Submission for Boron

Part A
1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine.

Boron (including boric acid, H_3BO_3, and borax, $Na_2B_4O_7$).

2. Proprietary name(s).

Not applicable.

3. Name of the company / organisation / individual requesting a reclassification.

Not applicable. This request is made on behalf of the natural health products industry.

4. Dose form(s) and strength(s) for which a change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

5. Pack size and other qualifications.

Not applicable. This request is made on behalf of the natural health products industry.

6. Indications for which change is sought.

Not applicable. This request is made on behalf of the natural health products industry.

7. Present classification of the medicine.

The classification of Boron was last reviewed by the Medicines Classification Committee in 2007.
At the present time, boron (including boric acid and borax) is:

- Unscheduled when in products for internal use containing 6 milligrams or less per recommended daily dose
- Unscheduled when in products for dermal use other than paediatric use in medicines containing 0.35% or less
- Unscheduled when present as an excipient
- A prescription medicine except in the above circumstances.

8. Classification sought.

It is proposed that the classification of boron is changed to:

- Unscheduled when in products for internal use containing **9 milligrams** or less per recommended daily dose
- Unscheduled when in products for dermal use other than paediatric use in medicines containing 0.35% or less
- Unscheduled when present as an excipient

- Prescription medicine except in the above circumstances.

The Committee is also asked to consider the toxicity level of 5 mg/kg/day (250 mg for a 70 kg person) cited by Osiecki (2014), and the toxicity level of 55 mg/kg/day (3850 mg for a 70 kg person) cited by the Alternative Medicine Review (2004) and determine an appropriate level above the requested 9 mg limit that could be applied.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Australia
Boron is:

- Unscheduled when in products for internal use containing 6 milligrams or less per recommended daily dose
- Unscheduled when in products for dermal use other than paediatric use in medicines containing 0.35% or less
- Unscheduled when present as an excipient
- Prescription medicine except in the above circumstances

Canada
Boric acid and salts are unscheduled in drugs [medicines] except in preparations for systemic use or ophthalmic preparations containing 2% or more.

No warning statements are required by Health Canada for natural health products containing boron.

UK
Borax is unscheduled for all preparations containing less than 5% (except ophthalmic preparations).
Boric acid is unscheduled in products for external use where the maximum strength is 2.5%.

Boron and salts/esters are not mentioned in the UK schedules.

10. Extent of usage in New Zealand and elsewhere (eg sales volumes) and dates of original consent to distribute.

No information was provided by either applicant.

11. Labelling or draft labelling for the proposed new presentation(s).

Not applicable.

12. Proposed warning statements if applicable.

No warning statements are considered to be necessary.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

Manufacturers of current dietary supplement-type products will likely increase the quantity of boron or boron salts in their products. It should be noted that all dietary supplement products

will be regulated under the NHP Bill. When the NHP Bill is passed, natural health products will have to meet a Code of Manufacturing Practice.

Medicines containing boron, boric acid or borax

The only medicines currently approved on the New Zealand market that contain Boron (or its salts or esters), boric acid or borax as an active ingredient are eye drops.
These will not be affected by the requested change since products applied to the eye are not allowed to be natural health products.

Part B Reasons for requesting classification change including benefit-risk analysis. This section should be supported by the following:

1. A statement of the benefits to both the consumer and to the public expected from the proposed change.

Neither applicant provided a statement of benefit but it can be assumed that increasing the limit would allow a wider range of natural health products to be made available.

Multi-ingredient supplements such as trace elements and essential nutrient formulations are usually taken to complement dietary intake of essential vitamins and minerals. Such products are generally regarded as dietary supplements.

At the present time, under the current Dietary Supplements Regulations regime, therapeutic claims are not permitted for dietary supplements. This creates a peculiar situation where, for example, iron supplements are recognised to aid in the treatment of iron deficiency and iron deficiency anaemia, and are taken for these purposes, yet such products cannot provide advice on their labels on how they should be used. The NHP Bill is intended to address this situation.

When the NHP Act comes into effect, certain health benefits will be able to be claimed for allowed health conditions, provided the manufacturer of the natural health product holds evidence to support the claim(s) being made. For example, iron deficiency anaemia is one of the allowed conditions permitted by the NHP Bill. Similarly, a claim for enhancing cognition, or for management of Candida albicans yeast infection with boron could be allowed if there was sufficient evidence.

The clear benefit of allowing the requested change is that it will enable easier implementation of the NHP system by allowing the essential vitamin or mineral to be present in effective quantities or in effective doses in natural health products.

Orally, boron is usually promoted for bone health, treating osteoarthritis, as an aid for building muscles and increasing testosterone levels, and for enhancing cognitive function and fine motor skills. A daily dose of 6 mg – 9 mg has been recommended for alleviating the symptoms of arthritis (Hechtmann 2012).

2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk.

The main concern over boron is boron toxicity. Various Upper Levels (UL) and toxicity levels have been cited in various publications, and there does not appear to be generally agreed limit. Orally, boron appears to be of low toxicity. In fact, borates have been widely used as food preservatives for many decades.

The following toxicity data were obtained from documents of the US Environmental Protection Agency, and the Center for Disease Control.

A review of 784 accidental human poisonings from 10 - 88 grams of boric acid reported no fatalities, with 88% of cases being asymptomatic, meaning they did not notice anything. However, gastrointestinal, cardiovascular, hepatic, renal, and central nervous system effects, dermatitis, erythema, and death have occasionally been observed in some infants, children and adults exposed to more than 84 mg boron/kg, corresponding to more than 40 grams of borax for 60 kg of body weight (EPA and CDC).

Animal studies have identified reproductive toxicity as the most sensitive effects of boron ingestion. Exposure of rats, mice, and dogs for several weeks showed some damage to the testes and sperm at doses of more than 26 mg boron/kg which corresponds to 15 grams of borax/day for 60 kg body weight. Most at risk is the developing foetus, and in the studied animals rats were most affected. In one study slight reductions in the foetal body weight were already found at 13.7 mg boron/kg/day used during pregnancy. The no effect dose during pregnancy was set at less than 13.7 mg/kg/day corresponding to about 7 grams of borax per day for 60 kg body weight. With an added safety factor a no effect value of 9.6 mg boron/kg/day was calculated corresponding to 5 grams of borax for 60 kg. However, a rat study lasting for 3 generations found no reproductive toxicity or effect on the parents or offspring at 30 mg boron/kg/day. This dose corresponds to 17 g of borax ingested for a body weight of 60 kg. In another 3-generation study no problem was found at 17.5 mg boron/kg/day, corresponding to 9 grams of borax/60 kg while the next higher tested borax dose of 58.5 mg/kg/day, corresponding to 30 grams of borax/60 kg, resulted in infertility. Therefore we can assume that the safe reproductive dose is below 20 grams/60 kg/day (EPA and CDC).

Human studies of the possible association between impaired fertility and high boron levels in water, soil and dust in a Turkish populations, and boron mining and processing workers, found no effect. One study even reported elevated fertility rates in borax production workers as compared to the U.S. national average (EPA and CDC).

Children who have ingested 5 grams or more of borates can have persistent nausea, vomiting, and diarrhoea leading to acute dehydration, shock, and coma. Adults who have ingested 15-20 grams of borate can exhibit nausea, vomiting, diarrhoea, epigastric pain, hematemesis, and a blue-green discoloration of faeces and vomit. Poisoning symptoms in adults and children may also include skin erythema, desquamation, exfoliation, hyperexcitability, irritability, tremors, convulsions, weakness, lethargy, headaches, and depression (Ellenhorn et al. 1997).

The Ministry of Health's 2006 publication Nutrient Reference Values for Australia and New Zealand does not include recommended intakes for boron. It is assumed that this was unnecessary in relation to boron dietary intake despite boron deficiency in New Zealand soils (Te Ara Encyclopedia). The Institute of Medicine considers that the collective body of evidence has yet to establish a clear biological function for boron in humans. Therefore, neither an Estimated Average Requirement, Recommended Dietary Allowance, nor Adequate Intake was established for boron in the US (IOM 2001).

Recommendations for boron in various jurisdictions vary greatly. Some of these are:

Canada	0.7 mg / day (HC Dose information for complementary medicinal ingredients)
Canada	UL of 20 mg / day (HC Dietary Reference Intakes, 2010)
Australia	6 mg / day
New Zealand	6 mg / day (from Medicines schedule)
USA	UL 20 mg / day (suggested)
European Food Safety Authority	UL of 10 mg per person per day for adults.
WHO (1998)	Tolerable intake (TI) of 0.4 mg/kg bw/day (28 mg for a 70 kg person)
Osiecki (2014)	Toxicity level of 5 mg/kg bw/day (350 mg for a 70 kg person)
Alternative Medicine Review (2004)	Toxicity level of 55 mg/kg bw/day (3850 mg for a 70 kg person)

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated.

Not applicable.

4. Relevant comparative data for like compounds.

Not applicable.

5. Local data or special considerations relating to New Zealand.

Not applicable.

6. Interactions with other medicines.

It had been suggested by Shils et al (1994) that concomitant supplementation may increase oestrogen levels. Studies since have found contradictory results (Naghii and Saman, 1997; Naghii et al 2011).

7. Contraindications and precautions.

No information provided by the submitters.

8. Possible resistance.

Not applicable.

9. Adverse events - nature, frequency, etc.

Adverse reactions below 10 mg per day are unlikely. Chronic use of 1 gram daily of boric acid or 25 grams daily of boric tartrate has been reported to cause dermatitis, alopecia, anorexia, and indigestion (IOM 2002).

10. Potential for abuse or misuse.

Boron is not habit-forming or a drug of abuse. No abuse or misuse is foreseen.

References

Alternative Medicine Review 9(4): 434-437 (2004). Boron – Monograph.

Ellenhorn MJ, Schonwald S, Ordog G, Wasserberger J. (1997) Ellenhorn's Medical Toxicology: Diagnoses and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams & Wilkins.

EPA and CDC: http://www.atsdr.cdc.gov/toxprofiles/tp26-c2.pdf

European Food Safety Authority (EFSA), Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies. 2006. Tolerable Upper Intake Levels for Vitamins and Minerals. http://www.efsa.europa.eu/en/ndatopics/docs/ndatolerableuil.pdf

HC Dietary Reference Intakes 2010. http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-eng.pdf

HC Dose information for complementary medicinal ingredients. Accessed on 15 April 2016: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=multi_vitmin_suppl&lang=eng

Health Canada. Multi-Vitamin / Mineral Supplements Monographs (Under consultation). http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=multi_vitmin_suppl&lang=eng

Hechtmann, L. (2012). Clinical Naturopathic Medicine (Revised edition) NSW, Australia: Elsevier.

IOM (2001). Institute of Medicine (US) Panel on Micronutrients. Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. National Academies Press, 2001. Chapter 13

IOM (2002). Food and Nutrition Board, Institute of Medicine. 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, 2002. www.nap.edu/books/0309072794/html/

Naghii MR, et al. (2011). Comparative effects of daily and weekly boron supplementation on plasma steroid hormones and proinflammatory cytokines. J Trace Elem Med Biol.

Naghii MR1, 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.

Osiecki, H. (2014). The Nutrient Bible (9th Ed). Page 161-162. QLD Australia: Bioconcepts Publishing.

Shils M, Olson A, Shike M. (1994). Modern Nutrition in Health and Disease. 8th ed. Philadelphia, PA: Lea and Febiger.

Te Ara Encyclopedia - Boron. http://www.teara.govt.nz/en/1966/fertilisers-lime-and-trace-elements/page-11

WHO (1998). Environmental Health Criteria 204: Boron. International Programme on Chemical Safety. http://www.inchem.org/documents/ehc/ehc/ehc204.htm#SectionNumber:1.3