Lithium borates: Human health tier II assessment

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Boric acid (H2B4O7), dilithium salt, pentahydrate	1303-94-2
Boron lithium oxide (B4Li2O7)	12007-60-2
Boric acid (HBO2), lithium salt	13453-69-5
Boric acid (HBO2), lithium salt, dihydrate	15293-74-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are lithium salts of boric acid. Following ingestion, these chemicals readily break down in the gastric pH, to boric acid (H_3BO_3) and lithium ions. The toxicokinetics and the toxicity of these chemicals are expected to be similar and will be driven by both lithium and borate ions, they are grouped together for human health risk assessment (NICNASa; NICNASb; NICNASc).

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

Although the National Pollutant Inventory (NPI) holds data for all sources of boron and compounds emissions in Australia, the data are not specific to these chemicals.

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers;
- Galleria Chemica;
- the Substances and Preparations in the Nordic countries (SPIN) database; and
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Lithium borate (CAS No. 12007-60-2), lithium tetraborate (CAS No. 1303-94-2) and lithium metaborate (CAS No. 15293-74-0) have reported commercial use, including in ceramics.

Lithium metaborate dihydrate (CAS No. 13453-69-5) and lithium tetraborate have reported site limited uses including in:

- vacuum spectroscopy; and
- metal refining and degassing.

Restrictions

Australian

Although no known restrictions have been identified for these chemicals or for lithium compounds, restrictions have been identified for boric acid and for boron as follows (NICNASa; NICNASb; NICNASc).

Boric acid is listed in the *Poisons Standard* (*Standard for the Uniform Scheduling of Medicines and Poisons*) (SUSMP, 2016) in Schedule 5 as follows:

'BORIC ACID (excluding its salts) and BORAX **except**:

(a) when included in Schedule 4;

(b) in preparations, other than insect baits, containing 1 per cent or less of boron; or

(c) in hand cleaning preparations'.

BORON, including boric acid and borax, is also listed in Schedule 4 for its non-industrial uses.

Schedule 5 chemicals are labelled with 'Caution'. These are substances with a low potential for causing harm, the extent of which can be reduced by using appropriate packaging with simple warnings and safety directions on the label.

International

No known restrictions have been identified for these chemicals.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemicals Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No exposure standards are available.

International

No exposure standards are available.

Health Hazard Information

There is a lack of data available in the literature to directly assess the toxicity of these chemicals. As these chemicals are lithium salts of boric acid and, following ingestion, readily break down in the gastric pH to lithium ions and boric acid (H_3BO_3), the toxicokinetics and the toxicity of these chemicals will be driven predominantly by lithium and borate ions. Undissociated boric acid is the main species present in the blood of mammals following exposure to borates, as well as lithium ions from these salts. Therefore, the data obtained from studies on lithium compounds and borates have been read across for the present assessment. For lithium, preference is given to data for lithium carbonate rather than the more basic lithium hydroxide (NICNASa; NICNASb; NICNASc).

Toxicokinetics

No data are available for these chemicals. As previously stated, their toxicokinetics will be driven by both lithium and borate ions.

Boric acid is readily and completely absorbed in humans and animals following oral administration. Inhalation absorption is also assumed to be 100 % (worst case scenario). Dermal absorption of boric acid through intact skin is very low and a dermal absorption rate of 0.5 % is assumed (absorption of salts will be lower). There is no evidence of boric acid accumulation in humans or animals. Boric acid is excreted rapidly with a half-life of <24 hours in humans and is mainly excreted in the urine (>90 %), regardless of the route of exposure (NICNASa).

Lithium is absorbed readily and almost completely from the gastrointestinal tract. Complete absorption occurs within approximately eight hours, with peak plasma concentration occurring 2–4 hours after an oral dose. Although lithium is rapidly distributed to the kidney, transfer to the liver, bone, muscle or the brain is slower. Lithium crosses the placenta and is excreted in breast milk. Lithium is not metabolised to any appreciable extent in the human body and is excreted almost unchanged in urine. Excretion of lithium is rapid, with >50 % and >90 % excreted within 24 and 48 hours, respectively. As excretion of the lithium is fast, bioaccumulation can be excluded. Dermal absorption of lithium is considered to be very low when included in non-corrosive compounds. Exposure to lithium as a vapour is also not expected to be toxicologically relevant (NICNASb; NICNASc).

Acute Toxicity

Oral

Although no data are available, the available information indicates that these chemicals are likely to be of low acute toxicity following oral exposure. This conclusion is based on the information available on boron- and lithium-containing compounds.

The median lethal dose (LD50) for boron oxide (CAS No. 1303-86-2) and boric acid (CAS No. 10043-35-3) is >2000 mg/kg bw in rats. Observed sub-lethal effects included central nervous system (CNS) depression, ataxia and convulsions (NICNASa).

Although lithium hydroxide anhydrous (CAS No. 1310-65-2) and lithium hydroxide monohydrate (CAS No. 1310-66-3) are of moderate acute toxicity following oral exposure, this is due more to the corrosive nature of the hydroxide ion rather than the lithium ions. Similarly, moderate acute toxicity following oral exposure to lithium carbonate (CAS No. 554-13-2) was due to the basic carbonate ion rather than the lithium ions (NICNASb; NICNASc).

Dermal

No data are available for the chemicals. The available information on borates and lithium-containing compounds indicates that the chemicals in this group are likely to be of low acute toxicity in animal tests following dermal exposure.

The LD50 for boric acid (CAS No. 10043-35-3) was reported to be >2000 mg/kg bw in New Zealand White (NZW) rabbits. The LD50 for boron oxide (CAS No. 1303-86-2) in rats was established as >2000 mg/kg bw (NICNASa).

Lithium carbonate (CAS No. 554-13-2) has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rabbits is >2000 mg/kg bw. No clinical signs, dermal signs or macroscopic changes were observed during the 14-day, post-treatment observation period (NICNASc).

Inhalation

No data are available for the chemicals. However, based on the information available for lithium salts and borates, these chemicals are likely to be of low acute toxicity following inhalation exposure.

The reported median lethal concentration (LC50) is >2 mg/L for boric acid (CAS No. 10043-35-3) and for boron oxide (CAS No. 1303-86-2) in rats. Ocular discharge, hypoactivity and hunched posture were noted during the first 30 minutes of exposure. Ocular discharge and/or nasal discharge persisted in most animals after removal from the chamber. All animals recovered by day seven. It was also noted in another study that the highest attainable concentration in these tests was 2 mg/L (NICNASa).

In an acute inhalation toxicity study, the LC50 for lithium carbonate (CAS No. 554-13-2) was estimated to be >2.17 mg/L (the maximum attainable concentration) in Sprague Dawley (SD) rats (five/sex) as a single four-hour whole-body exposure. The LC50 was based on the mortality for combined sexes. In another study, the LC50 was considered to be >0.80 mg/L (maximum attainable concentration) in SD rats (five/sex) for whole-body inhalation exposure for four hours (NICNASc).

Observation in humans

A review of more than 700 cases of acute boric acid exposures in adults and children found that 88.3 % of cases were without signs or symptoms. Although the report provided only limited information on dose response, dose ranges of 0.1–55 g and 0.01–89 g of boric acid were reported for symptomatic and asymptomatic cases, respectively.

There are case reports of lethal oral human exposures, involving accidental or intentional ingestion of high doses of boric acid. While oral lethal doses for boric acid have been quoted as 2–3 g for infants, 5–6 g for children, and 15–30 g for adults, the data are largely unsubstantiated. Further difficulty in making an appropriate quantitative judgment about lethal dose was also noted due to medical intervention in most cases. Following ingestion of a formula accidentally prepared with a 2.5 % aqueous solution of boric acid, five infants became lethargic, developed vomiting and diarrhoea, and died within three days after exposure (estimated dose of 4.5–14 g boric acid). Deaths have also occurred in a 77-year-old man following ingestion of 30 g of boric acid and in a 45-year-old man following ingestion of approximately 280 g of boric acid. In both instances, clinical signs were similar—vomiting, diarrhoea, erythema, cyanotic extremities, acute renal failure, cardiopulmonary hypertension and death from cardiac failure (NICNASa).

Lithium compounds are used extensively as psychiatric medications, especially lithium carbonate and lithium acetate, to treat bipolar disorder to control episodes of depression, mania and other abnormal moods. Lithium compounds are prescribed for long periods of time (even between episodes) as maintenance therapy to help prevent future manic and depressive episodes (Aral & Vecchio-Sadus, 2008).

Acute intoxication with lithium can occur either in the initial phase in a course of therapy, or at any time during long-term treatment, or after an acute overdose. Signs of toxicity vary with the plasma levels of lithium; serious signs of toxicity occur at plasma levels above 2.5 mmol/L lithium. These include fasciculations, muscle contractions, hyperreflexia and hypertonia, drowsiness, confusion, seizures, hypotension, coma and collapse. Clinical intoxication by lithium has also been observed as a result of overdose, either as a result of attempted suicide or by accident.

The CNS is the major target of lithium overdose, with residual effects in 10 % of cases. A probable oral lethal dose of 0.5 to 5 g/kg of lithium has been reported for a 70 kg human. Several reported cases of poisonings in humans have been reported: a 45-year-old man who died after a ingestion of 90 sustained release lithium tablets (450 mg each) with a peak level of 6.9 milliequivalents (mEq/L) despite haemodialysis; a 28-year-old man who survived an acute ingestion with a lithium level of 10 mEq/L; and an adult who recovered after an acute ingestion of 84 grams (210 tablets of 400 mg) of lithium (NICNASb; NICNASc).

Corrosion / Irritation

Skin Irritation

As no data are available for these chemicals, the available information on boron and lithium-containing compounds indicates that the chemicals in this group are not likely to be skin irritants.

Boric acid (CAS No. 10043-35-3) (500 mg) did not cause skin irritation when applied to the intact or abraded skin of NZW rabbits for 24 hours. In another study, 5 mL of a 10 % boric acid (CAS No. 10043-35-3) solution produced no skin irritation following application (period of exposure not reported) to the intact or abraded skin of NZW rabbits. Although details were not provided, boron oxide (CAS No. 1303-86-2) has also been reported not to be a skin irritant (NICNASa).

Lithium carbonate (CAS No. 554-13-2) (0.5 g) has also been reported not to irritate the intact skin of three NZW rabbits following exposure for four hours (NICNASc).

Eye Irritation

No data are available. Information available on boron and lithium-containing compounds indicates that these chemicals might be slight eye irritants; however, the effects would not be sufficient to warrant hazard classification for the chemicals in this group.

Boric acid (CAS No. 10043-35-3) (100 mg) caused slight eye irritation in NZW rabbits following application to one eye of each rabbit. Conjunctival redness, chemosis and minor effects on the iris were noted. Iridial lesions were reversed 48 hours after application and conjunctival lesions were reversed by day seven. Although details were not provided, boron oxide (CAS No. 1303-86-2) has also been reported not to be an eye irritant (NICNASa).

Lithium carbonate (CAS No. 554-13-2) has been reported to be a moderate eye irritant; eye irritation in this case has been attributed to the basic carbonate solution and not due to the lithium ion (NICNASc).

Observation in humans

Acute respiratory effects have been extensively documented in a number of studies, in workers following inhalation of boric acid, boron oxide and other borate compounds, as dusts. Effects included nasal and ocular irritation, throat irritation, coughing and breathlessness. No effects on lung function were observed and the effects identified by workers were ‘chemaesthetic’ (chemical sensibility of the skin and mucous membranes). These effects were regarded as sensory irritant effects that would typically be seen in normal populations in the absence of respiratory hypersensitivity. As these effects were not considered a ‘serious irritation to the respiratory tract’ and were most likely due to a physical effect, hazard classification as is not warranted (NICNASa).

Sensitisation

Skin Sensitisation

No data are available for these chemicals. However, the available information on boron and lithium-containing compounds indicates that the chemicals in this group are not likely to be skin sensitisers.

Boric acid (CAS No. 10043-35-3) was negative in a skin sensitisation test (Buehler) conducted in guinea pigs (male/female), according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 406. The chemical was applied at a concentration of 95 %, moistened with distilled water to enhance skin contact during both the induction and challenge phases (NICNASa).

Lithium carbonate (CAS No. 554-13-2) was negative in a skin sensitisation test (Buehler) conducted in guinea pigs (male/female) according to OECD TG 406. Animals were exposed topically to the undiluted chemical (0.30 g/animal) (six hours/day, once/week for three weeks) and then challenged topically at a new skin site with the chemical 14 days after the last induction. No skin reactions were observed in any of the animals at any time during the study (NICNASc).

Observation in humans

No evidence of skin, or respiratory sensitisation has been reported in humans occupationally-exposed to borates (NICNASa).

Repeated Dose Toxicity

Oral

As no data are available for these chemicals, the available information on borates and lithium salts has been used for the assessment of repeated dose oral toxicity.

A number of repeated dose oral toxicity studies on boric acid (CAS No. 10043-35-3) in animals have indicated that the main target organ for boron toxicity are the testes, leading to reproductive and developmental adverse effects. Although the possibility of these effects following ingestion of these chemicals cannot be ruled out, these are appropriately covered in the **Reproductive and developmental toxicity** section. Adverse haematological effects that indicate increased red blood cell destruction have also been observed as signs of boron toxicity (NICNASa).

A no observed adverse effect level (NOAEL) of 17.5 mg/kg bw/day for boron (equivalent to 100 mg/kg bw/day boric acid) has been determined from a two-year study of boric acid in rats, for effects on the testes and haematology. The lowest observed adverse effect level (LOAEL) was 58.5 mg/kg bw/day for boron (equivalent to 334 mg/kg bw/day boric acid) (NICNASa).

The limited data available in humans and animals indicate that repeated oral exposure to lithium compounds at therapeutic levels is not considered to cause serious damage to health. The active moiety for lithium compounds for systemic effects is the lithium ion. As stated previously, lithium compounds have been used in medications for the treatment of various psychiatric conditions in humans for almost half a century. The recommended dose for treating bi-polar disorder in humans is 450–900 mg/day lithium carbonate (CAS No. 554-13-2) (equivalent to 84–169 mg lithium/day). This dose does not produce any adverse effects in otherwise healthy individuals and can therefore be taken to be the NOAEL for oral repeated dose toxicity in humans.

In a repeated dose toxicity study, SD rats (10/sex/group) were fed boric acid (CAS No. 10043-35-3) in the diet at doses of 0, 15, 50, 149, 500 or 1490 mg/kg bw/day, for 13 weeks (equivalent to 0, 2.6, 8.8, 26, 88 and 260 mg/kg bw/day of boron). Rapid respiration, hunched position, bloody nasal discharge, urine stains on the abdomen, inflamed eyes, desquamation and swollen paws and tails were observed in animals at the two highest doses. Reduced food consumption and bodyweight gain were also noted in these animals. All animals at the highest dose died by week six. All the male rats at the two highest doses had atrophied testes, histologically complete atrophy of the spermatogenic epithelium, and decreased seminiferous tubule size. A 90-day NOAEL of 149 mg/kg bw/day (equivalent to 26 mg boron/kg bw/day) was established in this study based on body weight reduction, clinical signs of toxicity, and testicular atrophy (NICNASa).

In a repeated dose toxicity study, boric acid (CAS No. 10043-35-3) was fed to SD rats (35/sex/group) in the diet at doses of 0, 33, 100 or 334 mg/kg bw/day for two years (equivalent to 0, 5.9, 17.5 and 58.5 mg boron/kg bw/day) (see **Reproductive and developmental toxicity**). Males in the highest dose group showed hunched positions, inflamed eyes, tail skin and paw pad desquamation, reduced red cell volume and haemoglobin, shrunken scrotums, testicular atrophy and seminiferous tubule degeneration (at 6, 12 and 24 months), atrophied seminiferous epithelium and decreased tubular size in the testes at microscopic examination. An NOAEL of 100 mg/kg bw/day of boric acid (equivalent to 17.5 mg boron/kg bw/day) was determined based on clinical and haematological effects and the testicular atrophy observed at the highest doses (NICNASa).

In a repeated dose toxicity study, lithium chloride (CAS No. 7447-41-8) was administered to rats (strain unspecified) in drinking water at 20 mmol/L and 50 mmol/L for two years. The 20 mmol/L concentration had no effects on the behaviour and health of the animals, except for slight and transitory initial disturbances. The plasma levels at this dose were 1.5–2 mmol lithium. The 50 mmol/L concentration affected the animals in various ways, including decreased food and water intake within a few days of the dosing; progressive drowsiness and antisocial behaviour from 3–5 days; difficulty in rousing and, when roused, staggered gait. Animals exhibited fine muscular tremor and trembling when resting; and became unresponsive and stuporous for a few days, followed by deterioration progressing to death within two to three weeks. The plasma levels at these doses were 3 mmol lithium (behavioural changes) to 8 mmol lithium (death).

The lithium concentration of 20 mmol/L used in this study is comparable to the highest doses given temporarily to hospitalised patients (plasma lithium level about 2 mmol/L). An NOAEL of 13.9 mg lithium/kg bw/day can be derived in rats (NICNASb).

Dermal

No data are available.

Dermal absorption of boric acid through intact skin is very low in all species evaluated, including: rats, rabbits, new-born infants and adult humans. Dermal absorption of lithium is also considered to be very low and almost negligible in the case of non-corrosive solutions (see **Toxicokinetics**).

Inhalation

No data are available.

Observation in humans

In addition to numerous acute poisoning incidents with boric acid (see **Acute toxicity: Observation in humans**), some data are available on effects from repeated doses of boric acid or borax as treatments for medical conditions. Multiple oral and dermal exposures resulted in a variety of signs and symptoms including dermatitis, alopecia, loss of appetite, nausea, vomiting, diarrhoea and focal or generalised CNS effects (NICNASa).

Reports of toxic responses to lithium in workers are rare, despite the widespread use of lithium compounds. Occupational exposure to lithium-containing compounds can occur through inhalation and dermal contact at workplaces where lithium compounds are produced or used. Some of these operations include extracting lithium from its ores, preparing various lithium compounds, welding, brazing, enamelling and using lithium hydrides.

The general public could be exposed to small amounts of lithium via inhaling ambient air and ingesting food and drinking water, as lithium is found in various environmental media (NICNASb).

Genotoxicity

Although no data are available for these chemicals, the available information on borates and lithium compounds indicates that the chemicals in this group are not likely to have mutagenic or genotoxic potential.

Boric acid (CAS No. 10043-35-3) was negative in several in vitro tests and also in an in vivo mouse bone marrow micronucleus chromosome aberration test. It was concluded that boric acid (CAS No. 10043-35-3) was not considered to have mutagenic or genotoxic potential (NICNASa). Lithium hydroxide anhydrous (CAS No. 1310-65-2) and lithium hydroxide monohydrate (CAS No. 1310-66-3) were also negative in several in vitro tests (NICNASb; NICNASc).

While several studies have reported genotoxic effects of various lithium compounds at high doses (equivalent to therapeutic doses or higher), many other studies have failed to demonstrate an effect. Considering the chemical properties of the lithium compounds, the Nordic Expert Group stated it is unlikely that they act as direct mutagens. A secondary effect of increased cell survival caused by lithium inhibiting glycogen synthase kinase 3 (GSK3) production provided an explanation to the apparent genotoxicity noted (NICNASb; NICNASc).

Observation in humans

Patients on lithium therapy did not show an increase in the frequency of sister chromatid exchanges (SCE) in lymphocytes. No morphological evidence of chromosomal damage was noted. No elevated frequency of SCEs was found in another study in patients on lithium therapy (NICNASb; NICNASc).

Carcinogenicity

No data are available for these chemicals or for lithium compounds.

The available information on boric acid indicates that these chemicals are not likely to have carcinogenic potential. These chemicals are also not considered to have mutagenic or genotoxic potential (see **Genotoxicity**) (NICNASa).

No evidence of carcinogenicity was seen in a two-year dietary study with boric acid (CAS No. 10043-35-3). The chemical was administered to B6C3F1 mice (50/sex/group) in the diet at 0, 2500 or 5000 ppm (equivalent to 0, 446 and 1150 mg boric acid/kg bw/day). The NOAEL for carcinogenicity was equivalent to 1150 mg boric acid/kg bw/day (201 mg boron/kg bw/day), the highest dose tested. It was reported that less than one third of treated animals (10 animals/sex) of the control and the highest dose group in the rat study was used for macroscopic and histopathological examination. Animals in the low and mid-dose groups were not examined (NICNASa)

No evidence of carcinogenicity was seen in two two-year dietary studies in rats exposed to boron at 81 mg/kg bw/day, as boric acid; and dogs exposed to boron at 6.8 mg/kg bw/day, as boric acid. Conclusions were limited regarding carcinogenicity in the study in dogs as only 1–2 animals/sex/dose/time were macroscopically and histopathologically examined (NICNASa).

Reproductive and Developmental Toxicity

No data are available regarding reproductive or developmental effects of the chemicals in this group in animals and humans. Information on borates and lithium ions is presented below. Reproductive and developmental end points were the most sensitive effects in animals following exposure to boron (boric acid). Boric acid (CAS No. 10043-35-3) is classified as hazardous for reproductive and developmental toxicity—Category 1B; H360FD (May damage fertility. May damage the unborn child) in the HCIS (Safe Work Australia) (NICNASa). As the chemicals contain borate as the major component and borate is also likely to be associated with human health hazards of the chemical, reproductive and developmental human health hazards could be expected following exposure (NICNASa).

Further information on this endpoint, including an analysis of human epidemiological data for boron-containing compounds has been presented previously in an IMAP Tier II group assessment for boric acid, available at: **https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1330** (NICNASa).

As undissociated boric acid is the main species present in the blood of mammals following exposure to these chemicals, along with some lithium ions, this information on boric acid is sufficient to warrant classification for the chemicals in this group (refer to **Recommendation** section) (NICNASa).

The testes and the developing foetus have been identified as the most sensitive targets of boron toxicity in animal studies, with the rat being the most sensitive species. The reported testicular effects included reduced organ weight and organ to body-weight ratio; atrophy and degeneration of the spermatogenic epithelium;

impaired spermatogenesis; and reduced fertility. The reported developmental effects included high prenatal mortality; reduced foetal body weight; and malformations and variations of the eyes, CNS, cardiovascular system, and axial skeleton. An NOAEL for fertility of 100 mg/kg bw/day of boric acid (equivalent to 17.5 mg boron/kg bw/day) has been determined (based on testicular effects) from two-year and three-generation studies in rats. The critical endpoint NOAEL for developmental effects has been established at 55 mg/kg bw/day of boric acid (equivalent to 9.6 mg boron/kg bw/day) in rats (NICNASa).

In a repeated dose toxicity study, SD rats (35/sex/group) were fed boric acid (CAS No. 10043-35-3) in the diet at doses of 0, 33, 100, 334 mg/kg bw/day for two years (equivalent to 0, 5.9, 17.5, 58.5 mg boron/kg bw/day) (see **Repeated dose toxicity: oral**). Males of the highest dose group had shrunken scrotums. Testicular atrophy and seminiferous tubule degeneration were seen in the highest dosed males at six, 12 and 24 months. Microscopic examination of the tissue revealed atrophied seminiferous epithelium and decreased tubular size in the testes. A NOAEL of 100 mg/kg bw/day of boric acid (equivalent to 17.5 mg boron/kg bw/day) was determined, based on the testicular atrophy observed at the highest doses in SD rats (NICNASa).

In a developmental toxicity study, boric acid was contained in the diet of pregnant SD rats (60/group) on gestation days (GD) 0–20. The calculated average dose of boric acid consumed was 19, 36, 55, 76, and 143 mg/kg bw/day (3.3, 6.3, 9.6, 13.3, and 25 mg boron/kg bw/day). There was little evidence of maternal toxicity at any of the doses tested. A reduction in mean foetal body weights and an increased percentage of foetuses with skeletal malformations (wavy ribs, short rib XIII) per litter were noted on GD 20 at the highest two doses. The NOAEL for developmental toxicity was determined to be 9.6 mg boron/kg bw/day and the LOAEL was 13.3 mg boron/kg bw/day, based on decreased foetal body weight (NICNASa).

Information available on the lithium compounds from animal studies and in humans indicates that the lithium compounds are not likely to have specific reproductive or developmental toxicity (NICNASb; NICNASc).

It has also been suggested that the developing vascular system could be a target for lithium. The use of lithium in psychiatric medicine has been reported to cause congenital defects, especially of the cardiovascular system, such as Ebstein’s anomaly (a rare cardiac defect), when given to women during the first trimester of pregnancy. However, more thorough analysis of the records of mothers who received lithium treatment during the first trimester or the entire pregnancy, and a multi-centre study of pregnancy outcome after therapeutic lithium exposure during the first trimester, did not show any significant teratogenic risk. Similarly, others have also concluded that lithium given in therapeutic doses is not teratogenic (Aral & Vecchio-Sadus, 2008).

In controlled and prospective studies conducted in 138 and 148 women, lithium carbonate (CAS No. 554- 13-2) was administered at a mean daily dose of 927 mg for the treatment of major affective disorders during the first trimester of pregnancy. Rates of major congenital malformations did not differ between the lithium (2.8 %) and control (2.4 %) groups. In the second study, infants of lithium-treated mothers had significantly higher birth weights than the controls, despite identical gestational ages (NICNASc).

In a developmental toxicity study, lithium carbonate (CAS No. 554-13-2) was administered (by gavage) to 25 pregnant Crl:Cd (SD) rats on GD 6–19 at doses of 10, 30 or 90 mg/kg bw/day. The NOAEL for maternal toxicity was established as 30 mg/kg bw/day, based on slight but significant reductions in net weight change and food intake and piloerection. The NOAEL for developmental (foetal) toxicity was established as >90 mg/kg bw/day (the highest dose tested) (NICNASc).

In another study, pregnant rats (albino Wistar) were administered lithium chloride (CAS No. 7447-41-8) at a concentration of 20 mmol/L in drinking water producing plasma lithium levels of 1.5–2.0 mmol/L. The lithium concentration of 20 mmol/L was comparable to the highest doses given temporarily to hospitalised patients. The daily intake of lithium in rats was 2 mmol/kg bw/day (equivalent to 13.9 lithium mg/kg bw/day). Prolonged subtoxic lithium ingestion did not show any toxic signs or behaviour changes and no malformations or other defects in the lithium-exposed litters. There were no differences in size or weight among treated and untreated animals, or any other toxic effects. A NOAEL of 13.9 mg of lithium/kg bw/day was determined (NICNASc).

Other Health Effects

Neurotoxicity

As lithium compounds are extensively used for the treatment of bipolar disorder to control episodes of depression, mania and other abnormal moods, the primary target organ for lithium toxicity is the CNS. The occurrence of toxicity is related to the serum concentration of lithium. At very high doses, serious effects can include mental confusion, hyperreflexia, tremors, dysarthria, seizures and cranial-nerve and focal neurological signs, progressing to coma and death (Aral & Vecchio-Sadus, 2008; HSDB).

Even though CNS depression has been reported in humans poisoned with boric acid (CAS No. 10043-35-3) at very high doses, there was no indication that boric acid (CAS No. 10043-35-3) has neurotoxic properties. Therefore, based on the above, these chemicals are not likely to have neurotoxic properties (NICNASa; NICNASb; NICNASc).

In a study to evaluate potential neurotoxicity, SD rats (10/sex/dose) were administered boric acid (CAS No. 10043-35-3) as a single gavage dose of 2000 mg/kg bw followed by a 14-day observation period. Although there were no mortalities and no clinical signs of toxicity, a 16 % decrease in total body weight gain was noted in the treatment group compared with the control group at the end of the study. Functional observation battery and motor activity evaluations did not show any evidence of neurotoxicity and neurohistopathological findings were also negative. It was concluded that a single oral (gavage) dose of boric acid (CAS No. 10043-35-3) at a dose of 2000 mg/kg bw administered to rats was not neurotoxic (NICNASa).

Rats exposed to boron oxide (aerosol) at concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) for 10 weeks, 175 mg boron oxide/m^3 (27 mg boron/m^3) for 12 weeks, or 77 mg boron oxide/m^3 (12 mg boron/m^3) for 24 weeks did not show any gross or microscopic effects on the brain (NICNASa).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include reproductive and developmental toxicity.

Although the available animal data show clear evidence of reproductive and developmental toxicity, epidemiological studies of workers and general populations exposed to boron show no reproductive or developmental effects. However, there are limitations in the human studies and the available human data are not sufficient to invalidate the animal data. This information has previously been reported in an IMAP Tier II group assessment for boric acid, available at: **https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1330** (NICNASa).

Public Risk Characterisation

As chemicals in this group are not likely to be used by the public, exposure to the public is limited. Hence, the public risk from the use of chemicals in this group is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure of workers to the chemicals in this group may occur, particularly where manual or open processes are used. These might include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemicals in this group could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure to the chemicals are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking at a workplace (such as an employer) has adequate information to determine appropriate controls.

The available data support an amendment to the hazard classification in HCIS (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Not Applicable	May damage fertility or the unborn child - Cat. 1B (H360FD)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

References

Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at **http://www.safeworkaustralia.gov.au/sites/swa/about/publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf**

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Safe Work Australia. Hazardous Chemicals Information System (HCIS). Accessed June 2017 at **http://hcis.safeworkaustralia.gov.au/HazardousChemical**

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2016. Accessed November 2016 at **https://www.legislation.gov.au/Details/F2016L01638**

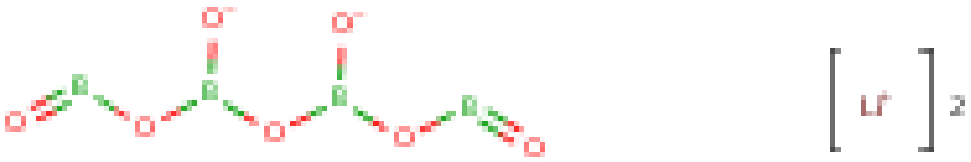
Last Update 30 June 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Boric acid (H2B4O7), dilithium salt, pentahydrate** dilithium tetraborate boron lithium oxide, pentahydrate
CAS Number	1303-94-2
Structural Formula	

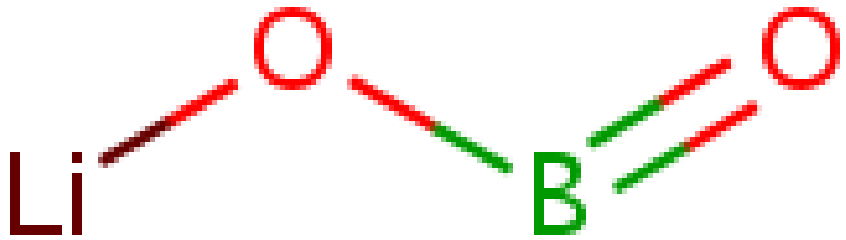
	  
Molecular Formula	B.5H2O.Li.O
Molecular Weight	259.193

Chemical Name in the Inventory and Synonyms	**Boron lithium oxide (B4Li2O7)** lithium borate lithium tetraborate dilithium tetraborate boric acid (H2B4O7), dilithium salt
CAS Number	12007-60-2
Structural Formula	



Molecular Formula	B.Li.O
Molecular Weight	169.12

Chemical Name in the Inventory and Synonyms	**Boric acid (HBO2), lithium salt** lithium metaborate
CAS Number	13453-69-5
Structural Formula	

	
Molecular Formula	BHO2.Li
Molecular Weight	49.75

Chemical Name in the Inventory and Synonyms	**Boric acid (HBO2), lithium salt, dihydrate** lithium metaborate (LiBO2), dihydrate
CAS Number	15293-74-0
Structural Formula	**No Structural Diagram Available**

Molecular Formula	BHO2.2H2O.Li
Molecular Weight	85.778

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