shown, despite the evidence from deficiency studies that boron does play a beneficial role in human physiology. Given that boron is trace mineral that may appear in multivitamin-multimineral supplements taken on a daily basis or in products with a specific therapeutic purpose should convincing supporting

evidence be provided with the Product Licence Application, the NHPD has set a lower Chronic Reference Dose (cRfD) and a higher maximum therapeutic dose, both calculated based on the same critical study (Price *et al.* 1996a) as was used by all other reputable international regulatory authorities studied.

A Chronic Reference Dose is an estimate of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. An Acceptable Daily Intake is the amount of a chemical a person can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering deleterious effects (USEPA-IRIS 2007).

For boron as a trace mineral without specific associated health claims but as one medicinal ingredient of multivitamin-multimineral natural health products consumed on a daily basis, the NHPD has used the same UF of 1000 as was used by the Pest Management Regulatory Agency in setting their Chronic Reference Dose. This UF includes the default x10 safety factor for interspecies and default x10 safety factor for intraspecies variation, plus a x10 safety factor to account for any possible fetal developmental and male and female reproductive toxicities. This default UF is used as a maximum value for the worst case scenario since multivitamin-multimineral natural health products are consumed on a daily basis over many years. This is an extremely conservative approach to risk mitigation given that all other international authorities that have set tolerance limits or acceptable daily intake levels have chosen to reduce the UF by either reducing the interspecies factor or intraspecies factor based on the evidence of similarities in pharmacokinetics.

The NHPD cRfD for boron is calculated as follows:

> 9.6 mg/kg bw/day / 1000 UF = 0.01 mg/kg bw/day x 70 kg reference body weight = 0.7 mg/day.

Natural health products with boron indicated for use as a trace mineral in multivitamin-multimineral preparations may be authorized to have health claims that are general (e.g. for the maintenance of good health) or with more specific claims related to other medicinal ingredients, but no specific health claim will be authorized to be associated with the boron content, in the absence of specific supporting evidence for safety and efficacy. These products will also be limited to “Adults only” but products providing less than or equal to 700 µg/day of boron will not require any additional cautionary labelling.

Since the Australian Therapeutic Goods Administration has authorized boron-containing health products with specific health claims related to bone mineralization, the NHPD anticipates that product licence applicants will be submitting evidence in support of such

claims to be on natural health products marketed in Canada. To set a safe dosage maximum for these therapeutic purposes, the NHPD has calculated a maximum Acceptable Daily Intake (ADI) value for all sources of boron exposure, based on the NOAEL of 9.6 mg/kg bw/day and a UF of 100, including the default x10 safety factor for interspecies and default x10 safety factor for intraspecies variation but not requiring the additional x10 safety factor as these products will be intended for older adults. Note that the UF of 100 is still much more conservative with respect to risk mitigation than is used by any other international jurisdiction for boron intake limitation. Using the reference body weight of 70 kg, the ADI will be:

> 9.6 mg/kg bw/day /100 = 0.096 mg/kg bw/day x 70 kg reference body weight = 6.72 mg/day.

The maximum permissible dose (in the absence of new evidence conclusively demonstrating safety at a higher dose) for boron in oral natural health products for a 70 kg Canadian adult must make allowance for boron intake from food and water (as recommended by EGVM 2003), so it is calculated as the ADI minus the 95th percentile of the dietary intake of 2.5 mg/day and water exposure of 0.86 mg/day:

> 6.72 mg/day - 2.5 mg/day - 0.86 mg/day = 3.36 mg/day.

This value closely corresponds to the maximum dosage permitted for boron in oral health products by the Australian Therapeutic Goods Administration, the jurisdiction with a regulatory environment most similar to Canada's.

At the maximum permissible dose of 3.36 mg for boron in oral therapeutic natural health products, the following conditions of use will apply:

- No specific health claim associated with the boron content in the absence of specific supporting evidence for safety and efficacy;
- Adults only;
- Contraindicated in pregnancy and breastfeeding;
- Caution to consult with a health care practitioner prior to use in the case of an estrogen-dependent cancer.

Please note that the maximum permissible doses for boron in oral natural health products are not recommended intake values. The purpose of these dosage limits is to mitigate any risks of toxicity. A natural health product with a quantity of boron per unit dose at or below this maximum supplement level will not automatically receive market authorization. It is the applicant's responsibility to prove the safety, efficacy, and quality of each particular product with sufficient scientific and clinical evidence.

With respect to non-compliant (e.g. unregistered) natural health products, those containing boron are considered to be in Product Category Priority 1 for compliance (Health Canada 2006), meaning that any boron-containing natural health product that did not have a Product Licence Application submitted to NHPD by June 1, 2004, is subject to targeted compliance action by the Health Products and Food Branch Inspectorate in accordance with their Compliance and Enforcement Policy 0001 (Health Canada 2005).

REFERENCES

Allen BC, Strong PL, Price CJ, Hubbard SA, Datson GP. 1996. Benchmark dose analysis of developmental toxicity in rats exposed to boric acid. *Fund. Appl. Toxicol.* 32:194-204.

Armstrong TA, Spears JW, Crenshwa TD, Nielsen FH. 2000. Boron supplementation of a semipurified diet for weanling pigs improves feed efficiency and bone strength characteristics and alters plasma lipid metabolites. *J. Nutr.* 130:2575-2581.

Barranco WT, Eckhert CD. 2004. Boric acid inhibits human prostate cancer cell proliferation. *Cancer Lett*. 8;216(1):21-29.

Benderdour M, Bui-Van T, Dicko A, Belleville F. 1998. In vivo and in vitro effects of boron and boronated compounds. *J. Trace Elem. Med. Biol.* 12:2-7.

Benson WH, Berge WJ, Durough HW. 1984. Absence of mutagenic activity of sodium borate (borax) and boric acid in the salmonella preincubation test. *Environ. Toxicol. Chem.* 3:209.

Chapin RE, Ku WW, Kenney MA, McCoy H, Gladen B, Wine RN, Wilson R, Elwell MR. 1997. The effects of dietary boron on bone strength in rats. *Fund. Appl. Toxicol.* 35:205-215.

Cöl M, Cöl C. 2003. Environmental boron contamination in waters of Hisarcik area in the Kutahya Province of Turkey. *Food Chem. Toxicol.* 41:1417-1420.

Coughlin JR, Nielsen FH. 1999. Advances in boron essentiality research: Symposium summary. In: *New Aspects of Trace Element Research*, Abdulla M, Bost M, Gamon S, Arnaud P, Chazot G (eds.). Smith-Gordon, London, pp. 33-41.

Cui Y, Winton MI, Zhang ZF, Rainey C, Marshall J, De Kernion JB, Eckhert CD. 2004. Dietary boron intake and prostate cancer risk. *Oncol. Rep.* 11:887-892.

Culver BD, Hubbard SA. 1996. Inorganic boron health effects in humans: an aid to risk assessment and clinical judgement. *J. Trace Elem. Exp. Med.* 9:175-184.

Devirian TA, Volpe SL. 2003. The physiological effects of dietary boron. *Crit. Rev. Food Sci. Nutr.* 43(2):219-31.

Dieter MP. 1994. Toxicity and carcinogenicity studies of boric acid in male and female B6C3F1 mice. *Environ. Health Perspect.* 1994 Nov.;102 Suppl. 7:93-97.

Dixon RL, Lee IP, Sherins RJ. 1976. Methods to assess reproductive effects of environmental chemicals: Studies of cadmium and boron administered orally. *Environ. Health Perspect.* 13:59.

ECETOC: European Centre for Ecotoxicology and Toxicology of Chemicals. 1994. Reproductive and general toxicology of some inorganic borates and risk assessment for human beings. Technical Report No. 65. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

Eckhert CD. 1998. Boron stimulated embryonic trout growth. *J. Nutr.* 128:2488-2493.

EFSA: European Food Safety Authority. 2004. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Boron (Sodium Borate and Boric Acid). 80:1-22.

EGVM: Expert Group on Vitamins and Minerals. 2003. Safe upper levels for vitamins and minerals. Food Standards Agency. United Kingdom. URL: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf accessed 2007-02-05.

Ellenhorn MJ. 1997. Ellenhorn's Medical Toxicology: Diagnoses and Treatment of Human Poisoning 2nd ed. Baltimore MD: Williams & Wilkins.

Fang W, Wu P, Hu R, Huang Z. 2003. Environmental Se-Mo-B deficiency and its possible effects on crops and Keshan-Beck disease (KBD) in the Chousang area, Yao County, Shaanxi Province, China. *Environ. Geochem. Health* 25:267-80.

Fort DJ, Propst TL, Stover EL, Strong PL, Murray FJ. 1998. Adverse reproductive and developmental effects in Xenopus from insufficient boron. *Biol. Trace Elem. Res.* 66:237-259.

Fort DJ, Stover EL, Strong PL, Murray FJ, Keen CL. 1999. Chronic feeding of a low boron diet adversely affects reproduction and development in Xenopus laevis. *J. Nutr.* 129:2055-2060.

Gallardo-Williams MT, Chapin RE, King PE, Moser GJ, Goldsworthy TL, Morrison JP, Maronpot RR. 2004. Boron supplementation inhibits the growth and local expression of IGF-1 in Human Prostate Adenocarcinoma (LNCaP) tumors in nude mice. *Toxicol. Pathol.* 32:73-78.

Hamilton EI, Minski MJ. 1973. Abundance of the chemical elements in man's diet and possible relations with environmental factors. *Sci. Total Environ.* 1:375.

Health Canada. 1991. Boron. Healthy Environments & Consumer Safety Branch, Safe Environments Programme, Water Quality & Health Bureau. URL: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/water-eau/doc-sup-appui/boron-bore/boron-bore_e.pdf, accessed 2007-04-09, 7 pp.

Health Canada. 2005. Health Products and Food Branch Inspectorate Compliance and Enforcement Policy POL-0001, Version 2. URL: http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/pol/pol_1_e.html accessed 2006-04-24.

Health Canada. 2006. Compliance Policy for Natural Health Products. URL: http://hc-sc.gc.ca/dhp-mps/prodnatur/legislation/pol/compli-conform/complian-conform_pol_e.html accessed 2006-04-24.

Heindel JJ, Price CJ, Field EA, Marr MC, Myers CB, Morrissey RE, Schwetz BA. 1992. Developmental toxicity of boric acid in mice and rats. *Fundam. Appl. Toxicol.* 18:266-77.

Hunt CD. 1996. Biochemical effects of physiological amounts of dietary boron. *J. Trace Elem. Exp. Med.* 9:185-213.

Hunt CD, Friel JK, Johnson LK. 2004. Boron concentrations in milk from mothers of full-term and premature infants. *Am. J. Clin. Nutr.* 80:1327-1333.

Hunt CD, Meacham SL. 2001. Aluminum, boron, calcium, copper, iron, magnesium, manganese, molybdenum, phosphorus, potassium, sodium, and zinc: concentrations in common western foods and estimated daily intakes by infants; toddlers; and male and female adolescents, adults, and seniors in the United States. *J. Am. Diet. Assoc.* 101:1058-1060.

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

Institute of Medicine. 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press.

Jansen JA, Andersen J, Schou JS. 1984a. Boric acid single dose pharmacokinetics after intravenous administration to man. *Arch. Toxicol.* 55:64-67.

Jansen JA, Schou JS, Aggerbeck A. 1984b. Gastro-intestinal absorption and in vitro release of boric acid from water-emulsifying ointments. *Food Chem. Toxicol.* 22:49-53.

Ku WW. Chapin RE. Wine RN. 1993. Testicular toxicity of boric acid relationship of dose to lesion development and recovery in the F344 rat. *Reprod. Toxicol.* 7:305-319.

Lanoue L, Taubeneck MW, Muniz J, Hanna LA, Strong PL, Murray FJ, Nielsen FH, Hunt CD, Keen CL 1998. Assessing the effects of low boron diets on embryonic and fetal development in rodents using in vitro and in vivo model systems. *Bio. Trace Elem. Res.* 66:271-298.

Lee IP, Sherins RJ, Dixon RL. 1978. Evidence of germinal aplasia in male rats by environmental exposure to boron. *Toxicol. Appl. Pharmacol.* 45:577.

Litovitz TL, Klein-Schwartz W, Oderda GM, Schmitz BF. 1988. Clinical manifestations of toxicity in a series of 784 boric acid ingestions. *Am. J. Emerg. Med.* 6:209-213.

Miljkovic D, Miljkovic N, McCarty MF. 2004 Up-regulatory impact of boron on vitamin D function -- does it reflect inhibition of 24-hydroxylase? *Med. Hypoth.* 63(6):1054-6.

Moore JA, and Expert Scientific Committee. 1997. An assessment of boric acid and borax using the IEHR evaluative process for assessing human developmental and reproductive toxicity of agents. *Reprod. Toxicol.* 11:123-160.

Mortier R, Vandecasteele C, Hoste J, den Hartog F. 1986. Determination of boron in magnesium oxide by charged particle activation analysis. *J. Radioanal. Nucl. Chem.* 105(1): 47-56.

Murray FJ. 1995. A human health risk assessment of boron (boric acid and borax) in drinking water. *Res. Tox. Pharm.* 22: 221-230.

Murray FJ. 1998. A comparative review of the pharmacokinetics of boric acid in rodents and human. *Biol. Trace Elem. Res.* 66:331-341.

Murray FJ, Anderson ME. 2001. Data-derived uncertainty factors: boric acid (BA) as a case study. *Hum. Ecol. Risk Assess.* 7(1): 125-138.

Naghii MR, Samman S. 1997. The effect of boron supplementation on its urinary excretion and selected cardiovascular risk factors in healthy male subjects. *Biol. Trace Elem. Res.* 56: 273-286.

National Toxicology Program. 1987. Toxicology and carcinogenesis studies of boric acid (CAS No. 10043-35-3) in B6C3F1 mice (feed studies). NTP Technical Report Series No. 324, Research Triangle Park, NC. URL: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr324.pdf accessed 2006-04-24.

Newnham RE. 1991. Agricultural practices affect arthritis. *Nutr. Health* 7(2):89-100.

Newnham RE. 1994. Essentiality of boron for healthy bones and joints. *Environ. Health Perspect.* 102(Suppl. 7):83-85.

Nielsen FH. 1986. Other elements. In: *Trace Elements in Human and Animal Nutrition,* Vol. 2, 5th ed. Mertz W (ed.). Academic Press, Orlando, FL. p. 415.

Nielsen. 1989. Dietary boron affects variables associated with copper metabolism in humans. "6th international Trace Element symposium, 1989 AS, B, Br, Co, Cr, F, Fe, Mn, Ni, Sb, Sc, Si, Sn and other trace elements" Jena: Friedrich-Schiller-Universität, pp. 1106-1111.

Nielsen FH. 1992. Facts and fallacies about boron. *Nutr. Today* 27:6-12.

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

Nielsen FH. 1998. The justification for providing dietary guidance for the nutritional intake of boron. *Biol. Trace Elem. Res.* 66:319-330.

Nielsen FH. 2004a. Dietary fat composition modifies the effect of boron on bone characteristics and plasma lipids in rats. *Biofactors* 20:161-171.

Nielsen FH. 2004b. The alteration of magnesium, calcium and phosphorus metabolism by dietary magnesium deprivation in postmenopausal women is not affected by dietary boron deprivation. *Magnesium Res.* 17(3):197-210.

Nielsen FH, Gallagher SK, Johnson LK, Nielsen EJ. 1992. Boron enhances and mimics some effects of estrogen therapy in postmenopausal women. *J. Trace Elem. Exp. Med.* 5:237-246.

Nielsen FH, Hunt CD, Mullen LM, Hunt JR. 1987. Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women. *FASEB J.* 1:394-397.

Nielsen FH, Mullen LM, Gallagher SK. 1990. Effect of boron depletion and repletion on blood indicators of calcium status in humans fed a magnesium–low diet. *J. Trace Elem. Exp. Med.* 3:45-54.

Nielsen FH, Mullen LM, Nielsen EJ. 1991. Dietary boron affects blood cell counts and haemoglobin concentrations in humans. *J. Trace Elem. Exp. Med.* 4:211-213.

Nielsen FH, Penland JG. 1999. Boron supplementation of peri-menopausal women affects boron metabolism and indicies associated with macromineral metabolism, hormonal status and immune function. *J. Trace Elem. Exp. Med.* 12:251-261.

Pahl MV, Culver BD, Strong PL, Murray FJ, Vaziri ND. 2001. The effect of pregnancy on renal clearance of boron in humans: a study based on normal dietary intake of boron. *Toxicol. Sci.* 60:252-256.

Pahl M, Culver D, Vaziri ND. 2005. Boron and the Kidney. *J. Ren. Nutr.* 15:362-370.

Peng X, Lingxia Z, Schrauzer GN, Xiong G. 2000. Selenium, boron, and germanium deficiency in the etiology of Kashin-Beck disease. *Biol. Trace Elem. Res.* 77:193-197.

Penland JG. 1994. Dietary boron, brain function, and cognitive performance. *Environ. Health Perspect.* 102 (Suppl. 7):65-72.

Penland JG. 1998. The importance of boron nutrition for brain and psychological function. *Biol. Trace Elem. Res.* 66:299-317.

PMRA: Pest Management Regulatory Agency. 2003. Toxicology re-evaluation of elemental boron. Health Canada Internal Memorandum from Lauri Stachiw to Connie Moase. August, 2003, updated September, 2004.

PQ Corporation. 2007. Magnesium Sulfate – Products and Specifications. URL: http://www.pqcorp.com/productlines/MagnesiumSulfateSpecs.asp accessed 2007-02-24.

Price CJ, Marr MC, Myers CB, Seely JC, Heindel JJ, Schwartz A. 1996b. Developmental toxicity of boric acid in rabbits. *Fund. Appl. Toxicol.* 34:176-187.

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

Rainey CJ, Nyquist LA, Christensen RE, Strong PL, Culver BD, Coughlin JR. 1999. Daily boron intake from the American diet. *J. Am. Diet. Assn*. 99(3): 335-340.

Rohm and Haas. 2007. Brine: boron removal from $MgCl_2$ and NaCl. URL: http://www.rohmhaas.com/ionexchange/IP/boron.html accessed 2007-02-24.

Rowe RI, Eckhert CD. 1999. Boron is required for zebrafish embryogenesis. *J. Exp. Biol.* 202:1649-1654.

Samman S, Naghii MR, Lyons Wall PM, Verus AP. 1998. The nutritional and metabolic effects of boron in humans and animals. *Bio. Trace Elem. Res.* 66:227-235.

Sayli BS, Tuccar E, Elhan AH. 1998. An assessment of fertility in boron-exposed Turkish subpopulations. *Reprod. Toxicol.* 12:297-304.

Schou RS, Jansen JA, Aggerbeck B. 1984. Human pharmacokinetics and safety of boric acid. *Arch. Toxicol.* Suppl. 7:232-235.

Siegel E, Wason S. 1986. Boric acid toxicity. *Pediatr. Clin. North Am.* 33:363.

USEPA-IRIS: United States Environmental Protection Agency – Integrated Risk Information System. 2004. Toxicological review of boron and compounds. U.S. Environmental Protection Agency. URL: http://www.epa.gov/iris/toxreviews/0410-tr.pdf accessed 2007-04-09.

USEPA-IRIS: United States Environmental Protection Agency – Integrated Risk Information System. 2007. Glossary of IRIS Terms. URL: http://www.epa.gov/iris/gloss8.htm accessed 2007-06-21.

Usuda K, Kono K, Iguchi K, Nishiura K, Miyata K, Shimahara M, Konda T, Hashiguchi N, Senda J. 1996. Hemodialysis effect on serum boron level in the patients with long term hemodialysis. *Sci. Total Environ.* 193:283-290.

Weir RJ, Fisher RS. 1972. Toxicologic studies on borax and boric acid. *Toxicol. Appl. Pharmacol.* 23(3):351-64.

WHO-IPCS: United Nations Environment Programme/ International Labour Organisation/ World Health Organization. International Programme on Chemical Safety. 1998. Environmental Health Criteria 204. Boron. URL: http://www.inchem.org/documents/ehc/ehc/ehc204.htm#PartNumber:1 accessed 2005-01-19.

Zittermann A. 2003. Vitamin D in preventive medicine: are we ignoring the evidence? *Br. J. Nutr*. 89(5):552-72.

Zook EG, Lehmann J. 1965. Total diet study. Content of ten minerals-aluminum, calcium, phosphorus, sodium, potassium, boron, copper, iron, manganese and magnesium. *J. Assoc. Off. Agric. Chem.* 48:850.