Proposed Re-evaluation Decision PRVD2012-03

Boric Acid and its Salts (Boron)

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Overview

What is the proposed Re-evaluation Decision ?

After a re-evaluation of the non-antisapstain uses of boric acid and its salts, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act,* is proposing continued registration of products containing boric acid and its salts in Canada. This re-evaluation includes the active ingredients boric acid, borax (pentahydrate), borax (disodium tetraborate decahydrate), disodium octaborate tetrahydrate and zinc borate, hereafter referred to as boron.

The antisapstain uses of boron were assessed separately. The results of the re-evaluation of the antisapstain uses of boron are presented in the Re-evaluation Decision Document RRD2004-08, *Re-evaluation of Antisapstain Use for 2-(thiocyanomethylthio) Benzothiazole (TCMTB), Copper-8-quinolinolate, Borax and Disodium Octaborate Tetrahydrate*. The wood joinery/millwork applications of boron will be assessed under a separate initiative by the PMRA.

An evaluation of available scientific information found that, under the proposed conditions of use:

- Most product types containing boron do not present unacceptable risks to human health or the environment when used according to revised label directions. As a condition of the continued registration for these particular boron uses, new risk-reduction measures are proposed to be included on the labels of certain products. Additional data are being requested as a result of this re-evaluation.

- Some uses of boron are being proposed for removal because the human health risks do not meet current standards. These uses are:

    - All dust/powder formulations for both commercial and domestic class products (including pressurized dust products).

    - All uses involving brush, trowel and/or putty knife application of the paste formulation for both commercial and domestic class products.

    - Uses involving brush application of the solution formulation for both commercial and domestic class products.

    - Uses of granular formulations involving application by pressure sprayer and seed spreader (commercial class products only).

This proposal affects all end-use products containing boron registered in Canada. Once the final re-evaluation decision is made, the registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for boron and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of boron.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *Pest Management Regulatory Agency Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Given the outcome of the human health risk assessments and a review of the chemistry of Canadian products, the PMRA is proposing a re-evaluation decision and appropriate risk-reduction measures for Canadian uses of boron. In this decision, the PMRA takes into account the Canadian use pattern and issues (for example, the federal Toxic Substances Management Policy [TSMP]).

For more details on the information presented in this overview, please refer to the Science Evaluation of this consultation document.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

What is boron?

The non-antisapstain uses of boron registered in Canada include the control of a broad range of insects and fungi in structures, wood and wood products. Zinc borate is registered for use as a wood composite preservative and as a material preservative for the manufacturing of paints, coatings, plastics and rubber. Boron inhibits reproduction of fungi by acting on the general metabolism, and act as a stomach poison in insects. Boron products are formulated as soluble powders, dusts or powders, pastes, granular formulations, pressurized products, solutions or solid rods. Boron products can be applied by a wide variety of application systems (for example crack and crevice treatment, dusting, broadcast spreading, aerosol or foam injection in drilled holes or openings, brush or roller, low pressure spraying, drops and baits, rod insertion, dip-diffusion, dip or spray, double vacuum system, bundle dipping, spray box system, flood coating and pressure treatment). Boron products can be applied by professional applicators or by homeowners.

Health Considerations

Can Approved Uses of Boron Affect Human Health?

Boron is unlikely to affect health when used according to the revised label directions.

Potential exposure to boron may occur while handling and applying the product or by entering treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for continued registration.

Boron is a known developmental and reproductive toxicant. The most sensitive endpoint that could result from short and longer term exposures to boron is an effect on the testes (small testicles, tubular atrophy, arrest of spermatogenesis), which was observed in all mammalian species examined (mouse, rat, and dog).

Due to the nature of these endpoints and their potential implications for the health of the young, extra protective factors were applied during the risk assessment to further reduce the allowable level of exposure to boron.

Residues in Food

Boron is not likely to pose dietary risks from food.

There are currently no registered food uses; as such a risk assessment for this scenario was not required.

Risks in Residential and Other Non-Occupational Environments

Residential and other non-occupational risks are not of concern for handlers for most uses of boron.

Most risk estimates associated with mixing, loading, and applying activities for boron reached the target Margin of Exposure (MOE) with the exception of dust/powder formulations when applied by a shaker can/squeeze bottle and for paste and solution formulations applied using a brush or trowel.

Residential risks for postapplication scenarios are not of concern for most uses of boron.

Most uses of boron are in areas that would not be frequented by persons and thus residential postapplication exposure is expected to be minimal. Indoor uses where boron is not placed in enclosed bait stations (for example open bait placement), do not reach the target MOE and therefore postapplication risks are of concern for these uses.

Occupational Risks from Handling Boron

Occupational risks to handlers are of concern for certain uses of boron.

Target MOEs for mixing, loading, and applying boron were reached for the following uses: enclosed bait stations; solid formulation; paste and solution formulations for open baiting; solution formulation while rolling or spraying; and granular formulation using a bellows-type duster/snuffer. All other assessed uses of boron (paste formulation applied by brush, trowel or putty knife; solution formulation by brush; dust/powder formulations; soluble powder formulation; pressurized dust formulation; and granular formulation using a pressure sprayer and/or a seed spreader) did not meet the target MOE and are of concern.

Occupational risks for postapplication scenarios are not of concern for most uses of boron.

Occupational postapplication risk assessments consider exposures to workers entering treated sites. Based on the current use pattern for boron, re-entry into treated sites is expected to be minimal for professional pest control operators.

Environmental Considerations

What Happens When Boron is Introduced Into the Environment?

An environmental risk assessment was not conducted on the boron use patterns described in this document as none of them result in significant environmental exposure. These uses include remedial treatment of wood utility poles and other wood structures. The exposure to the environment from these uses of boron is limited to a small area of soil in the immediate vicinity of the treated wood. Therefore, an environmental risk assessment is not required.

Proposed Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Additional Key Risk-Reduction Measures:

Human Health

Risk-reduction measures are being proposed to address potential risks identified in this assessment. These measures, in addition to those already identified on existing boron product labels, are designed to further protect human health. The following additional key risk-reduction measures are being proposed.

- The soluble powder formulation will be limited to use as a material preservative. Limitation on the amount handled per day as well as the use of additional personal protective equipment (PPE) or engineering controls will be required.

- Indoor uses where a product may be accessible to toddlers, children and pets will require enclosed bait stations.

The PMRA has assessed the available information and identified health risks of concern for certain uses of boron. Therefore, the PMRA is proposing to remove the following specific boron uses in Canada:

- All dust/powder formulations for both commercial and domestic class products (including pressurized dust products).

- All uses involving brush, trowel and/or putty knife application (paste formulation) for both commercial and domestic class products.

- Uses involving brush application of the solution formulation for both commercial and domestic class products.

- Uses of granular formulation involving application by pressure sprayer and seed spreader (commercial class products only).

What Additional Scientific Information is Being Requested?

Data are required as a condition of continued registration under section 12 of the *Pest Control Products Act*. The registrants of this active ingredient must provide these data or an acceptable scientific rationale to the PMRA within the timeline specified in the decision letter. Appendix I lists all data requirements.

Next Steps

Before making a final re-evaluation decision on boron, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision[2] document that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

Boric Acid and its Salts

1.0 Introduction

The non-antisapstain uses of boron registered in Canada include the control of a broad range of insects and fungi in structures, wood and wood products as well as a material preservative for the manufacturing of paints and coatings, plastics and rubber. Boron inhibits reproduction of fungi by acting on the general metabolism, and acts as a stomach poison in insects.

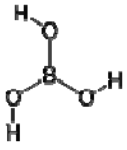
Following the re-evaluation announcement for boron, U.S Borax Inc., the registrant of the technical grade active ingredient and primary data provider in Canada, indicated its intention to provide continued support for all uses currently registered in Canada.

2.0 The Technical Grade Active Ingredients, their Properties and Uses

2.1 Boric Acid

2.1.1 Identity of the Active Substance

Active substance:	Boric (or boracic) acid
Function:	Insecticide, wood preservative
Chemical name:	
IUPAC:	Boric acid
CAS:	Boric acid (H_3BO_3)
CAS Number:	10043-35-3
Molecular Formula:	H_3BO_3
Molecular Mass:	61.83
Structural Formula:	



PCP Number:	18292
Purity of TGAI:	100% nominal

2.1.2 Identity of Relevant Impurities of Human Health or Environmental Concern

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including the Toxic Substances Management Policy (TSMP) Track 1 substances, are not expected to be present in the product.

2.1.3 Physicochemical Properties of Active Substance and Interpretation

Property	Result
Vapour pressure at 20°C	346 Pa
Ultraviolet (UV)/visible spectrum	The product has no UV chromophores
Solubility in water	Temperature (°C) — Solubility (%w) 0 — 2.52 20 — 4.72 25 — 5.78 100 — 27.53
n-Octanol–water partition coefficient	Not applicable for an inorganic compound
Dissociation constant	$K = 7.3 \times 10^{-10}$

2.2 Disodium Octaborate Tetrahydrate

2.2.1 The Active Substance and its Properties

Active substance:	Disodium octaborate tetrahydrate
Function:	Wood preservative
Chemical name:	
IUPAC:	Disodium octaborate tetrahydrate
CAS:	Boron sodium oxide ($B_8Na_2O_{13}$), tetrahydrate
CAS Number:	12280-03-4
Molecular Formula:	$Na_2B_8O_{13}•4H_2O$
Molecular Mass:	412.52
Structural Formula:	$Na_2O•4(B_2O_3)•4H_2O$
PCP Number:	24739
Purity of TGAI:	98% min.

2.2.2 Identity of Relevant Impurities of Human Health or Environmental Concern

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

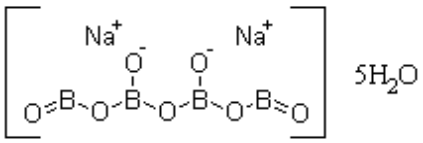
2.2.3 Physicochemical Properties of Active Substance and Interpretation

Property	Result
Vapour pressure	Not required for a salt
Ultraviolet (UV)/visible spectrum	The product has no UV chromophores
Solubility in water	Temperature (°C) / Solubility (%w) 0 / 2.4 20 / 9.5 50 / 32.0
n-Octanol–water partition coefficient	Not applicable for an inorganic compound
Dissociation constant	Not provided

2.3 Borax Pentahydrate

2.3.1 The active substance and its properties

Active substance: Sodium tetraborate (borax) pentahydrate
Function: Insecticide, material preservative, wood preservative
Chemical name:
IUPAC: Disodium tetraborate pentahydrate
CAS: Boron sodium oxide ($B_4Na_2O_7$), pentahydrate
CAS Number: 12179-04-3
Molecular Formula: $Na_2B_4O_7 \bullet 5H_2O$
Molecular Mass: 291.35
Structural Formula:



PCP Number: 19025
Purity of TGAI: 100% min.

2.3.2 Identity of Relevant Impurities of Human Health or Environmental Concern

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

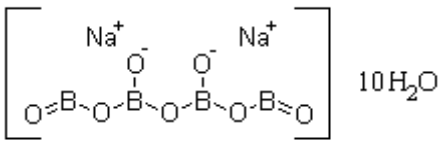
2.3.3 Physicochemical Properties of Active Substance and Interpretation

Property	Result
Vapour pressure	Not required for a salt
Ultraviolet (UV)/visible spectrum	The product has no UV chromophores
Solubility in water	Temperature (°C) % technical by wt. 0 1.52 20 3.59 25 4.43 100 50.13
n-Octanol–water partition coefficient	Not applicable for an inorganic compound
Dissociation constant	Not provided

2.4 Borax

2.4.1 The Active Substance and its Properties

Active substance: Borax
Function: Fungicide, herbicide, insecticide, wood preservative
Chemical name:
IUPAC: Disodium tetraborate decahydrate
CAS: Borax (B4Na2O7.10H2O)
CAS Number: 1303-96-4
Molecular Formula: $Na_2B_4O_7 \bullet 10H_2O$
Molecular Mass: 381.4
Structural Formula:



PCP Number: 18607
Purity of TGAI: 100% minimum

2.4.2 Identity of Relevant Impurities of Human Health or Environmental Concern

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.4.3 Physicochemical Properties of Active Substance and Interpretation

Property	Result
Vapour pressure	Not required for a salt
Ultraviolet (UV)/visible spectrum	The product has no UV chromophores
Solubility in water at 20°C	4.71 g/100 mL
n-Octanol–water partition coefficient	Not applicable for an inorganic compound
Dissociation constant	Not provided

2.5 Zinc Borate

2.5.1 The Active Substance and its Properties

Active substance: Zinc borate
Function: Material preservative
Chemical name:
IUPAC: Zinc borate $2ZnO•3B_2O_3•3.5H_2O$
CAS: Boron zinc oxide ($B_6Zn_2O_{11}$), hydrate (2:15)
CAS Number: 12447-61-9
Molecular Formula: $2ZnO•3B_2O_3•3.5H_2O$
Molecular Mass: 434.66
Structural Formula: $2ZnO•3B_2O_3•3.5H_2O$
PCP Number: 19027
Purity of TGAI: 100% minimum

2.5.2 Identity of Relevant Impurities of Human Health or Environmental Concern

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.5.3 Physicochemical Properties of Active Substance and Interpretation

Property	Result
Vapour pressure	Not required for a salt
Ultraviolet (UV)/visible spectrum	The product has no UV chromophores
Solubility in water	Virtually insoluble < 37.8°C, sparingly soluble at higher temperatures
n-Octanol–water partition coefficient	Not applicable for an inorganic compound
Dissociation constant	Not provided

2.6 Description of Registered Boron Uses

Appendix II lists all the boron products that are registered under the authority of the *Pest Control Products Act*. All non-antisapstain uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health risk assessments of boron.

3.0 Impact on Human and Animal Health

3.1 Hazard Identification

Borax, boric acid, disodium octaborate tetrahydrate, anhydrous borax and borax pentahydrate were considered to be toxicologically equivalent. Equivalency was based on a comparison of LD/LC_{50} values, NOAEL values, target organ toxicity, as well as metabolism studies, which showed inorganic borates were usually present as boric acid in the body. Thus, dose levels were standardized to boron equivalents.

The toxicology database for boron compounds is extensive, but dated. There are acute, short-term, long-term, reproductive, developmental and genotoxicity studies for borax and/or boric acid. As well, published studies done primarily with boric acid are also available. Although the majority of the studies do not meet current standards for pesticide testing, the overall information, with the addition of uncertainty factors, was considered adequate for conducting a human health risk assessment.

Metabolism of boron may not occur following oral administration because of the large amount of energy required to break the boron-oxygen bond. Borate compounds are usually present as boric acid in the body and are readily absorbed from the gastrointestinal tract. With oral dosing, appearance in the blood and tissues is rapid. In general, the plasma half-lives in rats range from 14-19 hours and in humans, 10-21 hours. However, significantly prolonged blood half-lives have been noted in rabbits that had damaged kidneys. Distribution, via passive diffusion, is uniform across the tissues, with a higher accumulation found in the bone and fat. The volume of distribution in the rat is 142 mL/100 g and in humans 104.7 mL/100g. Greater than 90% of boric acid is eliminated via the urine within 96 hours of administration and both pregnant and non-pregnant humans clear boron 3-4 times slower than the rat. However in the rat, bone levels of boron remain increased even at 32 weeks post exposure.

Acute toxicity data indicated that both borax and boric acid were of low toxicity via the oral route in rats and via the dermal route in rabbits. Boric acid was of moderate toxicity via the inhalation route of exposure in rats. In rabbits, borax was severely irritating to the eyes and non-irritating to the skin whereas boric acid was mildly irritating to the eyes and minimally irritating to the skin. No dermal sensitization studies were available for either compound.

Although most short-term toxicity studies were limited because of incomplete reporting, the primary toxic effect noted in all species (mouse, rat and dog) was on the testes (small testicles, tubular atrophy, arrest of spermatogenesis), with the dog being the most sensitive and the mouse the least sensitive species. There was a lack of detailed reporting on female reproductive organs. Effects at higher doses included mortality, decreased body weight gain, a general increase in clinical observations and effects on the skin. The dog also showed an increase in solid epithelial nests in the thyroid, which are considered to be pre-neoplastic lesions.

There were no adequate oncogenicity studies to fully assess the potential carcinogenic effects of boron. As with the short-term toxicity studies, the three chronic toxicity studies (two rat, one mouse) were considered supplemental because of insufficient data reporting. Neither the borax nor the boric acid long-term toxicity study in rats reported tumour data and, although the mouse study with boric acid did provide tumour data, only two dose levels were tested. In addition, low survival in male mice (60 and 42% for low and high dose, respectively) reduced the sensitivity of the study. The histopathological findings in female mice did not show a significant, dose-related increase in neoplasms. Boron compounds were classified by the USEPA in 1994 as Group D; not classifiable as to human carcinogenicity. There are no epidemiology studies showing that occupational or residential exposure to boron causes cancer. Genotoxicity studies using boric acid, including studies in bacteria, mammalian cells and mice in vivo, were negative.

Testicular toxicity was the primary effect noted in the long-term toxicity studies in dogs, rats and mice, which is consistent with the findings from short-term toxicity studies. As with short-term studies, the long-term studies lacked detailed reporting on female reproductive organs. In both of the two-year dog toxicity studies that were conducted (one with borax and the other with boric acid), testicular effects were noted at the highest dose tested. Since both studies were conducted at the same time, in the same laboratory, and used the same control group, combining the two studies was considered appropriate. As a result 5/7 dogs (n=8; one dog was excluded due to artifactual testicular distortion) had moderate to severe testicular atrophy, compared to 1/4 dogs

in the control that had a few foci in the testis at various stages of atrophy. Sperm analysis from two high dose animals for each compound indicated that 3/4 animals either could not produce sperm, or that sperm production was significantly diminished compared to the control.[3] Therefore, in contrast to the published article by Weir and Fisher (1972) that set a NOEL at the highest dose level, the PMRA has set a NOAEL for testicular atrophy at the mid-dose level (3.6 mg/kg bw/d), although recognizing that sperm analysis was not done on any dogs treated at the low- and mid-dose levels. As with the short-term studies, dogs treated for 2 years also showed a general increase in thyroid effects (primarily epithelial nests). In addition to the testicular effects (organ weight, atrophy of spermatogenic epithelium, decreased seminiferous tubules), the rat also showed chronic effects of decreased body-weight gain, hunched posture, respiratory involvement, and desquamation of pads and paws, while mice showed increased mortality and splenic lymphoid depletion.

Both the borax and boric acid reproduction toxicity studies in rats had a number of deficiencies. Provisional NOAELs were established for the parental generation, but reproductive NOAELs could not be determined due to the absence of information on clinical observations, organ weights and microscopic examinations. Furthermore, the fertility and lactation indices in the control animals for all generations were considerably lower than expected. Thus, interpretation of the results in the treated groups was limited. However, it was apparent that the primary target organs were the testis (atrophy) and ovary (congested, cystic), and no litters were produced by the high dose animals for either compound. When treated females were mated with control males, either no pups (boric acid) or very few pups (borax) were produced, indicating that exposure to these compounds resulted in decreased fertility in the female rat.

A reproduction toxicity study with boric acid in mice showed that mid-dose parental animals had decreases in fertility and body weight gain, and that the males also had lower testicular weights (absolute and relative), decreased sperm concentration and sperm and an increase in testicular atrophy and abnormal sperm. At the lowest dose, the F0 males had decreased sperm motility that did not carry over to the F_1 generation and the F_1 males had a reduction in epididymal sperm concentration. However, since there was no effect on fertility at this dose level, the effects in the males at the low dose were considered to be non-adverse. Mid-dose pups had decreased body weight gain, and at the high dose, F_1 litters were not produced. Cross-over mating of control animals with animals exposed to the mid-dose level, confirmed that the male was the predominantly affected sex in mice. In this study, only the low dose group was able to produce a second generation.

[3] Subsequent to this decision to combine the dog studies, an independent consultant (G. Smith), stated that the potential dose-effects within each of the dog studies need to be evaluated on an individual dog basis and treated groups should not be combined (see Annex I).

In a published study, Lee et al., (1978) reported that boron, at doses of ≥25 mg/kg bw when administered for ≥30 days to rats, caused a significant loss of germinal elements and a dose-related increase in testicular atrophy. Depletion of germ cells was complete after 60 days and this was associated with a significant increase in plasma follicle-stimulating hormone (FSH). Serial mating showed that the decrease in fertility was not associated with a change in copulatory behaviour. Another published study (Ku et al., 1993) reported that male rats, following short-term exposures to boric acid, had an increase in testosterone and serum FSH and luteinizing hormone (LH) levels.

Several developmental toxicity studies with boric acid in the rat showed sensitivity of the young. The following effects were noted in the foetuses, the incidences or severity of which increased with dose level: decreased foetal body weight, increased resorptions, cleft sterna, agenesis of rib XIII, short rib XIII, wavy ribs, enlarged lateral ventricles, cardiovascular defects, hydrocephaly (independent of foetal growth), short/curly tail, anophthalmia and microphthalmia. Increased incidences of variations were noted at all dose levels, whereas increased incidences of malformations were noted at the mid- and high-dose levels. A developmental NOAEL could not be established in this group of studies and all incidences of malformation occurred in the absence of maternal toxicity. A subsequent study established a developmental NOAEL at 9.6 mg/kg bw/d (LOAEL of 13.3 mg/kg bw/d), based on decreased body weight. Sensitivity of the young was also noted in the rabbit with boric acid as agenesis of the gallbladder at maternally non-toxic doses. At maternally toxic doses, increased resorptions and cardiovascular effects were also apparent in rabbits. There were no apparent effects on bone formation. Mice appeared to be less sensitive than rats or rabbits, showing rib variations similar to those observed in the rat, but in the presence of maternal toxicity.

According to Fail et al., (1998), reduced foetal growth noted in developmental studies probably results from a general inhibition of mitosis, while the rib malformations probably result from direct binding of boron to the bone tissue. Studies have shown that excessive feeding of boric acid to animals significantly inhibits the biosynthesis of DNA in liver, indicating anti-mitotic activity. Increased concentrations of RNA and protein in the same organs indicated that toxic quantities of boron interfere either with the enzymes involved in RNA and protein biosynthesis, or with RNAses and proteases (Dai et al., 1971).

Testicular Toxicity - Mode of Action

Despite the number of available studies, the mechanism of boron testicular toxicity remains unclear. Available data suggest an effect on Sertoli cells results in altered physiological control of sperm maturation and release (Fail et al., 1998). Ku and Chapin (1993, 1994) reported that testicular toxicity and any potential effects on FSH, LH and testosterone were not due to selective boron accumulation in the testis or brain/hypothalamus and that riboflavin deficiency was not involved. Boron showed no direct steroidogenic influence on isolated Leydig cells, supporting the hypothesis that boron testicular toxicity is not the result of a direct hormonal effect. Following nine weeks of exposure to boron, examination of sperm in rats showed that inhibited spermiation is not exclusively a high-dose effect and that it can occur at a lower boron concentration in the testis than levels associated with testicular atrophy (0.5-1 mM inhibits spermiation; 1-2 mM induces atrophy). The progression to atrophy was dose-dependent, with 52 mg/kg bw/d resulting in atrophy by week 9, whereas 68 mg/kg bw/d induced atrophy by

week 6. It was also reported that mildly inhibited spermiation can be identified only by histological examination, and that both inhibited spermiation and atrophy produced profound decreases in epididymal sperm count, which could affect fertility. During the post-treatment phase, recovery of spermiation was observed in animals that had inhibited spermiation only. However, once atrophy developed, the atrophy and inhibited spermiation was irreversible. The reason for lack of recovery is unknown, since it was clear that the spermatogonia were capable of dividing, yet they failed to mature. The gonadotropin response appeared to be intact; however, changes in the autocrine and paracrine interactions could not be ruled out. Impairment of recovery by covalent interactions was considered unlikely, since there was no appreciable tissue accumulation of boron (declined to background 72 h after cessation of exposure), there was no boron in the testicular tissue during recovery, and because boron interactions with biological molecules are reversible.

In summary, following continued dosing with boron, there is a disorganization of the normal ordered layering of the seminiferous epithelium, followed by germ cell sloughing and death, and finally, atrophy. In response to the atrophy, there is an increase in FSH and LH and either no effect on testosterone or a slight decrease. Testosterone levels appear to be dependent on the extent of disruption of homeostasis, but there are no studies that clearly outline the mechanism behind the hormonal changes. The study also showed that boron levels in bone were greater than those in blood and testes, and remained slightly elevated for 32 weeks after exposure.

Human Health

Dietary Intake: Boron is ubiquitous in the environment, it is a normal trace element in the diet and drinking water, and is present in dietary and nutritional supplements. A low level of boron in the human diet has not yet been proven essential. Therefore, a Recommended Dietary Intake value has not been established for boron. Previous workgroups have proposed Tolerable Upper Intake Levels (ULs), defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for most individuals, that range from 10-20 mg/day (EU Scientific Panel on Dietetic Products, Nutrition and Allergies, 2004: 0.15 mg/kg bw/day or 10 mg/day; NAS, 2001: 0.32 mg/kg bw/day or 20 mg/day). These are consistent with dietary reference doses established by other regulatory committees (0.2-0.4 mg/kg bw/day), all of which utilize decreased foetal body weight in a series of rat developmental studies as the primary endpoint of concern.

Published data indicate that the average boron consumption in Canadian women is 0.02 mg/kg bw/day (1.2 mg/day; Clarke and Gibson, 1988). According to Rainey et al., (2002), two 24-hour dietary recall interviews in the US resulted in the following average boron consumption: children 4-8 years = 0.80 ± 0.01 mg/day; males 14-18 years = 1.02 ± 0.04 mg/day; adult females = 1.0 ± 0.01 mg/day; and adult males = 1.28 ± 0.02 mg/day (n=15,267). Values for populations in the US were generally lower than other countries because of decreased intake of vegetables, fruits and legumes.

Boron intake from food and water are generally below the Tolerable Upper Intake Level (UL) of 10-20 mg/day. However, it is possible that some individuals may approach or exceed this level by consuming certain supplements containing boron. The high-end of this range exceeds the Tolerable Upper Intake Level (UL) or dietary references of 0.2 - 0.4 mg/kg bw/day, indicated above, without factoring in other exposures to such things as commercial products.

Additional Background Exposures: In the US, the estimated boron intake resulting from diet and drinking water combined varies considerably, ranging from 0.26-7.1 mg/day, with a mean of 1.9 mg/day (0.03 mg/kg bw/day, Moore, 1997). Moore, (1997) also provided an estimate of boron intake resulting from diet, drinking water and body-building supplements combined, that ranged from 8-27 mg/day (0.03-0.45 mg/kg bw/day), with a mean of 6 mg/day (0.1 mg/kg bw/day). Although the high-end of this range exceeds the Tolerable Upper Intake Level, the registrant indicated that some of the values cited in the paper by Moore were based on unsubstantiated anecdotal information. However, this information, including potential UL exceedences, has also been cited by other scientific and regulatory agencies including IPCS, (1998) and the National Academy of Sciences, (2001/2002). Nutritional supplements typically contain 1-3 mg boron/day, yet nutritionist-promoted dietary supplements are available that recommend 6-12 mg boron/day, and the Expert Group on Vitamins and Minerals (2003) also states that boron is marketed in a number of multi-vitamin and mineral food supplements at levels up to 10 mg/day. According to the Registrant (August 3, 2004), "borates are used in thousands of applications around the globe, such as adhesives, cosmetics, fabric softeners, semiconductors, detergents, soaps, eye drops, halogen lights, insulation, paint, porcelain enamels, shampoo and wood treatment products." One estimate from the UK on the boron contribution from cosmetics and other consumer goods has been estimated at 0.5 mg/day, however, it is unclear which products were considered in this estimate.

Human Metabolism: Pharmacokinetic data in humans follow a pattern similar to that seen in the rat. Distribution of boron in tissues was 104.7 mL/100 g in humans (rat: 142 mL/100 g) with accumulation in the bone. While the plasma half-life of boron is comparable between rats and humans (14-19 hours and 10-21 hours, respectively), clearance values in humans (pregnant and non-pregnant) are approximately 4 times slower. Both pregnant rats and humans clear boron faster than their non-pregnant counterparts. Hospital patients with compromised kidney function have significantly increased boric acid serum levels compared to those with normal kidney function.

Human Toxicity: Although case reports seem to indicate that infants are more sensitive to boron compounds than adults, lethal doses are not well documented. In general, death can occur at total doses of between 5-20 g of boric acid for adults and at 2-9 g for infants and children (Stokinger 1981; Litovitz, 1988). Early case reports have shown that death in newborns occurred within 5 days of ingesting less than 3 g of boric acid (Young, 1949). The most common symptoms of acute exposure to boron in children and adults are vomiting, diarrhea and abdominal pain. Adults given high acute doses of boron reported hair loss and widespread exfoliative dermatitis.

Subchronic oral exposure to infants (up to 10 weeks) was associated with severe neurological effects, seizures and death after exposure to a honey/borax mixture on soothers (exact dose unknown; O'Sullivan and Taylor, 1983). Infants exposed to boric acid by repeated topical applications of baby powder developed erythema over the entire body, excoriation of the buttocks, desquamation, gastrointestinal disturbances and seizures (Stein et al., 1973). Occupational exposure to boron oxide and / or boric acid via inhalation resulted in workers with significantly higher rates of eye irritation, dryness of mouth, nose or throat, sore throat and productive cough. NIOSH has concluded that boron oxide and boric acid produce upper respiratory and eye irritation at less than 10 mg/m^3 (0.22 mg boron/kg bw/day).

ATSDR (1992) case reports indicate neurological effects after accidental ingestion of high doses of boron as boric acid. Doses of about 500 mg boron/kg/day showed CNS involvement with headaches, tremors, restlessness and convulsions followed by weakness, coma and death. Histological examination revealed degenerative changes in brain neurons, congestion, and oedema of brain and meninges with perivascular haemorrhage and intravascular thrombosis. These results correlate with the reported convulsions and seizures of seven infants exposed to a honey-borax mixture for up to10 weeks (O'Sullivan and Taylor, 1983) and the clonic convulsive movements in 6 newborns accidentally poisoned with boric acid in their formula (Young et al., 1949).

Chronic ingestion of borate-containing mouthwash caused severe fatigue, anorexia, mental confusion and wide-spread alopecia in a 32 year-old female. Her blood level was 0.3 mg/100 mL (Stein et al., 1973). The authors suggest that the hair loss was a result of boric acid accumulation in hair follicles and the subsequent toxic effect on the hair bulbs.

A study on 28 Russian male workers exposed for 10 or more years to high levels of vapours or aerosols of boron salts reported low sperm count, reduced sperm motility and elevated fructose content (Tarasenko et al., 1972), whereas a US study with 542 participants found that exposure to inorganic borates did not appear to adversely affect fertility (Whorton et al., 1992, 1994). However, the US study had inherent limitations since it used a standardized birth ratio, which is less sensitive than direct measures of testicular effects. Also, exposure information was limited and the applicability of total US fertility rates is questionable (EPA-IRIS, 2004).

The toxicology profile for borax and boric acid is presented in Appendix III.

Reference Doses Proposed by other Regulatory Authorities:
In general, with the exception of the USEPA RED (1993), the published reference doses for other regulatory authorities consider the primary endpoint of concern to be decreased fetal body weight in the rat developmental toxicity studies. Most reviews have based their conclusions regarding the dog studies on a 1972 paper by Weir and Fisher. Some reviews appear to have considered only the borax data. These borax and boric acid studies had been conducted prior to GLP and, on the basis of the Weir and Fisher report, were considered by various regulatory bodies and review panels to be inadequate in that only 4 dogs/sex/dose were used (although this meets current OECD and USEPA guidelines), the same control was used for both boric acid and borax (although concurrent studies justifies the use of one control group), the dogs were sacrificed at various times, and the control animals showed some form of testicular lesion

(one control animal with a few foci). However, the PMRA noted that the original studies for both borax and boric acid showed consistent results with respect to testicular effects in dogs, and that these effects occurred at doses that were lower than what was reported by Weir and Fisher in their 1972 paper. Although the dog studies are dated and have been considered supplemental because of their lack of ovarian pathology data, a provisional NOAEL can be established for the males based on testicular effects. When the PMRA compared the paper by Weir and Fisher (1972) to the original study reports (also co-ordinated or supervised by Weir), many discrepancies were noted. Thus, where possible, the PMRA has relied on the data presented in the original borax and boric acid studies.

With the exception of Dourson et al., (1998, 1999), USEPA and USEPA- IRIS, most of the existing assessments state that the toxicokinetics are comparable between animals and humans and thus, the interspecies uncertainty factor (UF_A) can be reduced. However, the PMRA supports the scientific rationale provided by Dourson et al., that justifies retaining the UF_A on the basis that renal clearance in humans is about 4 times slower than that of the rat. Other assessments also consider the toxicology database for boron to be adequate for both animals and humans, resulting in some lowering the standard intraspecies uncertainty factor (UF_H) as well. However, decreasing the UF_H cannot be supported by the PMRA given the extensive human variability that has been demonstrated depending on age, pregnancy, health and kidney function status. Finally, the existing assessments do not consider the serious developmental effects occurring at non-maternally toxic doses in the rat developmental studies. In fact, most of the assessments consider that maternal toxicity (decreased maternal body weight gain) occurred at the mid-dose level. However, the purported effect on maternal body weight was actually due to differences in gravid uterine weight between control and treated dams (fewer/smaller pups in treated dams). Once the maternal body weight was corrected for gravid uterine weight, there was no difference between the dams in the treated and control groups.

3.2 Incremental Risk

Because boron is ubiquitous in the environment, it was necessary for the PMRA to conduct a human health risk assessment for boron exposure from pesticidal uses, in consideration of current background exposures. The risk assessment approach utilized for pesticidal products results in a target margin of exposure for boron pesticidal uses that, if achieved, will not contribute significantly to existing intakes, minimizing any additional contribution to the overall background levels for boron when used as a pesticide. The reference level (margin of exposure) established by the PMRA for boron pesticidal uses is intended to assess incremental risk from any exposure beyond what an individual consumes in his/her daily diet, including drinking water. Applying this reference point will ensure that exposure through boron pesticidal uses will not increase existing intakes to any significant degree, or compromise any subpopulation that may already have a high intake level.

External Consultation
In 2005, the PMRA contracted Graham Smith BVMS, MRCVS, MSc, DACVP (Clinical Pathology) to review the boric acid and borax dog toxicity studies and address questions with respect to combining the studies, NOAELs, relevance of histological findings, use of these data to inform the risk assessment and whether or not a new dog study, with full sperm analysis, is warranted. At the request of the registrant, the PMRA also convened a panel of experts (known as the Panel) to comment on the appropriate inter- and intra-species uncertainty factors (UF) and any additional UFs. The Panel was also asked to comment on the adequacy of the developmental and reproductive toxicity database, with regards to establishing reference doses for conducting appropriate risk assessments. A summary of both assessments, including the PMRA's comments, is provided in Annex I of Appendix III.

Incident Reports
Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc., to major effects such as reproductive or developmental effects, life-threatening conditions or death. The PMRA examines the incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures are taken.

As of March, 2012, the PMRA had received 125 incident reports involving the active ingredients borax (120 incidents) or boric acid (5 incidents). All but one incident occurred in Canada (the incident that occurred in the United States involved a Canadian product). All boron incidents related to ant control products, and most (67%) involved liquid formulations that are placed as bait in the open around the home. The remainder of the incidents involved enclosed bait stations or dust formulations.

There were 27 human incidents reported; all were minor or moderate in severity. Of these incidents, 71% were considered to be related to the pesticide. Adults were typically exposed via the skin during application of the product. People generally experienced minor skin or gastrointestinal effects within 15 minutes of exposure. There were two incidents involving children under the age of 6 years which were categorised as minor in severity (symptoms included vomiting and gagging) and related to the ingestion of the product after it had been placed in and around the home.

There were 98 domestic animal incidents reported (63 involving dogs and 35 involving cats). There were three cat incidents that reported the death of the animal, and one reported dog death. There was not a high degree of association between the reported exposure to the pesticide and the described symptoms for these deaths. Three of the deaths were considered to be possibly related to the reported exposure, and it was determined to be unlikely that the fourth incident was related.

Overall, 95% of domestic animal incidents were minor in nature and 89% of these were considered to be related to the pesticide. Most of the dogs and cats reported in these incidents ate the product after it had been placed in and around the home. Typical symptoms included vomiting, diarrhea, or lethargy.

Mitigation to address these concerns is proposed in Section 7.1 and Appendix V: Label Amendments.

Pest Control Products Act Hazard Characterization Section

For assessing risks in food and/or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre-and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

The toxicity database for boron contains both unpublished and published studies. Although the database is extensive, including two reproduction studies and several developmental studies, the unpublished studies are dated and do not meet current day standards. Both the borax and boric acid reproduction toxicity studies in rats had considerable deficiencies including the lack of a detailed examination of the ovaries. While the testes were the primary target, when treated females were mated with control males, either no pups (boric acid) or very few pups (borax) were produced, indicating that exposure to these compounds also resulted in decreased fertility in the female rat. No litters were produced at either the mid- or high-doses. In a mouse reproduction toxicity study with boric acid, fertility was decreased and was primarily related to testicular toxicity. No litters were produced at the highest dose tested.

Published developmental toxicity studies in the rat showed increased sensitivity of the young. In the absence of overt maternal toxicity, foetuses had decreased body-weight gain, increased resorptions, and incidences of cleft sterna, agenesis of rib XIII, short rib XIII, wavy ribs, enlarged lateral ventricles of the brain, cardiovascular defects, hydrocephaly, short curly tail, anophthalmia and microphthalmia. The developmental rabbit toxicity study also showed sensitivity of the young with agenesis of the gallbladder being observed at a non-maternally toxic dose.

As previously stated, the current database for boron is very dated and does not meet current day standards, however concerns for database uncertainties have been addressed with the application of an additional 3-fold uncertainty factor. Concerns for the observed pre- and post-natal toxicity are tempered by the fact that the dose-response in the rat developmental toxicity studies is well characterized, and the dose selected for the overall risk assessment is 4.5-fold lower than the NOAEL for malformations noted in the developmental rat toxicity study. Thus, based on these considerations, the *Pest Control Products Act* factor was reduced to 1-fold.

3.3 Toxicology Endpoint Selection for the Occupational and Bystander Risk Assessment

To estimate the risk from chronic exposure in the occupational scenario, a benchmark dose level (BMDL) of 2.90 mg/kg bw/d from the two 90-day dog toxicity studies was chosen. This BMDL was based on testicular weight. A target margin of exposure (MOE) of 300 was selected which included standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variation. An additional 3-fold for database uncertainty was applied since it is likely that histological changes in testes would occur at a dose below those at which testicular weight are noted (Ku and Chapin, 1993). This endpoint selection is considered protective of sensitive subpopulations, providing a margin of greater than 1300 to the NOAEL of 13.6 mg/kg bw/d for the malformation of cleft sterna noted in the rat developmental toxicity study. As discussed above, the *Pest Control Products Act* factor has been reduced to 1-fold.

3.4 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

Exposure to boron occurs when mixing, loading, or applying end-use products containing the following boron-related active ingredients: borax, boric acid, disodium octaborate tetrahydrate, zinc borate, and borax pentahydrate. In addition, postapplication exposure may result from re-entry into treated areas and/or handling of treated articles.

The use pattern of the boron cluster includes domestic and commercial applications in residential and industrial areas using several formulation types (paste, solution, rods, dust/powder, granular, aerosol, and soluble powder). Based on this use pattern and the application methodologies utilized, bystander exposure during application is expected to be minimal. A quantitative risk assessment was conducted to determine the amount of potential exposure to boron.

3.4.1 Dermal Absorption

Guideline studies to estimate the dermal absorption of boron compounds were not available. Information in the scientific literature suggests that dermal absorption of boron is low. However, there are limitations to these studies (for example no mass balance, formulations which are not relevant) that impact their use for regulatory purposes. Based on the strength and limitations of the literature information, a dermal absorption estimate of 50% was used in the risk assessment.

3.4.2 Occupational Mixer, Loader, and Applicator Exposure and Risk Assessment

Commercial class end-use products containing boron may be used for indoor structural, outdoor residential, wood preservation, and material preservative uses. These products are formulated as paste, solution, rods, dust/powder, soluble powder, pressurized dust, and granular formulations.

Antisapstain, joinery and/or millwork applications have not been addressed in this document; these exposure scenarios will be addressed in a separate assessment. Additionally, the pole bandaging scenario was not assessed as there was no data available to address this use; exposure and use pattern data will be required to maintain the pole bandaging use.

Based on the use pattern for the commercial class products of the boron cluster, mixer/loader/applicator exposure scenarios were considered to potentially encompass short-, intermediate- and long-term durations. Exposure scenarios for the uses of the commercial class products of the boron cluster are generated based on the different formulations and application methods available, and assuming PPE is used as outlined by product labels.

No acceptable chemical-specific handler exposure data were submitted for boron; therefore, dermal and inhalation exposures for all formulation types and application methods were estimated using data from the Pesticide Handlers Exposure Database (PHED), Version 1.1. PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE.

It is acknowledged that there is uncertainty in the assessment. Since no boron specific exposure data were submitted or available for the re-evaluation, PHED data were used as it represents the most reliable information available for assessing exposure to boron containing products. However, there are limitations with PHED as it does not contain exposure scenarios that correspond with all of the boron uses. As a result it was necessary in certain cases to extrapolate from the most representative PHED scenario. Application rate and amount handled estimates were derived from the product labels. Collectively, this methodology results in an assessment that does not underestimate exposure, but may be conservative. Additional information that may allow a more accurate estimate of exposure is identified in Section 7.3 of this document.

In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing coveralls or a respirator. This was estimated by incorporating a 75% clothing protection factor for coveralls and a 90% clothing protection factor for chemical resistant coveralls into the dermal unit exposure data. In addition, a 90% protection factor for a respirator was incorporated into the inhalation unit exposure data. Respirators were not considered in conjunction with closed systems.

The PMRA estimated handler exposure based on different levels of personal protective equipment:

Baseline PPE:	Long-sleeved shirt, long pants and chemical-resistant gloves (unless specified otherwise).
Mid-level PPE:	Coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves.
Maximum PPE:	Chemical-resistant coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves.

Exposure is calculated as the product of the PHED unit exposure for a given scenario, the label application rate(s) and the area treated per day (or total amount of product handled per day), divided by the body weight. Calculated MOEs for handlers of commercial end-use products containing boron are summarized in Table 1 of Appendix IV. Target MOEs are not achieved for certain use scenarios of occupational exposure even when risk mitigation measures are applied. The type of formulation was an important factor in the exposure assessment (for example scenarios involving dusts/powders applied using a mechanically powered duster inherently have a high exposure potential). The combined dermal and inhalation MOEs do not meet the target MOE of 300 for the following formulations and commercial application methodologies:

- Application of a paste formulation with a brush, trowel, or putty knife, with the applicator wearing coveralls over a single layer of clothing and gloves. The PHED - paintbrush scenario used in this risk assessment may be conservative in extrapolating paint exposure to estimate potential paste exposure; the volume of product applied in one day is also potentially an overestimate.

- Application of a solution with a brush with the applicator wearing a single layer of clothing and gloves.

- Zinc borate used during open mixing/loading for application as a material preservative in paints, coatings, plastics, rubbers, and wood composites.

- Application of a pressurized product without an injector tube; however, currently registered products have an injector tube requirement on labels. Exposure data is not available for application with an injector tube, however it is anticipated that its use would result in reduced risk.

- Dust, granular and soluble powder (applied as dry formulation) in crack and crevice applications (including pressurized dust products).

- Application with a granular spreader or granular formulations applied with pressure sprayer to dirt/cement-floored grow-out/layer houses. The amount of product applied in one day is also potentially an overestimate. Crack and crevice treatment using granular formulations were covered off by the dust/powder risk assessment. As that assessment results in an MOE that does not meet target MOE, exposure or use data are required in order to better estimate the amount of product handled. Otherwise removal of the crack and crevice application of the granular formulation is required.

In addition to the above mitigation measures, bait station products prepared in ready to use containers must be identified separately in the label statements from bait station refill and open placement products.

Where available, information on typical quantities handled per day were used in the exposure assessments. All proposed label changes, personal protective equipment, engineering controls, and other mitigation measures are described in detail in Appendix V.

3.4.3 Non-Occupational Exposure and Risk Assessment

Domestic end-use products containing boron may be applied by homeowners for indoor structural, outdoor residential, and remedial wood preservation uses. These products are formulated as paste, solution, rods, dust/powder, and granular formulations.

Similar to the occupational assessment (see Section 3.4.2), there is uncertainty in the residential (non-occupational) exposure assessment as no chemical or scenario specific data were available. Additionally, the pole bandaging scenario was not assessed as there was no data available to address this use. Exposure and use pattern data are required to maintain the pole bandage use. Dermal and inhalation exposure was estimated for the various formulations and application methods using the Pesticide Handlers Exposure Database, Version 1.1. While PHED did not contain data sets that portray typical exposure of boron in domestic settings, it was the best available data to estimate exposure because certain rates, the use pattern, and chemical specific exposure data were not provided.

Based on the domestic boron cluster use pattern, mixer/loader/applicator exposure scenarios were considered to be short-term (<30 days) in duration. For domestic exposure scenarios it was assumed that short sleeves, short pants, and no gloves are worn during application (unless otherwise specified). Certain PHED data sets used in the residential risk assessment included the use of PPE (for example gloves). As the use of PPE is not typically assumed for residential applicators, there may be an underestimate of risk in these cases.

Exposure is calculated as the product of the PHED unit exposure for a given scenario, the label application rate(s) and the area treated per day (or total amount of product handled per day), divided by the body weight. Calculated MOEs for handlers of domestic end-use products containing boron are summarized in Table 2 of Appendix IV. Target MOEs are achieved for most use scenarios of non-occupational exposure when risk mitigation measures are applied. The combined dermal and inhalation MOEs do not meet the target MOE of 300 for the following formulations and domestic application methodologies:

- Application of a paste formulation with a brush or trowel; with an applicator wearing personal protective equipment of long pants, long sleeves, and gloves.
- Application of a solution with a brush with the applicator wearing a single layer of clothing and gloves.
- Crack and crevice application of a dust/powder formulation with a squeeze bottle or shaker can.

In addition to the above mitigation measures, bait station products prepared in ready to use containers must be identified separately in the label statements from bait station refill and open placement products.

All proposed label changes, personal protective equipment, engineering controls, and other mitigation measures are described in detail in Appendix V.

3.4.4 Postapplication Exposure and Risk Assessment

Postapplication exposure and risk assessments were conducted together for the domestic and commercial end-use products containing boron which are used in the same sites and at the same rates for indoor structural and material preservation uses. The assessment considers exposure to persons coming into contact with boron residues previously applied. Outdoor residential and remedial wood preservation applications are limited to areas not frequented by, or inaccessible to, children (for example below groundline, spot treatment in gardens, attics, etc.). As such, the potential for postapplication exposure is minimal.

Indoor residential postapplication exposure scenarios were considered to be short-term (<30 days in duration). Postapplication exposure assessments were limited to the dust applications and exposure from open bait application of pastes and solutions (drops). Exposure assessments were based on default values recommended by the USEPA Draft Standard Operation Procedures (SOPs) for Residential Exposure Assessments for Crack and Crevice and Broadcast Treatment of Carpets and Hard Surfaces and Overview of Issues Related to the SOPs (August, 1999), and Recommended Revisions to the Standard Operation Procedures for Residential Exposure Assessment (February, 2001). A dissipation rate had not been determined for indoor applications of boron compounds, therefore, postapplication exposure is calculated for the day of application and it is assumed that residues do not dissipate on successive days. As data on application rates were unavailable, Tier 1 assumptions were made accordingly and this may have resulted in a conservative assessment.

Postapplication exposure and risk estimates for adults and children are summarized in Table 3, Appendix IV. Combined MOEs for dermal and non-dietary ingestion (hand-to-mouth) postapplication exposure did not meet the target MOE of 300 for the following scenarios:

- Domestic and commercial applications in crack and crevice applications as a dust (including granular and soluble powder formulations which are indicated to be applied as dusts and pressurized dust).
- Domestic and commercial applications of pastes and solutions as baits placed in the open.

When used as a material preservative in paints and coatings, plastic, rubber, or wood composites, there is potential for postapplication exposure of zinc borate to workers and consumers handling these products. The product label does not specify the resultant concentrations of zinc borate in treated substrates, and no data is available to assess exposure to workers and/or consumers handling treated material at this time.

All proposed label changes, engineering controls, and other measures that may potentially mitigate postapplication exposure, are described in detail in Appendix V.

3.4.5 Dietary Risk Assessment

There are no registered food uses. Therefore, a dietary exposure risk assessment was not required. Dietary and background exposure to non-pesticide sources of boron are discussed in Section 3.1 of this document.

3.5 Aggregate Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources as well as from all known or plausible exposure routes (oral, dermal, and inhalation) for pesticidal uses only. As there are no registered food uses of boron, the aggregate assessment consists of aggregating exposure from various routes (dermal and inhalation exposure) for occupational and domestic handlers and postapplication exposure only, which is included in Appendix IV.

4.0 Impact on the Environment

An environmental risk assessment was not conducted on the boron use patterns described in this document as none of them result in significant environmental exposure. These uses include remedial treatment of wood utility poles and other wood structures. The exposure to the environment from these uses of boron is limited to a small area of soil in the immediate vicinity of the treated wood. Therefore, an environmental risk assessment is not required.

5.0 Pest Control Product Policy Considerations

5.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and /or sediment, bioaccumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*).

During the review process, boron and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy* and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Boron does not meet Track 1 criteria, and is not considered Track 1 substances.
- Boron does not form any transformation products that meet all Track 1 criteria.

5.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern maintained in the *Canada Gazette*.[4] The list is used as described in the PMRA Notice of Intent NOI2005-01[5] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[6], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

Technical grade boron and related end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

6.0 Summary

6.1 Occupational Risk

The mixer/loader/applicator risks were of concern for certain use scenarios even when risk mitigation measures were applied. The risk concerns were impacted by formulations and their inherent exposure parameters (for example dust/powders).

As the treated sites are typically areas not frequented by the applicator, postapplication exposure is expected to be negligible and is not of concern.

6.2 Dietary Risk

As there are no food uses for boron, a dietary risk assessment was not conducted.

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4 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

5 NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

6 DIR2006-02, PMRA Formulants Policy.

6.3 Non-occupational Risk

The mixer/loader/applicator risks were not of concern for most use scenarios when risk mitigation measures were applied with the exception of scenarios involving the dust/powder formulations and the application of pastes and solutions using a brush/trowel.

Although the sites are not frequented by the applicator, postapplication exposure may occur around domestic settings where toddlers, children and/or pets may come into contact with treated sites.

6.4 Aggregate Risk

Risks of concern were identified for certain occupational use scenarios, even when mitigation measures were applied (see Section 6.1.1).

6.5 Environmental Risk

An environmental risk assessment was not conducted on the boron use patterns described in this document as none of them result in significant environmental exposure. These uses include remedial treatment of wood utility poles and other wood structures. The exposure to the environment from these uses of boron is limited to a small region of soil in the immediate vicinity of the treated wood. Therefore, an environmental risk assessment is not required.

7.0 Proposed Regulatory Decision

After a re-evaluation of boron, Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing continued registration of boron and associated end-use products for certain uses and formulations supported by the technical registrant, provided that the mitigation measures for health described in this document are implemented and the required confirmatory data are provided within a specified timeframe.

The uses of boron products proposed for continuing registration, together with proposed mitigation measures and use limitations, are presented in Appendix V.

7.1 Proposed Regulatory Actions

7.1.1 Proposed Regulatory Action Related to Human Health

Commercial
For occupational uses of commercial class products, the PMRA has determined that worker risks during mixing, loading, and application activities are of concern for certain scenarios. Risk-reduction measures are proposed to address these potential risks identified in this assessment.

- The soluble powder formulation will be limited to use as a material preservative. Limitation on the amount handled per day (for example 14.1 kg a.i. handled with single layer of clothes and gloves; or 21.1 kg a.i. handled with chemical resistant coveralls and gloves) as well as the use of additional personal protective equipment (for example chemical resistant coveralls) or engineering controls (for example closed system mixing/loading) will be required.

- Indoor and outdoor bait uses where products may be accessible to toddlers, children and pets will require enclosed bait stations.

- Bait station and bait station refill/open placement products must be identified separately in the label statements.

The PMRA has assessed the available information and concluded that certain uses of boron present risks that are of concern. In order to address these risks, removal of the following commercial class boron products in Canada is proposed:

- All dust/powder formulations (including pressurized dust products).
- All uses involving brush, trowel, or putty knife application (paste and solution formulation).
- Use of granular formulation involving application by pressure sprayer and seed spreader.

Domestic

For uses of domestic class products, the PMRA has determined that risks during mixing, loading, and application activities are of concern for certain scenarios. Risk-reduction measures are proposed to address these potential risks identified in this assessment.

- Indoor and outdoor bait uses where products may be accessible to toddlers, children and pets will require enclosed bait stations.
- Bait station and bait station refill/open placement products must be identified separately in the label statements.

The PMRA has assessed the available information and concluded that certain uses of boron present risks that are of concern. In order to address these risks, removal of the following domestic boron products in Canada is proposed:

- All dust/powder formulations.
- All uses involving brush and/or trowel application (paste and solution formulations).

7.1.2 Proposed Mitigation for Mixer, Loader, and Applicator Exposure

Based on exposure assessments described in Table 1 and 2 of Appendix IV, recommendations to mitigate exposure include the proposal to add personal protective equipment, engineering controls, and limiting the amount of active ingredient handled per day.

7.2 Additional Data Requirements

7.2.1 Additional Data Requirements Related to Toxicology

No additional toxicology data are required at this time. However, the boron database contains many toxicological studies on both borax and boric acid that are outdated and poorly conducted, and raises concerns with respect to testicular effects in non-rodent species, thus warranting a database uncertainty factor. Re-examination of the database uncertainty factor would require an updated dog toxicity study, of approximately 6 months in duration, in order to better inform the risk assessment for boron.

7.2.2 Additional Data Requirements Related to Exposure

Under section 12 of the *Pest Control Products Act*, the following studies are required for the continued registration of boron-related compounds.

Additional use pattern and exposure data are required to refine the crack and crevice uses with dusts, powder, and granular formulations. Use pattern and exposure data are also required to assess the pole bandaging scenario. Adequate data were not available to quantitatively assess this use. These requirements can be addressed through:

DACO 5.2 Use Description/Scenario (Application and Postapplication) - Information which fully describes the use of the product and human activity associated with its use.

Commercial Crack and Crevice Application

- Application rates in g a.i/cm^2 for all commercial products
- Area treated per day (ATPD) for commercial application using paintbrush and aerosols.
- Treatment frequency (for example number of days of exposure per year) for commercial applicators.
- Working duration for pest control operators.
- Number of days of exposure per year for residents.

DACO 5.4/5.5 Mixer/Loader/Applicator - Passive dosimetry or biological monitoring data and/or transferable residues.

DACO 5.6/5.7 Postapplication - Passive dosimetry or biological monitoring data and/or transferable residues.

- Postapplication exposure to boron is expected to occur from contact with remedial treated wood and soil surrounding treated wood (primarily decks). A study which estimates the amount of boron that can be dislodged or transferred from the treated wood surface and a study which quantifies the amount of boron in soil surrounding treated lumber are required. Alternative studies may include an acceptable passive dosimetry or biological monitoring study.

DACO 5.9c Indoor transferable residue and dissipation data following crack and crevice application in residential scenarios based on the Canadian use pattern (for example application rates). This study methodology needs to be consistent with the transfer coefficient in the USEPA Residential SOPs.

DACO 5.10 Indoor air monitoring data and dissipation data following crack and crevice application in residential areas based on the Canadian use pattern (for example application rates).

7.3 Data to Refine the Exposure Assessment

As noted in Section 3.4 of this document, the chemical, formulation and scenario specific data available to assess the potential applicator and postapplication exposure to boron are limited. The PMRA acknowledges that submission of additional data may allow the current exposure assessment to be refined. These data may include:

DACO 5.4/5.5 Mixer/Loader/Applicator - Passive dosimetry or biological monitoring data and/or transferable residues.

DACO 5.6/5.7 Postapplication - Passive dosimetry or biological monitoring data and/or transferable residues.

DACO 5.8 Formulation specific dermal absorption (in vivo) studies. It is recommended that a scientific rationale be provided if dermal absorption data are extrapolated from one formulation to serve as surrogate data for other formulations containing boron.

List of Abbreviations

ADI	Acceptable Daily Intake
a.i.	Active Ingredient
ARfD	Acute Reference Dose
bw	body weight
CAS	Chemical Abstracts Society
d	day(s)
DACO	Data Codes
DFR	Dislodgeable foliar Residues
DT_{50}	Dissipation Time to 50% of initial concentration
EP	End Use Product
g	grams
h	hour(s)
kg	kilogram(s)
K_{oc}	Absorption quotient normalized for organic carbon
K_{ow}	*n*-Octanol–water partition coefficient
LC_{50}	Median Lethal Concentration to 50%
LD_{50}	Median Lethal Dose to 50%
LOAEL	Lowest Observable Adverse Effect Level [mg a.i./kg bw]
m	metre
mg	milligram
mg/kg bw/day	Milligrams per Kilogram of Body Weight per Day
MOE	Margin of Exposure
NOAEL	No Observed Adverse Effect Level
PRVD	Proposed Re-evaluation Decision Document
PCP	Pest Control Product
PHED	Pesticide Handlers' Exposure Database
pKa	Dissociation Constant
PMRA	Pest Management Regulatory Agency
PPE	Personal Protective Equipment
Reg. No.	Registration Number (*Pest Control Products Act*)
SPSF	Product Specification Form
TGAI	Technical Grade Active Ingredient
TSMP	Toxic Substances Management Policy
TWA	Time-weighted Average
µg	Microgram
US	United States
USA	United States of America
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WP	Wettable Powder

Appendix I Additional Data Requirements

The following data are required as a condition of continued registration under section 12 of the *Pest Control Products Act*. The registrants of this active ingredient are required to provide these data or an acceptable scientific rationale within the timeline specified in the decision letter that will be sent to registrant(s) of the technical active ingredients by the PMRA.

Additional Data Requirements Related to Exposure

Additional use pattern and exposure data are required to refine the assessment of crack and crevice uses with dusts, powder, and granular formulations. Use pattern and exposure data are also required to assess the pole bandaging scenario. Adequate data were not available to quantitatively assess this use. These requirements can be addressed through:

DACO 5.2 Use Description/Scenario (Application and Postapplication) - Information which fully describes the use of the product and human activity associated with its use.

Commercial Crack and Crevice Application

- Application rates in g a.i/cm^2 for all commercial products
- Area treated per day (ATPD) for commercial application using paintbrush and aerosols.
- Treatment frequency (for example number of days of exposure per year) for commercial applicators.
- Working duration for pest control operators.
- Number of days of exposure per year for residents.

DACO 5.4/5.5 Mixer/Loader/Applicator - Passive dosimetry or biological monitoring data and/or transferable residues.

DACO 5.6/5.7 Postapplication - Passive dosimetry or biological monitoring data and/or transferable residues.

- Postapplication exposure to boron is expected to occur from contact with remedial treated wood and soil surrounding treated wood (primarily decks). A study which estimates the amount of boron that can be dislodged or transferred from the treated wood surface and a study which quantifies the amount of boron in soil surrounding treated lumber are required. Alternative studies may include an acceptable passive dosimetry or biological monitoring study.

DACO 5.9c Indoor transferable residue and dissipation data following crack and crevice application in residential scenarios based on the Canadian use pattern (for example application rates). This study methodology needs to be consistent with the transfer coefficient in the USEPA Residential SOPs.

DACO 5.10 Indoor air monitoring data and dissipation data following crack and crevice application in residential areas based on the Canadian use pattern (for example application rates).

Appendix II Registered Products containing boron as of 1 April 2012[1]

Registration Number	Registrant Name	Product Name	Marketing Class	Formulation Type	Guarantee (%)
Boric Acid					
21996	Acuity Holdings, Inc.	R Value'S Roach Kil	Domestic	Dust of powder	99
22379	Acuity Holdings, Inc.	Borid With Boric Acid	Commercial	Dust of powder	99
28231	Aerokure International Inc.	Insect Stop Crawling Insect Destroyer Powder	Domestic	Dust of powder	100
27023	Basf Canada Inc.	Prescription Treatment Brand Perma Dust Pressurized Boric Acid Dust	Commercial	Pressurized product	35.5
21003	Blue Diamond Ext. & Mfg. Co. Inc.	Blue Diamond Magnetic Roach Food 2000 Paste Formula	Commercial	Paste	33.3
29169	Blue Diamond Ext. & Mfg. Co. Inc.	Professional Roach Bait	Commercial	Paste	33.3
30293	Blue Diamond Ext. & Mfg. Co. Inc.	Homeowners DIY Roach Bait	Domestic	Paste	33.3
23338	Canada Colors & Chemicals Ltd.	Boric Acid Manufacturing Concentrate	Manufacturing concentrate	Soluble powder	100
27902	Ecolab Co.	Eco2000-XP Freshbait	Commercial	Paste	43.4
25360	Ecolab Inc.	Eco2000-XP Cockroach Bait	Commercial	Paste	51.4
29154	Ecolab Inc.	Eco2000-RX Freshbait Cockroach Bait	Commercial	Paste	44.95
20478	FMC Corporation	Drax Ant Kil Gel	Commercial	Paste	5.0
25353	FMC Corporation	Drax II Ant Kil Gel	Commercial	Paste	5.0
26399	FMC Corporation	Drax Ant Kil PF	Commercial	Paste	5.0

Registration Number	Registrant Name	Product Name	Marketing Class	Formulation Type	Guarantee (%)
27751	FMC Corporation	CB Attrax Roach Bait With Carbohydrates	Commercial	Paste	50
27752	FMC Corporation	CB Attrax Roach Bait With Proteins	Commercial	Paste	50
25580	Genics Inc.	Cobra(Tm) Rod	Commercial	Solid	4.7
27214	Genics Inc.	Genics Postguard	Domestic	Solid	4.7
27553	Genics Inc.	Cobra(Tm) Crush Mdt Wood Preservative	Commercial	Soluble powder	7.93
27814	Searles Valley Minerals Operations Inc.	Three Elephant Boric Acid Granular Technical	Technical	Granular	99.75
25735	S.C. Johnson & Son Ltd.	Raid Ant Roach & Earwig Gel Baits	Domestic	Solid	2.0
21054	Surekiller Products Ltd.	Surekiller Bug Buster Insect Powder	Domestic	Dust or powder	100
26872	Surekiller Products Ltd.	Surekiller Insect Powder	Domestic	Dust or powder	80
19480	Agrium Advanced Technologies Rp Inc.	Pro Boradust Insecticide Dust	Commercial	Dust or powder	99
19919	Agrium Advanced Technologies Rp Inc.	Pro Roach Powder Insecticide Dust	Domestic	Dust or powder	96
20468	Agrium Advanced Technologies Rp Inc.	Farm & Ranch Brand Darkling Beetle Insecticide Dust	Commercial	Dust or powder	98
26564	Nisus Corporation	Niban Granular Bait D	Domestic	Granular	5.0
26565	Nisus Corporation	Niban Granular Bait C	Commercial	Granular	5.0
24314	Les Produits De Controle Superieur Inc	The Insect Destroyer	Domestic	Dust or powder	100
19424	Roach Remover Inc.	Roach Die-It	Commercial	Paste	50

Registration Number	Registrant Name	Product Name	Marketing Class	Formulation Type	Guarantee (%)
27124	Sure-Gro Ip Inc.	Green Earth Homecare Ant, Roach & Crawling Insect Killer Dust	Domestic	Dust or powder	99
28921	Ultrasol Industries	Go Green Doktor Doom Granular Bait C	Commercial	Granular	5.0
28922	Ultrasol Industries	Go Green Doktor Doom Granular Bait D	Domestic	Granular	5.0
18292	U.S. Borax Inc.	20 Mule Team Boric Acid Technical	Technical	Soluble powder	100
24642	Waterbury Companies Inc.	Aerosol Boric Acid	Commercial	Pressurized product	20
Disodium octaborate Tetrahydrate					
21939	Arch Wood Protection Canada Corp.	F2 Concentrate T2154 Liquid Microbiocide	Commercial	Emulsifiable concentrate or emultion	16.8
27632	Arch Wood Protection Canada Corp.	Antiblu F2 Concentrate T2154 Liquid Microbiocide	Commercial	Solution	3.1
26973	Canadian Building Restoration Products Inc.	Pre-Ser-Vor 25-3	Domestic	Solution	5.29
25580	Genics Inc.	Cobra(Tm) Rod	Commercial	Solid	90.6
27214	Genics Inc.	Genics Postguard	Domestic	Solid	88.9
27553	Genics Inc.	Cobra(Tm) Crush MDT Wood Preservative	Commercial	Soluble powder	80.43
28154	Genics Inc.	Genbor RTU	Commercial	Solution	23.6
28155	Genics Inc.	Genbor RTU-2	Domestic	Solution	23.6
28298	Genics Inc.	Canadian Shield	Domestic	Solution	23.6
29940	Genics Inc.	Bo-Rod	Commercial	Solid	98
29941	Genics Inc.	Can-Bor	Commercial	Soluble powder	98

Registration Number	Registrant Name	Product Name	Marketing Class	Formulation Type	Guarantee (%)
28108	Searles Valley Minerals Operations Inc.	Three Elephant Disodium Octaborate Tetrahydrate Technical	Technical	Soluble powder	20.9
29344	Innovative Pest Control Products	Greenway Liquid Ant Killing Bait	Domestic	Solution	1.0
29345	Innovative Pest Control Products	Greenway Liquid Ant And Roach Killer	Commercial	Solution	1.0
21324	Kai R. Spangenberg Eftf I/S	Impel (Boron) Rods Wood Preservative	Commercial	Solid	98
23398	Kai R. Spangenberg Eftf I/S	Impel (Boron) Rods II Wood Preservative For Remedial Treatment Of Utility Poles	Commercial	Solid	98
24493	Kai R. Spangenberg Eftf I/S	Boracol 20-2 Remedial Wood Preservative	Commercial	Solution	19.6
25664	Kai R. Spangenberg Eftf I/S	Boracol 20-2 Bd Preventive And Remedial Wood Preservative For Structures	Commercial	Solution	19.6
25665	Kai R. Spangenberg Eftf I/S	Boracol 10-2 BD Preventive & Remedial Wood Preservative	Commercial	Solution	9.8
28805	Societa' Chimica Larderello S.P.A.	Borowood	Commercial	Soluble powder	20.9
28829	Societa' Chimica Larderello S.P.A.	Borowood Disodium Octaborate Tetrahydrate Technical	Technical	Soluble powder	20.9
30157	Nisus Corporation	Bora-Care Termiticide And Insecticide Concentrate	Commercial	Solution	8.4
25662	Perma-Chink Systems Inc.	Shell-Guard	Domestic	Solution	5.29

Registration Number	Registrant Name	Product Name	Marketing Class	Formulation Type	Guarantee (%)
26430	Sashco Incorporated	Penetreat	Commercial	Soluble powder	98
18879	U.S. Borax Inc.	20 Mule Team Tim-Bor Industrial Wood Preservative	Commercial	Soluble powder	98
20477	U.S. Borax Inc.	Polybor 3 Darkling Beetle Control	Commercial	Soluble powder	98
24091	U.S. Borax Inc.	Tim-Bor Professional	Commercial	Soluble powder	98
24739	U.S. Borax Inc.	Octabor Technical	Technical	Soluble powder	98
29828	Wood Care Systems	Bor8®-Rods Wood Preservative	Commercial	Solid	98
Borax					
26687	Aerokure International Inc.	Aerokure Ant Trap	Domestic	Paste	5.0
23339	Canada Colors & Chemicals Ltd.	10 Mol Borax Manufacturing Concentrate Insecticide	Manufacturing concentrate	Soluble powder	100
22083	IBC Manufacturing Company	Curap 20 Wood Preservative Paste	Commercial	Paste	40
27026	IBC Manufacturing Company	Curap 20 Pak Wood Preservative Wrap	Commercial	Paste	38.98
27621	Copper Care Wood Preservatives Inc.	Cu-Bor Remedial Wood Preservative	Commercial	Paste	43.5
28468	Innovative Pest Control Products	Gourmet Liquid Ant Bait	Domestic	Liquid	5.4
29055	Innovative Pest Control Products	Gourmet Liquid Ant Bait-C	Commercial	Liquid	5.4
29056	Innovative Pest Control Products	Gourmet Liquid Ant Bait-CR	Commercial	Liquid	5.4

Registration Number	Registrant Name	Product Name	Marketing Class	Formulation Type	Guarantee (%)
29057	Innovative Pest Control Products	Gourmet Liquid Ant Bait MUP	Manufacturing concentrate	Liquid	5.4
30173	Innovative Pest Control Products	Green Way Ant Bait Gel	Domestic	Paste	1.35
18449	S.C. Johnson & Son Ltd.	Raid Ant Killer Liquid	Domestic	Solution	7.7
30270	Les Marques Metro S.E.N.C.	Selection Ant Control System	Domestic	Paste	5.0
16487	Pic Corp.	Pic Ant Traps Kills Ants	Domestic	Paste	5.0
23422	Pic Corp.	Pic Ant Control System II	Domestic	Paste	5.0
24074	Les Produits De Controle Superieur Inc.	Super Ants Killer	Domestic	Solution	5.4
29620	Les Produits De Controle Superieur Inc.	Superior Ant Traps Kills Ants	Domestic	Paste	5.0
20203	Woodstream Canada Corporation	Safer'S Attack Ant Killer	Domestic	Solution	5.4
24355	Woodstream Canada Corporation	Safer'S Attack Ant Trap	Domestic	Paste	5.4
14116	Sure-Gro Ip Inc.	Wilson Liquid Antout	Domestic	Solution	5.4
23446	Sure-Gro Ip Inc.	C-I-L Ant Trap	Domestic	Paste	5.0
27017	Sure-Gro Ip Inc.	Wilson Antout Ant Traps	Domestic	Paste	5.0
28793	Sure-Gro Ip Inc.	Wilson Antout Ant Bait	Domestic	Paste	5.0
29090	Sure-Gro Ip Inc.	Green Earth Homecare Liquid Ant Bait	Domestic	Liquid	5.4
30040	Sure-Gro Ip Inc.	Wilson Antout Outdoor Ant Stakes	Domestic	Paste	5.0

Registration Number	Registrant Name	Product Name	Marketing Class	Formulation Type	Guarantee (%)
9167	Scotts Canada Ltd.	Ortho Home Defense Max Ant Eliminator Liquid	Domestic	Solution	5.4
23372	Scotts Canada Ltd.	Ortho Home Defense Max Ant Traps	Domestic	Paste	5.0
30014	Scotts Canada Ltd.	Scotts® Ecosense Ant-B-Gon® Ant Eliminator Liquid	Domestic	Solution	5.4
18607	U.S. Borax Inc.	20 Mule Team Borax Technical	Technical	Soluble powder	100
29553	Wal-Mart Canada Inc.	Great Value Ant Control System	Domestic	Paste	5.0
Borax pentahydrate					
30037	Aerokure International Inc.	Aerokure Ant Killer Liquid	Domestic	Solution	5.0
23351	Canada Colors & Chemicals Ltd.	5 Mol Borax Manufacturing Concentrate	Manufacturing concentrate	Soluble powder	100
19025	U.S. Borax Inc.	20 Mule Team Neobor Technical	Technical	Soluble powder	100
Zinc borate					
19027	U.S. Borax Inc.	Zinc Borate Technical	Technical	Soluble powder	100
23283	U.S. Borax Inc.	Borogard ZB Corrosion Inhibitor, Biocide & Fire Retardant	Commercial	Soluble powder	100
30274	U.S. Borax Inc.	Composinor®	Commercial	Soluble powder	100

[1] Discontinued products or products with a submission for discontinuation are not included.

Appendix III Toxicology Profile for Borax and Boric Acid [Boron]

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified. Dose levels in repeat-dose studies are expressed as boron equivalents.

Study/Species/ # of animals per group	Results/Effects
Metabolism/Toxicokinetic Studies	
Primarily animals, see "Human Data" for more detail on human pharmacokinetics	Absorption: readily absorbed from gi tract in all species. Insignificant dermal absorption, unless damaged or abraded skin (this includes human newborns). Distribution: via passive diffusion, plasma ½ life in rats is 14-19 h and in humans, 10-21h. Distribution is generally uniform across the tissues, with higher conc found in fat and bone. Volume of distribution in the rat was 142 mL/100g and in the human was 104.7 mL/100g. Metabolism and Excretion: actual metabolism of boron may not occur because of the large amount of energy to break the boron-oxygen bond. Borate compounds are usually present as boric acid in the body and eliminated as such (>90%) within 96 h of admin (rat and human). Average clearance values are 3.6 and 4.9 fold slower for pregnant and non-pregnant individuals compared to pregnant and non-pregnant rats. Lab experiments done on rabbits with damaged kidneys showed that the ½ life of boric acid in the blood was significantly prolonged.

Study/Species/ # of animals per group	Dose Levels/Purity of Test Material	Results/Effects
Acute Toxicity Studies		
Oral / Rat - Sprague Dawley 5/sex/dose 1249395	3090, 3870, 4880, 6140, 7730 and 9740 mg/kg bw **Borax** in 0.5% aqueous methyl cellulose. Purity: 104%, assume 100%	LD_{50} (♂) = 4.55 g/kg LD_{50} (♀) = 4.98 g/kg LD_{50} (♂ + ♀) = 4.76 g/kg **Low Toxicity**
Oral / Rat - Sprague Dawley 5/sex/dose 1249441	2000, 2510, 3160, 3980, 5010 and 6310 mg/kg bw **Boric Acid** in 0.5 % aqueous methyl cellulose. Purity: 100%	LD_{50} (♂) = 3.45 g/kg LD_{50} (♀) = 4.08 g/kg LD_{50} (♂ + ♀) = 3.76 g/kg Signs: depression, slight diarrhoea, laboured respiration, ataxia **Low Toxicity**
Dermal / Rabbit - NZW 5/sex 1249400	2000 mg/kg bw **Borax** Purity: ?	LD_{50} > 2 g/kg bw **Low Toxicity**
Dermal / Rabbit - NZW 5/sex 1249377	2000 m g/kg bw **Boric Acid** Purity: ?	LD_{50} > 2 g/kg bw **Low Toxicity** EPA: Necropsy revealed enlarged fallopian tubes in 4/5 ♀ and one of these rabbits showed pale yellow, congested kidneys and gas filled intestines.
No inhalation study with **Borax**		

Study/Species/ # of animals per group	Results/Effects	
Inhalation / Rat - Sprague Dawley 5/sex 1249378	0.16 mg/L **Boric Acid** Purity: 100%	LC_{50} > 0.16 mg/L **Moderate Toxicity**
Eye Irritation / Rabbit - Albino NZW 6 animals (1 ♂, 5 ♀) 1249401	100 mg **Borax**	-mild iritis and mild to moderate conjunctivitis characterized by erythema, edema and discharge. Mucous membrane of eyelid appeared blistered. Burned/necrotic areas of conjunctiva noted until day 10. Mild to moderate corneal opacity also noted until day 10. Maximum Irritation Score= 34.5 at 24 hours. **Severely Irritating** (because of burned/necrotic and opacity up until day 10)
Eye Irritation / Rabbit - Albino 12 animals	100 mg **Boric Acid**	Produced slight to mild conjunctivitis lasting for 3 days after treatment. Maximum Irritation score = 20 **Mildly Irritating**
Skin Irritation / Rabbit - NZW 6 ♂ 1249403	500 mg **Borax**	No irritation was noted. **Non-Irritating**
Skin Irritation / Rabbit - NZW 3/sex 1249377	500 mg **Boric Acid** / skin site	Primary irritation score = 0.21 **Minimally Irritating**
Sensitization		No sensitization studies on either boric acid or borax are available for review.

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
Subchronic Toxicity Studies			
13-week dietary toxicity - SD rat 10/sex/group **Borax** 1249406	♂**:** 0, 1.25, 13.3, 38.8, 120.5, 560.8 mg **Boron**/kg bw ♀**:** 0, 4.34, 14.2, 43.5, 128.8, 527.1 mg **Boron**/kg bw	Provisional 38.8 mg/kg bw	**≥120.5/128.8 mg/kg bw**: 1 ♂ died; ↓ bwg and fc, abs and rel testes wt, abs and rel ovary wt. **@ 560.8/527.1 mg/kg bw**: all animals died. **Supplemental** (no haematology, opthal, histo. on relevant organs)

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
13-week dietary toxicity - SD rat 10/sex/group **Boric Acid** 1249381	Dose levels (♂ only) calculated from test article intake. 0, 3.9, 12.8, 38.0, 123.6,≈500 (all animals died) mg **Boron**/kg bw	Provisional ♂:12.8 mg/kg bw ♀: 38 mg/kg bw	**@ 38 mg/kg bw**: 1 ♂ had incomplete testicular atrophy (1/3 of tubules completely atrophic, rest in arrested spermatogenesis, 1° spermatocyte stage). **≥123.6 mg/kg bw**: ↓ fc, BW, hunched position, emaciated, coarse fur, piloerection, desquamation of skin and paws, inflamed eyes, rapid or laboured respiration, protruding penis/shrunken scrotum. ↓ rel (to brain) liver, spleen, testis/ovary weights. All ♂ had complete atrophy of the spermatogenic epithelium, ↓ seminiferous tubule size, and ↑ interstitial tissue, 4 ♂ had ↑ adrenal lipid content. **@ ≈500 mg/kg bw**: all ♂ dead by 3 wks, all ♀ dead by 6 wks. **Supplemental** (no haematology, histo etc.)
13-week dietary toxicity - mouse B6C3F1 10/sex/dose Range-Finding **Boric Acid** 1214936	♂**:** 0, 34, 70, 141, 281, 563 mg **Boron**/kg bw ♀**:** 0, 47, 97, 194, 388, 776 mg **Boron**/kg bw	**Potential NOAELs:** ♂: 34 ♀: 47 Testis Effects: NOAEL = 70	**≥34/47 and 70/97 mg/kg bw**: min - mild extramedullary hematopoiesis of the spleen. **≥141/194 mg/kg bw**: ↓ bwg, degeneration / atrophy of the seminiferous tubules. **≥281/388 mg/kg bw:** 10% mortality in the ♂. **≥563/776 mg/kg bw:** hyperkeratosis + acanthosis of stomach, >60% mortality.
90-day dietary toxicity - dog 5/sex/dose **Borax** 1237735	0.0, 0.4, 5.0, 46.2 mg **Boron**/kg bw	Provisional ♀: 46.2 ♂ : 5.0	**≥0.4 mg/kg bw:** dose-related ↓ in abs+rel testis wt, but not seen in 2-yr dog at this dose level. **≥5.0 mg/kg bw:** all 5 ♂ had artifactual distortion of the tubules in the outer 1/3 of the gland. The ♂s also had a greater proportion of small and solid epithelial nests (thyroid) and ♀ adrenal cortex was distinctly widened (considered non-adverse). **@46.2 mg/kg bw:** severe testicular atrophy in all dogs, complete degeneration of the spermatogenic epithelium in 4/5 dogs, with partial degeneration in 1 ♂ (dog died on day 68- congestion of kidneys and small and large intestines),↑ interstitial cells and Leydig-like cells. Abs testicular wt ↓ 40 - 44%, rel to BW and brain wt ↓. Liver, Spleen, Kidney : hemosiderin pigment accumulation from the breakdown of RBC. Effect more severe in ♂, but number of animals affected not given. **Supplemental** (no ovary data, poor reporting of control data, no individual path. reports) **No sperm analysis**

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
90-day Boric Acid dietary toxicity - dog 5/sex/dose **Boric Acid** 1249382	0.0, 0.46, 4.2, 35 mg **Boron**/kg bw Dose levels for ♂ calculated from actual test article intake/boron equivalent intake.	Provisional ♀: 35.0 ♂: 4.2	**≥4.2 mg/kg bw:** ↓ in abs and rel (to BW) testes wt, but not seen in 2-yr dog at this dose level, testes of all 5 ♂ had artifactual distortion of the tubules in the outer 1/3 of the gland. The ♂ had ↑ in small and solid epithelial thyroid nests (2 with squamous metaplasia). **@ 35 mg/kg bw:** ↓ rel thyroid (♂). Severe testicular atrophy in all ♂s. Degeneration of the spermatogenic epithelium was generally complete except in one dog where some activity remained in 2/3 of tubules, ↑ in interstitial tissue. ♀: ↑ of lymphoid infiltration and atrophy of the thyroid. **Supplemental** (no ovary data, poor reporting of control data, no individual path. reports) **No sperm analysis**
Chronic Toxicity/Oncogenicity Studies			

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
2-year dietary toxicity - dog 4/sex/dose **Borax** Sacrifice schedule for concurrent borax and boric acid studies: (control and high-dose), 1 animal sacrificed at 54 wks, 2 at 2-yrs and 1 after a 13-wk recovery period. 1249414 and **38-week dietary** toxicity - dog 4/sex/dose (follow-up study) Sacrifice - Control: 2/sex/dose at wks 26 and 38; Treated grp: 2/sex/dose at wk 26, 1/sex/dose at wk 38 (1 allowed to recover for 25 days for evaluation of stored boron depletion). 1237740 and 1249410	0.0, 1.4, 3.0, 8.8 mg **Boron**/kg bw 4 animals served as control for the borax and the concurrent boric acid study (2-yr) - see below 0 and 40 mg **Boron**/kg bw 4 animals served as the same control for both the borax and the concurrent boric acid 38-wk study.	Provisional ♀: 8.8 ♂ : 3.0	The testis of the control dog, sacrificed after 13-wk recovery, had a few single tubules or foci at various stages of atrophy. The other three ♂ dogs had normal testes. **@1.4 mg/kg bw:** at 2-yrs, both ♂ had a few atrophied tubules / degenerative changes / spermatogenic arrest. **@3.0 mg/kg bw:** 1 ♂ at 2-yrs had a small # of atrophied tubules in the outer half of gland. Spermatogenesis arrested in the spermatocyte stage in other tubules. **@8.8 mg/kg bw:** 1 ♂ at 2-yrs excluded because of artifactual distortion. The seminiferous epithelium of the other ♂ at 2-yrs had in a majority of the tubules in various stages of atrophy, focal leukocytic infiltration, epididymis empty and atrophy of tubules progressed to a complete loss of germinative cells. No apparent affect on testicular wt (see comments for boric acid, below). **Sperm analysis**: 2 ♂/control and high-dose grp: the sperm of both treated ♂ was azoospermic (0-10,000/cu mm for treated ♂ vs 90 - 120,000/cu mm for control) with no or low motility (0-50% for treated ♂, vs 50-100% for controls). General ↑ in severity and number of thyroid effects at 2-yr sacrifice, all doses. **Control dogs:** at wk 26, ½ had spermatogenesis and 5% atrophy. At 38 weeks, 1 dog had spermatogenesis and the other testicular atrophy. **Treated dogs**: testis smaller and firmer. No sperm specimen could be obtained from any dog. At wk 26, both sacrificed dogs had complete testicular atrophy and spermatogenic arrest. Abs and rel testes wt ↓. At 38 weeks, testicular effects in the one dog were not sign different from control. **Recovery dogs**: ♂ had moderate degree of degeneration and evidence of complete cessation of spermatogenesis. The ovaries of ♀ had old corpora lutea, indicating that cyclic function had continued during the test period. However, some of the follicles were atrophied. Sporadic changes in the thyroid gland, primarily an ↑ in follicular nests. **Supplemental** (lack of ovary pathology) **Sperm analysis NOT done on low and mid-dose grps.**

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
2-year dietary toxicity - dog 4/sex/dose **Boric Acid** <u>Sacrifice schedule for concurrent borax and boric acid studies</u>: (control and high-dose), 1 animal sacrificed at 54 wks, 2 at 2-yrs and 1 after a 13-wk recovery period. 1249387 and	0, 1.6, 3.6 and 9.4 mg **Boron**/kg bw	Provisional ♀: 9.4 ♂: 3.6	The testis of 1 control dog, sacrificed after 13-wk recovery, had a few single tubules or foci at various stages of atrophy. The other 3 dogs had normal testes. **@1.6 mg/kg bw:** 1 ♂ at 2 yrs had "smaller testicles", some tubules in various stages of atrophy. **@3.6 mg/kg bw:** 1 ♂ at 2 yrs had ↓ in thickness of the seminiferous tubules, tubules were irregularly vacuolated, spermatogenesis did not proceed to completion (amorphous material from vas deferens). **@9.4 mg/kg bw:** All ♂s affected. ♂ at 1 yr had partly atrophied tubules scattered through central portion of organ. At 2 yrs, one ♂ had tubular degeneration, adjacent to central raphae (this ♂ produced adequate sperm), other ♂ had very small testicles with complete atrophy and slight focal calcification (this ♂ could not produce sperm). **Recovery** ♂: 10-20% of tubules had degenerative changes, progressing to complete atrophy of spermatogenic epithelium. Degeneration mainly in central portion of organ, a few foci of interstitial mononuclear leukocytic infiltration. A number of tubules contained inspissated (dried) spermatozoa; ↑ in % of epithelial nests (thyroid) in ♂s . **Sperm analysis**: ½ ♂s produced an adequate sperm sample with 100% motility. **Control dogs:** at week 26, ½ had spermatogenesis with 5% atrophy. At 38 weeks, one animal had spermatogenesis and the other had testicular atrophy. **Test dogs**: testis smaller and firmer (3/4), ↓ in testis wt and testis/BW ratio, no sperm from any dog. After 26 wks, testis of both dogs had uniform spermatogenic arrest, progressing to complete atrophy of the seminiferous epithelium in various tubules, % of interfollicular nests variable (thyroid: follicles generally inactive). After 36 wks, the one ♂ dog had complete atrophy of seminiferous tubules and ↑ interstitial tissue (both testis). ♀ ovaries were inactive and many follicles were atrophied. **Recovery dogs**: evidence of regeneration of testis "...seminiferous tubules were lined by thick spermatogenic epithelium... moderately active in most instances."(contradicts Ku and Chapin's NTP study in rats -see mechanistic studies pg19); evidence of previous function in ovaries. **Supplemental** (lack of ovary pathology) **Sperm analysis NOT done on low and mid-dose grps.**
38-week dietary toxicity - dog 4/sex/dose (follow-up study) 1249383	0 and 40 mg **Boron** /kg bw 4 animals served as the same control for both the borax and the concurrent boric acid 38-wk study.		

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
2-year dietary toxicity study - albino rat (SD) 35/sex/dose **Borax** 1249413	0, 7.3, 17.4, 58.2 mg **Boron**/kg bw	NOAEL: 7.3 (systemic toxicity only)	**≥ 17.4 mg/kg bw:** ↓ bwg **@ 58.2 mg/kg bw:** coarse hair coats, hunched posture, inflamed and bleeding eyes, dark pink swollen paws, ↓ hct and hgb, ♂ had shrunken scrotum, ↓ testis weight (abs and rel) and testicular tubular atrophy. **Supplemental** (no mention of tumour / sperm analysis)
2-year dietary toxicity study - albino rat (SD) 35/sex/dose Control: n=70/sex The above (borax) study had groups 1,2,3 and 4. This study had groups 1, 5, 6 and 7. Appears that one control used for both borax and boric acid studies, but not specified). **Boric Acid** 1249385	♂: 0, 5.2, 15.9, 57.7 mg **Boron**/ kg bw ♀: 0, 6.3, 18.8, 70.0 mg **Boron**/ kg bw Doses calculated from weekly compound consumption.	LOAEL: 5.2/6.3	↑ in grading of focal tubular atrophy (n=10). **≥ 5.2/6.3 mg/kg bw:** ↓ BW, (dose-response, but not s.s); signs of respiratory involvement that became more frequent and pronounced as study proceeded - unable to confirm since no pathol. done and individual/cage-side observations not reported (observation made in passing, in author's summary). ♂: ↓ cell volume and hgb at 565 days and termination. ♀: ↓ hgb at ≥1 yr, ↓ urinary pH. **≥15.9/18.8 mg/kg bw**: ↓ abs kidney wt (termination only). Appears to be slight ↑ in the severity of ovarian effects (anovulatory, involution). **@ 57.7/70.0 mg/kg bw:** coarse hair, scaly tails, hunched position, swollen eyelids, bloody discharge from eyes, swelling and desquamation of pads and paws. Scrotum of all ♂ shrunken; ↓ BW, cell volume and hgb (all time points); ↑ urinary RBC, WBC (♂) and epithelial cells; complete testicular atrophy by 6 months, atrophied seminiferous epithelium and ↓ tubular size. **Supplemental** (no ovary wts, no sperm analysis, no tumour tables, no histo, comparison of n=70 in control to n=35 in dose groups makes interpretation difficult, etc.)
2-year dietary toxicity / oncogenicity study - B6C3F1 mice 50/sex/group **Boric Acid** 1214936	0, 78, 201 mg **Boron**/kg bw	No NOAEL could be set	**≥78 mg/kg bw:** ↑ ♂ mortality and incidence of splenic lymphoid depletion. **@ 201 mg/kg bw:** ↓ bwg, testicular atrophy and interstitial cell hyperplasia. No tumours were attributed to the administration of boric acid. However, the low number of surviving ♂ reduced sensitivity of the study. **Supplemental** (low number of surviving ♂s)

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
Reproductive and Developmental Toxicity Studies			
Reproduction Study, Three Generations Sprague Dawley rats 8 ♂, 16 ♀/group **Borax** 1249415	♂: 0, 9.6,28.3, 83.1 mg **Boron** / kg bw ♀: 0, 10.1, 31.2, 92.8 mg **Boron**/ kg bw	Parental NOAEL: 23.8 (provisional) Reproduction NOAEL cannot be set	Parental: **@ 83.1 / 92.8 mg/kg bw:** ↓ BW and bwg, food efficiency (P1 ♀ only) atrophied testes and ↑ ovarian findings (cyst formation, congestion and infection). Reproductive: **@ 83.1 / 92.8 mg/kg bw:** P1 - no litter when treated ♂s mated with treated ♀s; **also ↓ number of pup/litters and pup survival when treated ♀ were mated to control ♂ - thus ↓fertility and pup survival also influenced via ♀** **Supplemental** (no clinical obs., BW, fc during gestation, no organ wt, etc., questionable results in control
Reproduction Study, Three Generations Sprague Dawley rats (8 ♂, 16 ♀/group) **Boric Acid** 1249388	♂: 0, 8.5, 26.6, 85.0 mg **Boron** / kg bw ♀: 0, 9.7, 29.0, 91.6 mg **Boron**/ kg bw Doses calculated from test article intake data.	Parental NOAEL: 26.6 Reproductive NOAEL cannot be set.	Parental: **@ 85.0/91.6 mg/kg bw:** ↓ bwg, beginning 2nd and 3rd weeks, rough fur coats, marked respiratory involvement. Scaly tails, inflamed eyelids and staining of the fur and abdomen. ♂s had small, soft testes (↓ 75% in wt, compared to 11% in low dose and 9% in mid-dose) and ovaries in a few ♀ appeared congested or cystic (50% were nonfunctional or showed ↓ function). P1 parents failed to produce litters. **P1 ♀ mated with control animals still failed to produce litters- thus, ↓fertility and pup survival also affected via ♀** Reproductive: Small sickly pups with wrinkled brown or blue skin in all litters, all groups, including the control. No pathology, exact numbers not supplied, but states more frequent in F3 litters. **≥8.5/9.7 mg/kg bw:** ↓ mean pup BW at weaning - depending on the generation, up to 9%, but not consistent. **≥26.6/29.0 mg/kg bw:** ↓ mean pup BW at weaning - depending on generation, up to 12% - consistent, except for F3b (reverse happens). **Supplemental** (Same gaps as above study, also see Appendix 2 re: low fertility and lactation indices in the control)

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
Reproduction Study, Two Generations - CD-1 Swiss Mice (n=40 for control, then 20/sex/dose **Boric Acid** 1237745	♂: 0, 23.5, 101.8, 236.2 mg **Boron** /kg bw ♀: 0, 28.6, 135.5, 276.8 mg **Boron** / kg bw	Parental and Reproductive NOAELs: 23.5 / 28.6 Boron	Parental: **≥ 101.8/135.5 mg/kg bw:** ↓ BW, testis wt (abs, rel), sperm conc., sperm motility, ↑ atrophy and abnormal sperm. Reproductive: **≥ 101.8/135.5 mg/kg bw:** ↓ fertility and pup wts. **@ 236.2 / 276.8 mg/kg bw:** no litters produced. Cross-over mating of control ♂ with 135.5 mg/kg bw ♀ confirmed that the ♂ was the predominantly affected sex.
Teratology **Dietary feeding study, gd 0-17** Mice-Swiss (CD-1) 28-29 mice/group **Boric Acid** 1237749	0, 43, 79, 176 mg **Boron**/kg bw	Maternal NOAEL: cannot be set Developmental NOAEL: 43	Maternal: **≥ 43 mg/kg bw:** ↑ renal dilation, dose-response, with / without regeneration. **@ 176 mg/kg bw:** pale kidneys, ↓ in gravid uterine wt, ↑ abs + rel kidney wts. Developmental: **≥ 79 mg/kg bw:** ↓ fetal body weight **@176 mg/kg bw:** ↑ in resorptions/litter, short rib XIII, agenesis and fused ribs.
30 and 60 day dietary toxicity SD rat 18 ♂/dose 5 serially mated; 10 assessed for FSH, LH and testosterone; 3 for histology	0, 12.5, 25, 50 mg **Boron** / day	**Supplemental Journal Article** Ku and Chapin; 1993	**≥25 mg:** at both 30 and 60 days, sign. loss of germinal elements, ↓ seminiferous tubular diameter, and accumulation of testicular boron. Dose-response in testicular atrophy and depletion of germ cells was complete after 60 days of dosing. Germinal depletion associated with sign. ↑ plasma FSH, both time and dose-dependent. **Serial mating studies**: ↓fertility, no change in copulatory behaviour. **@ 50 mg:** germinal aplasia, elevated FSH, and infertility persisted for at least 8 months following exposure. Altered FSH is likely secondary to testicular function and thus, not a true endocrine disrupter (Fail et al; 1998).

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
Teratology **Dietary feeding study, gd: 0-20 OR 6-15** Sprague Dawley Rat 29/dose for first 3 dose levels, then 14/dose for last dose **Boric Acid** 1237748	0, 13.6, 28.5, 57.7, 94.3 mg **Boron** / kg bw 0, 13.6, 28.5 and 57.7 mg/kg bw during gd 0-20 and 0 and **94.3 mg/kg bw during gd 6-15**. Dosing from gd 0-20 was to allow plasma boron levels to reach a steady-state prior to implantation, thus creating an appropriate model for long-term low-level exposure such as occurs from food or drinking water sources.	Maternal NOAEL: ⩾94.3 Developmental: No NOAEL could be set (concurs with USEPA-IRIS,2004).	No Maternal Toxicity: **@ 94.3 mg/kg bw:** no treatment-related effects. Developmental: <u>For dosing during gestational days 0-20 (13.6, 28.5 and 57.7 mg/kg bw)</u> **≥13.6 mg/kg bw:** ↑ variations (short rib XIII, wavy ribs, ↓ fetal BW) **≥28.5 mg/kg bw:** cleft sterna **≥57.7 mg/kg bw:** ↑ % resorptions, agenesis of rib XIII, enlarged lateral ventricles (ELV) of the brain. <u>For dosing during gestational days 6-15 (94.3 mg/kg bw)</u> **@94.3 mg/kg bw:** ↓ fetal BW, ↑ prenatal mortality/resorptions, cardiovascular defects, short and/or curly tail, anophthalmia and microphthalmia, one fetus with hydrocephaly and 13 fetuses had cleft sternum. <u>Overall (0, 13.6, 28.5, 57.7 and 94.3 mg/kg bw)</u> - % lit with malform [21, 21, 50, 100, 100] - % lit with skeletal malform [14, 18, 46, 100, 100] - % lit with gross malform [4, 0, 4, 4, 71] - % lit with visceral malform [7, 4, 0, 36, 86] **FETAL SENSITIVITY**
Teratology- **Dietary feeding study, gd 6-15 with Post-natal Development Phase** Sprague-Dawley Rat 42-76/group **Boric Acid**	**Phase I**(dosing gd 6-15): 0, 52.3, 63.2, 75.6, 96.1 mg **Boron**/kg bw **Phase II** (dams allowed to deliver and rear pups to pnd 21): 0, 49.5, 64.4, 76.0, 98.4 mg **Boron**/kg bw		**All doses:** ↑ Resorptions/late fetal death on gd 20, postnatal death at all exposures by pnd 21. ↓ offspring BW in all groups on gd 20 and on pnd 0. Except for high dose, pup wt comparable with controls on pnd 14 and 21. High dose group still 76% of control on pnd 21. **High dose:** Craniofacial malformations (primarily anophthalmia and microphthalmia) were observed in high-dose fetuses on gd 20 and on pnd 21. -This study pointed out that in the previous study the ↑ in ELV seemed to correlate with ↓ fetal BW. After adjusting for fetal BW by covariant analysis in the present study, the incidence of ELV showed no significant dose-response relationship. -Unlike the previous study, this study showed an ↑ in hydrocephaly (0, 2, 1, 5 and 15% of pups; control - high-dose). Covariant analysis showed that lower fetal BW was associated with higher incidence and greater severity of hydrocephaly, but after adjusting for fetal BW, ***there remained a significant dose-related effect on hydrocephaly incidence and severity in all dose groups of this study indicating that the CNS effects of this compound are independent of fetal growth.***

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
			Supplemental NTP study to support the above 1990 NTP study. Results support interpretation that boric acid exposure during organogenesis adversely affects rat CNS development, independent of its effects upon fetal growth.
Teratology **Dietary feeding study, gd 0-20 with postnatal phase** Sprague Dawley Rat 30/dose- teratogenic evaluation 30/dose- postnatal evaluation **Boric Acid**	0, 3.3, 6.3, 9.6, 13.3, 25.0 mg **Boron**/kg bw	Developmental NOAEL: **9.6 mg/kg bw**; the conclusive developmental NOAEL that could not be set in the previous studies.	**No Maternal Toxicity:** As in the previous CNS study, there were no maternal effects after correcting for gravid uterine wt: "No maternal deaths occurred and no distinctive treatment-related clinical signs of toxicity were observed during either study (this study and the original NTP developmental study)." <u>Developmental</u>: Phase I (teratogenic evaluation (gd 20)) **≥9.6 mg/kg bw:** ↑ in short rib XIII **≥13.3 mg/kg bw:** ↑ in wavy rib, ↓ in fetal BW Phase II (postnatal) There was recovery from the ↓ in fetal BW. **@ 25 mg/kg bw:** ↑ in short rib XIII (pnd 21). **Supplemental NTP study to support the 1990 NTP study.** **FETAL AND OFFSPRING SENSITIVITY**
Teratology Study, Rabbit - NZW 30/group **Gavage, gd 6-19** **Boric Acid** 1149190	0, 10.9, 21.8, 43.7 mg **Boron**/kg bw	Maternal NOAEL: 21.8 Developmental NOAEL: 10.9	Maternal: **@ 43.7 mg/kg bw:** ↑ in vaginal bleeding. Developmental: **≥21.8 mg/kg bw:** ↑ in agenesis of the gallbladder. **@ 43.7 mg/kg bw:** ↑ in resorptions, post-implantation loss, ↓ in viable fetuses per dam (88% less pups, compared to control), ↑ cardiovascular defects (enlarged aortas, intravascular-septal defects, great vessels arising from the right ventricle). **FETAL SENSITIVITY**
Genotoxicity Studies			
Ames Salmonella assay - TA 98, TA100, TA1535, TA1537, TA 1538 strains 1139720	10-2500 µg/plate ± S9 > 99% pure **Boric Acid**	Negative	

Study/Species/ # of animals per group	Dose Levels in Boron Equivalents	NOAEL (mg/kg bw/day)	Results/Effects
In vitro mouse lymphoma cell mutagenesis assay - L5178Y cells (TK+/-) 1139717	1200-5000 µg/ml + S9 > 99% pure **Boric Acid**	Negative	
UDS (In vitro) - primary rat hepatocytes 1139718	0.5-5000 µg/ml > 99% pure **Boric Acid**	Negative	
In vivo bone marrow micronucleus test-CD-1 mouse 10/sex/group 5/sex/group sacrificed 24 and 48 hr after final dose 1139719	0, 900, 1800, 3500 mg/kg; daily oral dose for 2 days > 99% pure **Boric Acid**	Negative	

Annex I: External Reviews

A. Dr. Graham Smith, CanBioPharma Consulting Inc.

In 2005, the PMRA contracted Graham Smith DACVP (Clinical Pathology) to review the boric acid and borax dog toxicity studies and address questions with respect to combining the studies,[7] NOAELs, relevance of histological findings, use of these data to inform the risk assessment and whether or not a new dog study, with full sperm analysis, is warranted.

Dr. Smith did not recommend combining the boric acid and borax dog toxicity studies. Because of the large variability in nominal dosing, it was Dr. Smith's recommendation that each dog in the 2-year toxicity studies be evaluated on an individual dog basis. Although Dr. Smith was not asked about combining the 90-day dog studies, the variability in nominal to actual doses was also apparent in these shorter-term toxicity studies.

With respect to setting NOAELs for testicular toxicity, Dr. Smith stated, "...at this time I am reluctant to ascribe these dose levels [1.6 and 1.4 mg/kg bw/d] as definitive NOAELs or NOELs for testicular effects in dogs for a number of reasons. These reasons include: the low number of male dogs evaluated pathologically after 2 years administration of test article at 1.6 and 1.4 mg/kg bw/d (2/dose level); the variability in actual dose levels administered on a mg/kg basis over the course of the study; potential effects on ejaculate volume and/or motility were not evaluated at nominal dose levels of 1.6 or 1.4 mg/kg even though potential treatment-related effects on these parameters were identified for high-dose males; and unknown or potentially

[7] Compound identifiers were removed and replaced with Compound A (boric acid) and Compound B (borax).

questionable quality of histological sections of testes available for microscopic examination in both studies...". "Also, the reported occurrence of decreased absolute testicular weights at 0.4 mg/kg in the 90-day dog studies for Compound B (borax) potentially undermines the validity of ascribing a NOAEL or NOEL for testicular effects based on absence of reported findings at the low dose levels used in the 2-year dog studies for Compound A (boric acid) and Compound B (borax)."

Dr. Smith also stated that, "...the identification of treatment-related histopathologic findings in the testis of rat and/or dog in toxicity studies should be viewed as a signal that needs to be understood and underlying mechanisms/exposures characterized wherever possible in order to project the relevancy of findings in rat or dog testes for humans." As well, Dr. Smith stated, "There would appear to be a need to characterize the NOAEL for testicular effects in a sensitive, relevant animal species (potentially dog) and this information was not clearly provided by results for the two 2-year dog studies."

Concerning data requirements, Dr. Smith stated, "Presumably there is a need to characterize minimal adverse effect dose levels and/or the NOAEL for testicular effects as part of the human health risk assessment for the test article and therefore there is a scientific need to conduct a repeat-dose toxicity study to current day standards in a relevant species. Therefore conduct of a repeat-dose toxicity study in sexually mature dogs to fully characterize the toxic potential of the test article is warranted (presuming the dog to be the most relevant animal species). It may be that a study duration of less than 1-year could be sufficient to characterize potential testicular and other effects of test article administration. In this prospective study, testes should be fixed in Davidson's solution or in Bouins. It is recommended that prostate as well as testes is weighed and evaluated microscopically and that pathologic evaluations include female reproductive organs."

B. Expert Panel Report

At the request of the registrant, the PMRA convened a panel of experts (known as the Panel) to comment on the appropriate inter- and intra-species uncertainty factors (UF) and the applicability of any additional UFs. The Panel was also asked to comment on the adequacy of the developmental and reproductive toxicity database, with regards to establishing reference doses for conducting appropriate human health risk assessments.

Panel Comment: The Panel agreed with the PMRA that the testicular effects in the dog are of concern. The Panel combined the 90-day dog studies for boric acid and borax and calculated a benchmark dose (BMD) using testicular weight as the endpoint of concern. Using 4 models for continuous data, the following BMDLs were obtained: the Hill model (2.90 mg/kg bw/d), the Linear model (14.00 mg/kg bw/d), the Polynomial model (5.31 mg/kg bw/d) and the Power model (14.00 mg/kg bw/d). The Panel considered the Hill and Polynomial models to be less accurate and recommended using a BMDL of 14 mg/kg bw/d and an additional 3-fold for database uncertainty since histological effects and sperm effects would likely occur at lower dose levels than those causing a decrease in testicular weight.

PMRA Response: Although the Panel was made aware of the differences in nominal to actual dose levels for each dog, this was not taken into account in their BMD assessment. The PMRA, using the same criteria as the Panel, calculated BMDs for each individual study. Both individual studies gave lower BMDL values than the combined studies. A BMDL value of 2.9 mg/kg bw/d was chosen by the PMRA, based on combined study data and model selection criteria from USEPA guidance (Nov. 2008). While the Panel chose a value of 14 mg/kg bw/d, basing their selection on the smallest difference between the BMD and BMDL values, the PMRA maintains that since the BMDL estimates are not sufficiently close (range 2.90 - 14.0 mg/kg bw/d), the model with the lowest BMDL value should be used for the risk assessment. The 2.90 mg/kg bw/d value is also more consistent with the expected dose-response profile in the mid- and long-term dog studies.

The PMRA agrees with the Panel that an additional 3-fold factor should be applied to the BMDL to account for database uncertainty regarding testicular histopathological effects that are expected to occur at doses below those doses causing a decrease in testicular weight. This gives a projected value of approximately 1 mg/kg bw/d, which is close to the potential NOAEL in the 2 year dog toxicity studies.

Panel Comment: The Panel divided the standard interspecies extrapolation factor of 10-fold into 4-fold for interspecies toxicokinetics and 2.5-fold for interspecies toxicodynamics. Taking into consideration what the Panel referred to as 5 "acceptable" core studies (mouse oncogenicity, reproduction toxicity in mice, and developmental toxicity in mice, rats and rabbits), and published toxicokinetic data from pregnant women and rats, the Panel recommended decreasing the toxicokinetic factor from 4.0-fold to 3.3-fold (total extrapolation factor of 8.3-fold). The PMRA indicated to the Panel that data for pregnant women and rats were highly variable; that the rat appears to have a one-compartment metabolism and humans a 3 compartment metabolism and that humans tend to clear boron 3-4 times slower than the rat. The Panel responded that these "known" differences were taken into consideration in the extrapolation factor of 8.3-fold, referencing the USEPA IRIS risk assessment to support their response.

PMRA Response: The PMRA has considered the Panel's input and has determined that retaining a full 10-fold factor for interspecies extrapolation is more appropriate for the following reasons:

- Of the 5 core studies referenced by the Panel in support of decreasing the interspecies extrapolation factor, 3 of the studies were conducted in the mouse, the species that is least sensitive to the effects of boron. Moreover, there were numerous limitations in these studies.

- Although the Panel cited the USEPA IRIS document to support their interspecies extrapolation factor reduction, they do not explain that this assessment did not divide the interspecies factor into 4.0-fold and 2.5-fold. The USEPA IRIS assessment divided the 10 fold factor into 3.3-fold for toxicokinetics and 3.16-fold for toxicodynamics. Also of note is the fact that the USEPA IRIS assessment did not decrease the total interspecies factor, but rather maintained a total factor of 10.4-fold (3.3-fold × 3.16-fold). This is in close agreement with USEPA Office of Pesticide Programs (USEPA OPP), which also maintained a full 10-fold for interspecies extrapolation.

- The Panel recommended using the dog studies to establish reference doses for boron. However, there is little to no data on the toxicokinetics of boron in dogs to allow a meaningful comparison to humans and therefore a determination of the appropriate interspecies extrapolation factor for dog to human.

Panel Comment: For the intraspecies variability factor, the Panel recommended dividing the10-fold factor into 3.2-fold for toxicokinetics and 3.2-fold for toxicodynamics. Similar to the interspecies factor, the Panel recommended decreasing the toxicokinetic portion from 3.2-fold to 2.0-fold. The total intraspecies factor proposed was 6.4-fold. The Panel referenced the USEPA IRIS document and stated that there was less concern for pregnant women because of increased glomerular filtration (GFR) and "...the pregnant human is the population associated with B's [boron] critical effect and thus, its choice fulfills several criteria for endpoint selection from the existing guidelines." "Furthermore, B's elimination is the kinetic area with the most variability—absorption and distribution of B are expected to be very similar among humans and B is not metabolized."

PMRA Response: The PMRA has considered the Panel's input and has determined that retaining the full 10-fold intraspecies variability factor is more appropriate for the following reasons:

- The Panel cited the USEPA IRIS document as their support for why the intraspecies toxicokinetic factor could be decreased. However, with respect to pregnant females, USEPA IRIS states that, "Lack of controls on exposure magnitude and timing would be expected to contribute substantially to the variance of the measurements. The high variability reported by Pahl et al. (2001), therefore, is attributed to experimental 'noise' and should not be included in the estimate of true population variability." To support this position, USEPA IRIS states, "In contrast, in the controlled infusion exposure study of Jansen et al., (1984), the boron clearance coefficient of variation (CV) was 0.09." USEPA IRIS states that the Jansen study shows little variance in clearance. However, two of the eight men in the Jansen study were excluded from the study because they either had highly variable plasma ½ lives or they did not fit the predicted 3-compartment pharmacokinetic model. Thus, 25% of the men had to be excluded because of their high pharmacokinetic variability. These two men were not included in USEPA IRIS's assessment of variability. Although the PMRA informed the Panel of this discrepancy, it was not addressed in the final justification for decreasing the intraspecies toxicokinetic variability factor.

- The majority of pregnant animals, including humans, have increased GFR because the kidney undergoes volume expansion, vasodilation and decreased resorption during pregnancy. Although pregnant rats had increased GFR, this did not protect the fetus from developmental effects of boron (malformations), which were observed at maternally non-toxic doses. This fact must be taken into consideration when assessing potential risk to the unborn child, by ensuring adequate margins between potential exposure levels and the noted malformations in the developmental rat study.

- The studies used by USEPA IRIS included small sample groups of individuals of similar age, sex (all males), health (free of any disease), weight, and ethnicity. Consideration of the variability within the human population needs to be taken into account. For example, gestational diabetes would likely have a significant effect on the toxicokinetics of boron since the kidneys are often a target organ of diabetes.

- In their most recent assessment the USEPA OPP retained a full 10× for intraspecies variation.

Panel Comment: The Panel considers the database to be adequate for conducting risk assessment. The application of an additional 3× for database uncertainty, pertaining to testicular toxicity, is sufficient protection.

PMRA Response: The PMRA concurs with the Panel that, with the addition of uncertainty factors, a risk assessment can be conducted for elemental boron.

Appendix IV Mixer/Loader/Applicator and Postapplication Risk Assessment

Table 1 Dermal and Inhalation Margin of Exposures for M/L/A of Commercial End-use Products Containing Boron

Formulation	Application Description/Site	Assessment Used	Amount Applied (kg ai/day) [f]	PPE and Engineering Controls	Margin of Exposure		
					Dermal[v]	Inhalation [w]	Combined[x]
paste	open bait	PHED - liquid, open pour, low pressure handwand (M/L/A)	0.43 [g]	single layer, gloves [q]	990	10300	**900**
	crack and crevice with putty knife	PHED - paintbrush application		Single layer, gloves	21	630	**20**
	brush, trowel	PHED - paintbrush application	1.08 [h]	chemical resistant coveralls with gloves [r]	8.4	250	**8.1**
solution	Open baiting, refill bait station	PHED – liquid, open pour, low pressure handwand (M/L/A)	0.02 [i]	single layer, gloves	20500	2.1×10^5	**19000**
	Roller or spray [a]	PHED - liquid, open pour, low pressure handwand (M/L/A)	0.94 [j]	single layer, gloves	460	4800	**420**
	Brush [a]	PHED - paintbrush application	0.94 [j]	single layer, gloves	8	290	**8**
	Enclosed bait	n/a [c]	-	-	-	-	**-**
solid	rod	n/a [c]	-	-	-	-	**-**
dust/powder	crack and crevice, bellows duster, power duster, or other	PHED – granular bait dispersed by hand [d]	0.17 [k]	single layer, gloves [s]	15	1900	**15**
soluble powder	brushing, spraying, or dipping wood	PHED - paintbrush application [e]	2.16 [l]	single layer, gloves	3.6	130	**3.5**
	Drill and injection or dusting	PHED – granular bait dispersed by hand [d]	2.36 [j]	single layer, gloves	1.1	140	**1.1**
	crack and crevice [b]	PHED – granular bait dispersed by hand [d]	0.24 [k]	single layer, gloves [s]	11	1400	**11**
	additive; material preservation process	PHED - wettable powder (open M/L)	3.39 [m]	single layer, gloves	230	1100	**190**

pressurized product	small openings, cracks, crevices, and closed voids, injection tube required	PHED - aerosol application	0.032 [n]	Chemical resistant coveralls, gloves, respirator	160	39000	**150** [y]
granular	Voids, bait trays, or bellows-type duster/snuffer	PHED - push-type spreader	0.10 [o]	long pants, long sleeves, no gloves	650	5.7×10^5	**650**
	fertilizer or seed spreader	PHED - granular, open pour, belly grinder	31.26 [p]	single layer, no hand data used [t]	0.74	81	**0.74**
	pressure sprayer	PHED - wettable powder, open pour, low-pressure handwand	31.26 [p]	single layer, gloves [u]	0.66	4.6	**0.57**

Values are rounded. Shaded cells indicate the MOEs did not reach the target MOE of 300.

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a Assuming the maximum label application rate of 1 L / 1 m^2 (in two applications, therefore 2 × 0.5 L / m^2): As the average area treated/day unknown, assumed 18.75 L/day based on USEPA assumption that commercial applicators of antifouling paint are capable of applying 18.75 L of paint per day (using a paintbrush, based on professional judgement).

b Applied as powder, NOT formulated into solution from soluble powder.

c Exposure assumed negligible for:

- Enclosed bait stations (applicator required to perforate holes on sides of enclosed container with nail).

- Rods. Exposure would likely be limited to incidental exposure resulting from dissolution of the product with sweat from hands and subsequent transfer to mouth or eyes; however, due to the physical nature of the rods (i.e., fused anhydrous boron), the amount of boron available from the rod for dermal or oral absorption is expected to be negligible. Potential exposure may be minimized by wearing non-absorbent gloves while working with the product. PPE required on label indicates "chemical resistant gloves" required in cases of prolonged contact. Risk assessment not performed.

d Based on PHED, granular bait dispersed by hand (assuming single layer and gloves). This estimate is assumed to be conservative, however use specific data is not available for this application scenario.

e Risk assessment for solution and foam formulated from soluble powder. Although PHED - liquid, open pour, low pressure handwand exposure values may be considered more representative of both the spray and inject application methods, this scenario does not take into account paintbrush application of product; PHED -paintbrush exposure values considered more conservative and covers off various application methodologies.

f Amount applied (kg ai/day) presented as percent boron equivalence using the following conversion factors:
for BNS ($Na_2B_4O_7$ - 10 H_2O) , boron equivalent (%/100) = 0.11338
for BOA (H_3BO_3) , boron equivalent (%/100) = 0.17491
for BOC ($Na_2B_8O_{13}$ - $4H_20$) , boron equivalent (%/100) = 0.20965
for ZBT ($2Zn0$ - $3B_2O_3$ - $3.5H_2O$) , boron equivalent (%/100) = 0.14927
In addition to boron equivalence factors (above), values presented for amount applied (in kg active ingredient/day), also take into account specific gravities (where applicable) and guarantees.

g For putty knife use paintbrush scenario in PHED (assuming single layer, and gloves). Based on largest area treated by PCO with bait stations/per day (apartments/residences), assume max of 1380 m^2 treated per day. Max rate provided = 1.8 g a.i./m^2 × 1380 m^2 = 2484 g/day.

h Estimate 18.75 L (or 23.87 Kg product) applied based on USEPA assumption that commercial applicators of antifouling paint apply 18.75 L of paint (using a paintbrush) per day (based on professional judgement). Full reference in USC file for Antifouling Paints. Assumed paintbrush scenario for application directly to poles and application to wraps attached to poles. PHED paintbrush data is not considered overly conservative and was deemed the most adequate data to use in this scenario. Note: "Pole Bandaging" application not reviewed in this assessment.

i Area treated per day not specified, assume 1 package used per day. Maximum package size 10 L, however the specific gravity value was unknown and assumed to be 1.

j As average area treated/day unknown, assume 18.75 L/day based on USEPA assumption that commercial applicators of antifouling paint are capable of applying 18.75 L of paint per day (using a paintbrush, based on professional judgement).

k Assumed 1 kg product applied per day. Based on communications with Structural Pest Management Association of Ontario and Canadian Pest Management Association of Canada (PMRA# 2179313). PCOs typically apply 1 kg of dust/powder pesticidal product per day (in homes and construction). For equivalent dust/powder product used in poultry house or barn, 11 kg of product is used (based on label rate): this results in a combined MOE of 1.4.

l Typical area treated per day not determined. 98% guarantee, assumed 18.75 L based on USEPA assumption that commercial applicators of antifouling paint apply 18.75 L of paint per day (using a paintbrush, based on professional judgement). Full reference in USC file for Antifouling Paints. However, for application with a paintbrush, must prepare a 15% solution (add 180g of powder per litre of treating solution required: therefore 18.75 L × 0.18 Kg/L = 3.375 kg product. Mixing is required for this product.

m 100% guarantee, net contents = 22.7 kg (assume one package used per day). Rate of addition unclear.

n 35.5% guarantee, net contents = 255 g per can (assume max of 2 per day). Application rate unclear.

o Based on basement treated by PCO with push-type spreader, assume max basement size of $600ft_2$ ($55m^2$). 10 basements treated per day = $550m^2 \times 2kg/100m^2 = 11kg$. Note: this assessment only applies to the broadcast application of the granular formulation. The crack and crevice application of this granular product is covered by the dust/powder risk assessment. As that assessment results in an MOE that does not meet target MOE, clarification or removal of the crack and crevice application of the granular formulation is required.

p Label provides worst case (greatest area treated) 150 Kg product per 3000 m^2 house, assume one house treated per day (note that this rate is provided for pressure spray on label.

q For PHED-liquid, open pour, low pressure handwand scenario, only gloved data is available.

r PPE required include coveralls, chemical goggles/face shield, chemical resistant gauntlets (long sleeve gloves), chemical resistant apron, head gear, boots. Assumed chemical resistant coveralls with gloves from PHED; based on a comparison of paintbrush exposure studies.

s Based on PHED, granular bait dispersed by hand (assuming single layer and gloves).

t Single layer and no gloves were assumed for the PHED, granular/open pour/belly grinder M/L/A; no adequate hand data available. Additional gloved data from other scenarios were not considered as a surrogate for hand exposure values because the MOE values were well below the target without hand exposure already.

u PPE not indicated for spray treatment, assume single layer with gloves (no hand data without gloves)

v Dermal MOE $= \frac{BMDL\ dermal}{Exposure\ dermal}$ The dermal BMDL is 2.9 mg/kg bw/day; the target MOE is 300. Dermal absorption = 50%.

w Inhalation MOE $= \frac{BMDL\ inhalation}{Exposure\ inhalation}$ The inhalation BMDL is 2.9 mg/kg bw/day; the target MOE is 300.

x Dermal and inhalation risks were based on the same endpoints, therefore the risk from these routes were combined in the following equation:

$$\frac{1}{MOEdermal} + \frac{1}{MOEinhalation} = \frac{1}{MOEcombined}$$

y The combined MOE does not meet the target MOE of 300, however this may be attributed to PHED not taking into account the use of engineering controls such as the injection tube which is required with use of these pressurized products. The impact of this engineering control on exposure cannot be quantified.

Table 2 Dermal and Inhalation Margin of Exposures for M/L/A of domestic End-use Products Containing Boron

Formulation	Application Description/Site	Assessment Used	Amount Applied (kg ai/day) [d]	PPE and Engineering Controls	Margin of Exposure		
					Dermal[q]	Inhalation[r]	Combined[s]
paste	enclosed bait	n/a [b]	-	-	-	-	-
	open bait	PHED - liquid, open pour, low pressure handwand (M/L/A)	0.00065 [e]	short pants, short sleeves, gloves [m]	1.4×10^5	6.9×10^6	**1.4×10^5**
	continuous bead, or injection, crack and crevice	PHED - liquid, open pour, low pressure handwand (M/L/A)	0.10 [f]	short pants, short sleeves, gloves [m]	910	4.5×10^4	**890**
	brush, trowel	PHED - paintbrush application	0.1434 [g]	long pants, long sleeves, gloves [n]	54	1900	**53**
solution	Open baiting, refill bait station	PHED – liquid, open pour, low pressure handwand (M/L/A)	0.01 [h]	Short pants, short sleeves, gloves [m]	8700	4.3×10^5	**8600**
	drops	PHED - paintbrush application	0.0012 [i]	short pants, short sleeves, no gloves	640	2.2×10^5	**640**
	Spray, or inject [a]	PHED - liquid, open pour, low pressure handwand (M/L/A)	0.25 [j]	long pants, long sleeves, gloves [o]	1700	18000	**1600**
	Brush [a]	PHED - paintbrush application	0.25 [j]	long pants, long sleeves, gloves [o]	31	1100	**30**
	enclosed bait	n/a [b]	-	-	-	-	-
solid	rod	n/a [b]	-	-	-	-	-
	enclosed bait	n/a [b]	-	-	-	-	-
dust/powder	squeeze bottle or shaker can	PHED - granular bait dispersed by hand [c]	0.035 [k]	short pants, short sleeves, no gloves	47	9600	**47**
granular	crack and crevice by hand	PHED - granular bait dispersed by hand [c]	0.0044 [l]	short pants, short sleeves, no gloves	380	7.7×10^4	**380**
	mechanical spreader	PHED - push-type spreader		long pants, long sleeves, no gloves [p]	1.4×10^4	1.3×10^7	**1.4×10^4**

Values are rounded. Shaded cells indicate the MOEs did not reach the target MOE of 300.

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a Risk assessment also covers foam formulated from solution.

b Exposure assumed negligible for:

- Enclosed bait stations (applicator required to perforate holes on sides of enclosed container with nail).

- Rods. Exposure would likely be limited to incidental exposure resulting from dissolution of the product with sweat from hands and subsequent transfer to mouth or eyes; however, due to the physical nature of the rods (i.e., fused anhydrous boron), the amount of boron available from the rod for dermal or oral absorption is expected to be negligible. Potential exposure may be minimized by wearing non-absorbent gloves while working with the product. PPE required on label indicates "chemical resistant gloves" required in cases of prolonged contact. Risk assessment not performed.

c Based on PHED, granular bait dispersed by hand (assuming short pants, short sleeves, and gloved data with a 10x protection factor because only gloved data was available but PPE is not typically assumed to be used in domestic scenarios). This estimate is assumed to be conservative, however data is not available for this application scenario.

d Amount applied = Amount product handled (kg product/day) × guarantee × boron equivalence factor. Amount applied (kg ai/day) presented as percent boron equivalence using the following conversion factors:

for BNS ($Na_2B_4O_7$ - 10 H_2O)	, boron equivalent (%/100)	= 0.11338
for BOA (H_3BO_3)	, boron equivalent (%/100)	= 0.17491
for BOC ($Na_2B_8O_{13}$ - 4H_20)	, boron equivalent (%/100)	= 0.20965
for BNP $Na_2B_4O_7$ - 5 H_2O	, boron equivalent (%/100)	= 0.14842

In addition to boron equivalence factors (above), values presented for amount applied (in kg active ingredient/day), also take into account specific gravities (where applicable) and guarantees.

e Quantity used per day based on 2 bottles used per day (37 g/ bottle) = 74 g product per day.

f Typical area of wood treated per day is not known, therefore quantity used per day speculated: assume 1 package used/day, net contents = 1.27 kg.

g Assuming net contents (4.55 L ≡ 6.32 kg) used/day and PHED paintbrush data was thought to be representative of potential domestic use scenario. Note: "Pole Bandaging" application not reviewed in this assessment.

h Area treated per day not specified, assume 1 package used per day. Maximum package size 5 L, however the specific gravity value was unknown and assumed to be 1.

i Products packaged as 200 mL and 240 mL bottles. Speculate that for localized droplet application (as indicated on labels), not more than 100-mL of product would be applied in one day; this, in addition to utilization of PHED paintbrush data (as representative of droplet application), results in conservative estimate of exposure.

j Typical area of wood treated per day is not known therefore speculate 1 package used per day; net contents = 4.67 kg (or 3.79 L). Note, this product also packaged in 1.17 kg quantity (0.95 L), however largest package size was selected for risk assessment (considered to be conservative).

k Application rates on labels not specified (for example, apply a thin film), therefore, amount of dust/powder applied per day assumed to be 1 package per day. Net contents and guarantee range from 0.25 kg and guarantee of 80% and up to 0.5 kg with a highest guarantee of 100%. The smallest package size and lowest guarantee were shown for this scenario and indicates MOE values far below the target.

l Assume 1 package used/day, net contents = 0.5 kg.

m End-use product labels do not specify to use gloves, however for PHED-liquid, open pour, low pressure handwand scenario, only gloved data is available.

n Gloves to be used (as required by product label); in order to refine the assessment, exposure calculated assuming long pants and long sleeves are worn during application.

o Exposure assessment assumed long sleeves, long pants, and gloves (as per end-use product label)

p Exposure assessment assumed long sleeves, long pants, and no gloves. This was the only PHED scenario with available data most appropriate for push type spreader.

q Dermal MOE $= \frac{BMDL\ dermal}{Exposure\ dermal}$ The dermal BMDL is 2.9 mg/kg bw/day; the target MOE is 300. Dermal absorption = 50%.

r Inhalation MOE $= \frac{BMDL\ inhalation}{Exposure\ inhalation}$ The inhalation BMDL is 2.9 mg/kg bw/day; the target MOE is 300.

s Dermal and inhalation risks were based on the same endpoints, therefore the risk from these routes were combined in the following equation:

$$\frac{1}{MOEdermal} + \frac{1}{MOEinhalation} = \frac{1}{MOEcombined}$$

Table 3 Postapplication Margin of Exposures Resulting From Commercial and Domestic Application of Boron-related Compounds.

Formulation	Application Description/Site	Postapplication Margin of Exposure		
		Adult Dermal	Child Dermal	Child Incidental Oral
paste	Enclosed bait	**n/a**		
	open bait, or crack and crevice with putty knife or injection, continuous bead application [a]	**n/a**	**9**	**130**
	brush, trowel	**n/a**		
solution	brush, roller, spray, or inject	**n/a**		
	Open bait, refillable bait station	**n/a**	**3**	**48**
	drops	**n/a**	**23**	**340**
	Enclosed bait	**n/a**		
solid	rod	**n/a**		
	Enclosed bait	**n/a**		
dust/powder	crack and crevice, bellows duster, power duster, or other [b]	**3**	**2**	**23**
soluble powder	brushing, spraying, or dipping wood	**n/a**		
	drill and injection or dusting, **crack and crevice** [c]	**16**	**10**	**150**
	additive; material preservation process	**n/a**		
pressurized product	small openings, cracks, crevices, and closed voids, w/ injection tube [d]	**n/a**	**24**	**350**
granular	**crack and crevice**, voids, bait trays, or bellows-type duster/snuffer [e]	**14**	**8**	**120**
	fertilizer or seed spreader	**n/a**		
	pressure sprayer	**n/a**		

MOE values presented represent the worst case scenario.
Vales are rounded. Shaded cells indicate the MOEs did not reach the target MOE of 300.
"n/a" = not applicable. Postapplication exposure was deemed negligible for these scenarios.

a Postapplication exposure assumed negligible if application is restricted to sites truly inaccessible to children and pets (i.e. within crack and crevice or void). However, open bait scenarios could occur in sites accessible to children and potential exposure could occur.

b All domestic and commercial dust/powder formulations containing boron (including boric acid and sodium octaborate tetrahydrate) and used for crack and crevice application; based on conservative (Tier 1) exposure estimate due to limited exposure data.

c Assessed for crack and crevice application of dry soluble powder (along walls and baseboards).

d Use of injector tube is assumed to localize application and therefore mitigate post application exposure to meet the target MOE.

e Postapplication exposure assessment was only performed for crack and crevice application of granular product (along walls and baseboards).

Tier 1 Postapplication Exposure Calculations

For broadcast application or surface application

Calculation of Dermal Dose from Hard Surface:

Exposure (mg/kg bw/day) = $\frac{\text{Residue [mg/cm}^2\text{]} \times \text{TC [cm}^2\text{/hr]} \times \text{DR [unitless]} \times \text{ET [hr/day]}}{\text{BW [kg]}}$ **Equation (1)**

Where:

Residue (mg/cm²) = AR [mg/cm²] × FR [unitless] × $(1\text{-}D)^t$ [unitless] **Equation (2)**

Where:

TC = Transfer Coefficient
DR = Dislodgeable Residue (from hard surfaces)
ET = Exposure Time
AR = Application Rate
FR = Fraction Retained on Surface (%)
D = Fraction of Residue Dissipating Daily (%)
t = postapplication day on which exposure is being assessed

Note that a dissipation rate has not been determined for indoor application. Therefore, postapplication is calculated on the day of application, and it is assumed that residues do not dissipate on successive days. Consequently, FR is assumed to 100%, and D is assumed to be 0%. Therefore, Equation (2) reduces to

Residue (mg/cm²) = AR [mg/cm²] **Equation (3)**

Postapplication exposure from crack and crevice and spot treatment is considered to 25% of surface exposure. Thus, for calculation postapplication from indoor hard surfaces, Equation (1) can be re-written as:

Exposure (mg/kg bw/day) = $\frac{\text{AR [mg/cm}^2\text{]} \times \text{TC [cm}^2\text{/hr]} \times \text{DR [unitless]} \times \text{ET [hr/day]}}{\text{BW [kg]}} \times 0.25$ **Equation (4)**

Assumptions:

- Application Rate (AR) = product specific, based on application methods outlined in Tables 1 and 2 above.
- Transfer Coefficient (TC) = 6000 cm²/hr (for child dermal, indoor surfaces)
- Dislodgeable Residues (DR) = 10% (for hard surfaces)
- Exposure Time = 4 hours
- Body Weight (BW) = 15 kg (for child)
- No dissipation of active on successive days

Calculation of Child hand-to-mouth Exposure

$$\text{Exposure (mg/kg bw/day)} = \frac{\text{AR [mg/cm}^2\text{]} \times \text{DR [unitless]} \times \text{ET [hr/day]} \times \text{SA [cm}^2\text{/event]} \times \text{HME [events/hr]} \times \text{SEF [0.5]}}{\text{15 kg bw}} \times 0.25$$

Assumptions:

- Application Rate (AR) = product specific, based on application methods outlined in Tables 1 and 2 above.
- Dislodgeable Residues (DR) = 10% (for hard surfaces)
- Median Surface Area of two to three fingers (SA) = 20 cm²/event
- Exposure Time (ET) = 4 hrs
- Hand to Mouth Events per hour (HME) = 20 (short term exposure)
- Saliva Extraction Factor (SEF) = 50%
- No dissipation of active on successive days
- Postapplication exposure from crack and crevice and spot treatment is considered to 25% of surface exposure

Appendix V Proposed Label Amendments for Boron compounds

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Additional information on labels of currently registered products should not be removed unless it contradicts the following label statements.

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

The labels of end-use products in Canada should be amended to include the following statements to further protect workers and homeowners.

Label Amendments Related to Exposure

Certain labels are unclear and include multiple uses on the same label that could cause confusion (for example, PCP# 29344 and 29345). All labels with bait station, bait station refill, and open baiting uses should include separate and specific use directions as follows:

1.1 Add to

DIRECTIONS FOR USE:

The different uses are to be clearly stated using the following sub-headings and statements:

- "Product X" may be used in devices that provide entry to ants, carpenter ants and cockroaches, but protect the bait from exposure to humans, domestic animals and the elements. The bait can be dispensed in pre-filled bait stations, or can be used to refill ant and cockroach bait stations sold with the bait or in ant and cockroach bait stations designed for the addition of bait.

- When using bait stations, wash hands thoroughly before handling to remove any odours that may be repellent to ants, carpenter ants or cockroaches, i.e. tobacco, garlic, chemicals/cleaners.

Bait Station Traps

- To activate "Product X" bait station, place station on a flat surface with the cone facing up. If cone is filled with liquid, move station from side to side rapidly and liquid will leave the cone. 2. Cut the top of the cone with scissors, so that the top of the remaining cone is level with top of surrounding circular surface. 3. Place bait station according to label directions. (Optional: illustrations of bait station activation).

- Indoors: Place traps 1.5-3.0 metres apart where ants, carpenter ants or cockroaches are numerous. Replace bait stations as needed. Place stations under food cabinets, sinks, stoves, refrigerators, food storage areas, attics, garages, basements, storage areas and closets. Place on exterior windowsills and in doorways to help prevent entry of ants, carpenter ants or cockroaches. Some bait stations may be designed to be affixed to a wall or placed on a flat surface.

- Outdoors: Place bait stations near where ants enter dwellings and near ant-hills in lawns or gardens. For best results place stations in shaded areas or create shade for the bait station. Whenever possible, avoid placing bait station where it will receive direct sunlight whenever possible.

- Around structures: The number of bait stations to use will vary with the type of ant and the size of the colony. For initial placement – place one bait station every 15 metres (50 feet) around the structure to be treated. If any of the bait stations are emptied in less than a week, double the initial placement. Replace baits as needed until feeding activity ceases.

Bait Station Refills

- "Product X" must be used at full strength for control of cockroaches or carpenter ants. For other ant species, the volume of available bait may be increased by dilution with water or other food grade liquid 1:1 to make bait containing 0.5% active ingredient.

Open Placement Baiting

- **In the house** – make small, pea sized placements and/or long thin lines where ants, carpenter ants or cockroaches are a problem.

- **In the garden** – place a few drops on a smooth, firm surface and place on runs and nests.

1.2 Add to PRECAUTIONS:

I) For all boron products;

A. The statement:
"Wash after use."

Should be replaced with the following statement:
"Wash hands thoroughly after use."

B. The following statement should be removed:
"re-apply as necessary"

II) The following statements are required to be added to all boron products:

> **DO NOT** apply by brush.
> **DO NOT** apply on animals.

III) The following statement is required to be added to all labels of commercial class products:

> Not for use by homeowners or other uncertified users.

IV) The following additional label statement is required to be added to all domestic class labels:

> Keep out of reach of children and pets.

1.3 Personal Protective Equipment, Maximum kg a.i. Handled per Day and Engineering Controls.

Additional label statements are required for the material preservative uses of boron regarding personal protective equipment and engineering controls for the purpose of mitigating the risk of exposure to zinc borate and in the interest of maintaining consistency between labels.

The following statements are required to be added to all zinc borate labels in a section entitled DIRECTIONS FOR USE:

For workers using an open mixing/loading system:

> Wear chemical resistant coveralls over long pants, long-sleeved shirt, chemical resistant footwear, and chemical resistant gloves when mixing, loading and applying boron. Pants should be worn outside footwear to prevent pooling within boots. Under these provisions, workers can handle up to 21 kg of active ingredient in one day.

For workers using a closed mixing/loading system:

> Wear long pants, long-sleeved shirt, chemical resistant footwear, and chemical resistant gloves when mixing, loading and applying boron. Pants should be worn outside footwear to prevent pooling within boots. Under these provisions, workers can handle up to 410 kg of active ingredient in one day.
>
> Remove protective equipment immediately after handling this product. Wash outside of gloves and footwear before removing. As soon as possible, wash thoroughly and change into clean clothing. Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this products concentrate.

Do not reuse them. Contaminated clothing must be laundered separately in hot water before reusing. Wash hands and face thoroughly after handling and before eating, drinking, chewing gum, smoking, or using toilet.

These restrictions are in place to minimize exposure to individual workers. Application may need to be performed over multiple days or using multiple workers.

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