Cobalt borate, neodecanoate complexes: Human health tier II assessment

24 April 2015

CAS Number: 68457-13-6

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

Chemical Identity

Synonyms	cobalt borate neodecanoate cobalt borate neodecanoate complexes cobalt boron neodecanoate
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight (g/mol)	Unspecified
Appearance and Odour (where available)	A black solid, waxy paste
SMILES	C(=O)(O)C(C)(C)CCCCCC

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;
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic uses, including in:

- adhesives, binding agents; and
- paints, lacquers and varnishes.

The chemical has not been reported as present in any domestic products in the United States of America (USA) (Household Products Database, US Department of Health and Human Services).

The chemical has reported commercial uses including:

- as a rubber adhesion agent; and
- in coatings and inks for professional use.

The chemical has reported site-limited use as intermediate.

The chemical has been identified as having non-industrial uses as non-agricultural pesticides and preservatives.

Restrictions

Australian

Although no known restrictions have been identified for the chemical, restrictions have been identified for cobalt compounds, boric acid and for boron (NICNASa; NICNASb).

Cobalt and its compounds are listed in Schedule 10 (prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals) of the Work Health and Safety Regulations (WHS, 2014) for restricted use in abrasive blasting at a concentration of greater than 0.1 % cobalt.

International

No known restrictions have been identified for the chemical.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 0.05 mg/m^3 time weighted average (TWA) in Canada, the USA, Switzerland, and Japan. The chemical also has an exposure limit of 0.15 mg/m^3 short-term exposure limit (STEL) in Canada and the USA.

Health Hazard Information

The chemical is a salt of neodecanoic acid (C-10 carboxylic acid) and is a member of the metal carboxylates group. As cobalt and boron can associate with neodecanoic acid in a variety of stoichiometries, the chemical is referred to as 'complexes'. The dissociation of the chemical is dependent on pH. In the low pH environment of the digestive tract (e.g. pH 1.2), it is expected that cobalt boron neodecanoate (CAS No. 68457-13-6) will completely dissociate into neodecanoic acid, cobalt ions and boric acid (US EPA, 2008).

Therefore, when administered orally, the absorption and resulting toxicity of the chemical would be due to the independent action of the neodecanoic acid, the free (ionised) cobalt, and boric acid. It has also been shown that the hazard of the metal carboxylates is largely dependent on the metal, and not the carboxylic acid.

Toxicity data for soluble cobalt salts have indicated that the contribution of the respective anion to the toxicity of the compound is negligible compared with that of the cobalt cation and, as such, the toxicity is related to the cobalt ion and independent of counter ions. Similar results would be expected for the present chemical. Therefore, the data obtained from studies on soluble cobalt compounds and borates have been 'read across' for the present assessment (US EPA, 2008; NICNASa; NICNASb; NICNASc). The use of data from these compounds have been read across according to the principles of the OECD (2014).

Toxicokinetics

No data are available on the chemical.

The chemical readily breaks down in the stomach pH to neodecanoic acid, the free cobalt ions, and boric acid. Therefore, the toxicokinetics of the chemical will be driven by the neodecanoic acid, the free cobalt ions, and boric acid. As stated above, the toxicity of soluble cobalt salts is related to the cobalt ion and independent of counter ions. Therefore, the data obtained from soluble cobalt compounds and borates have been discussed below.

Boric acid is readily and completely absorbed in humans and animals following oral administration; inhalation absorption is also assumed to be 100 % as a worst case scenario. Dermal absorption of boric acid through intact skin is very low in all species; a dermal absorption rate of 0.5 % is assumed, while 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 animals and is mainly excreted in the urine (>90 %), regardless of the type of exposure (NICNASb).

The amount of cobalt absorption in humans varies from 3–97 % depending on the type and dose of the cobalt compounds. It has been demonstrated that upon oral administration, absorption, disposition and elimination of various cobalt salts are the

same, and that the original identity of the salts does not affect cobalt ion absorption in vivo once the compounds have dissociated (NICNASa).

Dermal absorption of cobalt has been demonstrated to be relatively low and a value of 1.08 % has been stated for cobalt chloride hexahydrate (CAS No. 7791-13-1) in an in vitro study using human skin. Similarly, while absorption through the intact skin of guinea pigs was also very low (<1 %), absorption through abraded skin was almost 80 % after a three-hour exposure (NICNASa).

Absorption following inhalation exposure to cobalt depends on the particle size. Particles larger than 2 µm are deposited in the upper respiratory tract, whereas smaller particles are deposited into the lower respiratory tract. Larger particles can be absorbed into the blood after dissolution or can be moved into the gastrointestinal tract by mucociliary action. Smaller particles are either dissolved or phagocytosed by macrophages (NICNASa).

Once absorbed, the cobalt ion is widely distributed in the body, including the skeleton, with the highest concentration found in the liver and kidneys.

The estimated long-term half-life of cobalt after oral intake by a female volunteer was 625 days. Faecal elimination is the primary route of elimination after oral exposure. Faecal elimination varies from 3–99 % in individuals, depending on the dose, form and nutritional status of the individual. Although the liver and kidneys had the highest initial cobalt concentrations after exposure, concentrations were considered low after 100 days. One study demonstrated that cobalt sulfate (CAS No. 10124-43-3) administered orally results in a dose-dependent increase in cobalt levels in foetal blood and amniotic fluid.

After inhalation exposure, although there is a high initial excretion in faeces, the primary route of elimination is via the urine (NICNASa).

Acute Toxicity

Oral

The chemical has moderate acute toxicity following oral exposure in animal tests. The reported oral median lethal dose (LD50) is 1098 mg/kg bw for female rats. A hazard classification is therefore warranted (refer to **Recommendation** section).

In an acute oral toxicity study, the chemical was administered (gavage) to female Crj: CD(SD) rats at doses of 175 mg/kg bw, 550 mg/kg bw, and 2000 mg/kg bw. While clinical signs of toxicity were not observed in rats dosed at 175 mg/kg bw, all rats dosed at 550 mg/kg bw or 2000 mg/kg bw exhibited clinical signs including various staining, wet fur, high carriage, diarrhoea, lethargy, ataxia, clear ocular discharge, laboured breathing, brown discharge from the vulva, prostrate posture, and/or decreased muscle tone. All rats dosed at 2000 mg/kg bw were found dead at one, three, or four days following dosing. All other animals survived until euthanised (REACH).

Dermal

Although no data are available, the available information indicates that the chemical is likely to be of low acute toxicity following dermal exposure. This conclusion is based on the information available on borates and the analogue chemical, cobalt neodecanoate (CAS No. 27253-31-2).

Although no data are available for the analogue chemical cobalt neodecanoate (CAS No. 27253-31-2), given that the toxicokinetics data show low dermal absorption, acute toxicity through the dermal route is not expected (NICNASa)

The LD50 in New Zealand White rabbits is >2000 mg/kg bw for boric acid (CAS No. 10043-35-3). Local effects including erythema, oedema, atonia, desquamation, necrosis and some incidence of skin irritation were noted 24 hours after treatment. An LD50 value of >2000 mg/kg bw in rats has also been determined for boron oxide (CAS No. 1303-86-2) (NICNASb).

Inhalation

Although no data are available, the available information indicates that the chemical is likely to be of low acute toxicity following inhalation exposure. This conclusion is based on the information available on borates and the analogue chemical, cobalt neodecanoate (CAS No. 27253-31-2).

Although no data are available for the analogue chemical cobalt neodecanoate (CAS No. 27253-31-2), it has been noted that due to the physical properties of the chemicals in this group (cobalt salts of carboxylic acids) being predominantly waxy solids, the compounds are not able to be available in an inhalable atmosphere; therefore, testing is considered to not be technically feasible (NICNASa).

The reported median lethal concentration (LC50) in rats is >2 mg/L for boric acid (CAS No. 10043-35-3) and for boron oxide (CAS No. 1303-86-2). 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 following exposure (NICNASb).

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 symptoms. Although the report provided only limited information on dose response, dose ranges of 100 mg to 55 g and 10 mg to 89 g of boric acid were reported for symptomatic and asymptomatic cases, respectively.

There are case reports of lethal oral exposures of humans 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 appropriate quantitative judgment about a 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 insufficiency (NICNASb).

Corrosion / Irritation

Skin Irritation

Although limited information is available, the weight of evidence approach indicates that the chemical is not irritating to the skin. The available information on boric acid (CAS No. 10043-35-3) and on the analogue cobalt neodecanoate (CAS No. 27253-31-2) supports this conclusion (NICNASa; NICNASb).

In a study carried out on three female New Zealand White rabbits according to the OECD Test Guideline (TG) 404, cobalt boron neodecanoate (CAS No. 68457-13-6) (0.5 g) was applied to an area on the side, approximately 5–7 centimetres down from the backbone for four hours. Very slight erythema (grade 1) was noted in 2/3 test animals, which cleared by day seven following exposure (REACH).

The skin irritation potential of the chemical was also tested according to the OECD TG 431—in vitro skin corrosion: Human Skin Model Test. The relative absorbance values were decreased to 20.7 % after three minutes exposure to the chemical. The test item was considered to be corrosive (REACH).

Eye Irritation

Although limited information is available, the weight of evidence approach indicates that the chemical is irritating to the eyes in an animal study. The effects were sufficient to warrant a hazard classification under the adopted GHS (refer to **Recommendation** section).

In an eye irritation study conducted according to the OECD TG 405, the chemical (0.1 mL) was applied to one eye each of two New Zealand White rabbits, which were observed up to 14 days after instillation. Scattered or diffuse corneal opacity was noted only in one treated eye. Iridial inflammation was noted in both treated eyes at the 24- and 48-hour observations and persisted in one treated eye at the 72-hour observation. Chemosis was noted in both eyes, with lesions in one eye fully reversible within seven days and in the other eye within 14 days. Moderate conjunctival irritation was noted in both treated eyes at at the 24-, 48- and 72-hour observations, with lesions in one eye fully reversible within seven days and in the other eye within 14 days and a score of two for both eyes.

The chemical does not meet the criteria for classification under the Approved Criteria. However, based on scores of two for conjunctival redness, the chemical is recommended for classification under the adopted GHS (REACH).

In a study carried out according to the OECD TG 437 (in vitro), the chemical was administered to bovine corneas for 240 minutes at a volume of 0.75 mL (20 % w/v). The chemical test was performed in triplicate. After exposure, a mean score of 1.04 for the chemical was determined. The mean scores for the negative controls, with an increase in opacity or permeability of the corneas, was approximately 1.11, whereas the mean scores for the positive control was approximately 226.56, with clearly identified observations of opacity of the cornea, corresponding to a corrosive effect. Under the experimental conditions reported, the chemical was not considered corrosive to the eyes (REACH).

Observation in humans

Acute respiratory effects have been extensively documented in workers following inhalation of boric acid, boron oxide and other borates as dusts, in a number of studies. Effects include nasal and eye irritation, throat irritation, coughing and breathlessness. No effects on lung function were observed and the effects identified by workers were ‘chemaesthetic’ (physical presence of dusts on the sensory system of workers). 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, a hazard classification as irritating to respiratory system is not warranted (NICNASb).

Sensitisation

Respiratory Sensitisation

No data are available on the chemical or on boron-containing compounds.

Although an inhalable atmosphere is not technically feasible with cobalt complexes of carboxylic acids (due to their waxy physical properties), inhalation could be possible in downstream processes where these chemicals are included in mixtures and effectively acting like soluble cobalt compounds. Therefore, based on read across from the human data available on the analogue chemical, cobalt chloride hexahydrate (CAS No. 7791-13-1) (refer to **Observations in humans**), a hazard classification is warranted for the chemical (refer to **Recommendation** section) (NICNASa).

Skin Sensitisation

No data are available for the chemical. The available information on boron-containing compounds indicate that the chemical is not likely to be a skin sensitiser due to boron content.

However, based on read across animal data available on the analogue chemical, cobalt stearate (CAS No. 13586-84-0), and human data on cobalt chloride (CAS No. 7646-79-9) (see **Observations in humans**), hazard classification is warranted for the chemical (refer to **Recommendation** section).

In a mouse local lymph node assay (LLNA) carried out according to the OECD TG 429, a volume of 25 mL of either 12.5, 25 or 50 % solution of cobalt stearate (CAS No. 13586-84-0), diluted in acetone/olive oil, was applied to groups of five female CBA mice for each dilution. The chemical was applied at the dorsal surface of each ear, once daily over three consecutive days. The stimulation index was reported as 5.6, 9.7 and 8.1 for the 12.5, 25 and 50 % concentrations of the chemical, respectively.

Considering the stimulation indices at all three concentrations were above three, the chemical, cobalt stearate (CAS No. 13586-84-0), is considered to be a skin sensitiser (NICNASa).

Observation in humans

Occupational inhalation exposure to cobalt chloride (CAS No. 7646-79-9) aerosols can produce an asthmatic response in sensitised individuals based on evaluation for specific Immunoglobulin E (IgE) and Immunoglobulin A (IgA) antibodies to cobalt (NICNASa).

In a study conducted in human volunteers, skin patch tests showed a positive reaction in 286/4034 patients to 1 % cobalt chloride (CAS No. 7646-79-9) in petroleum jelly 24 hours after exposure. In another two patch test studies, 225/1415 patients and 24/373 patients showed a positive reaction to cobalt chloride when applied to the upper back using occlusive patches. There appears to be an increased incidence of positive testing in females compared with males in all tests. In an occupational study with 853 hard metal workers patch tested with an initial test of 1 % cobalt chloride (CAS No. 7646-79-9), 62 % showed a positive sensitisation reaction (NICNASa).

In another study, flaring of eczema was observed following an oral administration with 1 mg of cobalt sulfate (CAS No. 10124-43-3) to cobalt-sensitised people, with exposure once a week over three weeks. The allergic dermatitis reported was considered a positive allergic response to cobalt (NICNASa).

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

Repeated Dose Toxicity

Oral

As no data are available for the chemical, the available information on borates and soluble cobalt compounds has been used here for assessment.

Reading across from the soluble cobalt compounds, the main effects with repeated oral exposure are expected to be polycythaemia (increased erythrocytes), increased haematocrit and increased haemoglobin levels which are reversible shortly after exposure ceases (NICNASa; NICNASb; NICNASc).

A number of repeated dose oral toxicity studies on boric acid (CAS No. 10043-35-3) in animals has indicated that the main target organ for boron toxicity is the testis, leading to adverse reproductive and developmental 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 indicative of increased red blood cell destruction have also been commonly noted as signs of boron toxicity (NICNASb).

An overall no observed adverse effect level (NOAEL) of 17.5 mg boron/kg bw/day (equivalent to 100 mg boric acid/kg bw/day) 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 boron/kg bw/day (equivalent to 334 mg boric acid/kg bw/day) (NICNASb).

In a repeated dose toxicity study, boric acid (CAS No. 10043-35-3) was fed to Sprague Dawley (SD) rats (35/sex/group) 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 **Reproductive and developmental toxicity**). Males in the highest dose group showed hunched positions; inflamed bleeding eyes; desquamation of the tail skins and pads on the paws; significant reduction in red cell volume and haemoglobin; shrunken scrotums; testicular atrophy and seminiferous tubule degeneration (at six, 12 and 24 months); and atrophied seminiferous epithelium and decreased tubular size in the testes at microscopic examination. A two-year 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 (NICNASb).

In a short-term repeated dose toxicity study, SD rats were administered (oral) with 0, 2.5, 10 and 40 mg/kg bw/day cobalt chloride hexahydrate (CAS No. 7791-13-1) for six weeks, seven days a week in gelatine capsules. The NOAEL was established as 2.5 mg/kg bw/day and the LOAEL as 10 mg/kg bw/day, based upon dose- and time-related increases in haemoglobin content

and numbers of erythrocytes. In a longer-term study over seven months, oral doses of 0.2 and 10 mg/kg bw/day cobalt chloride hexahydrate (CAS No. 7791-13-1) administered (gavage) to rats six times/week, stimulated polycythaemia and decreased leukocyte function in rats. The NOAEL in this study was 0.2 mg/kg bw/day (NICNASa).

Increased heart weight was reported in male rats exposed to 122 mg/kg bw/day of cobalt chloride hexahydrate (CAS No. 7791-13-1) in drinking water. Degenerative heart lesions were observed after administration of 124 mg/kg bw/day of cobalt sulfate heptahydrate (CAS No. 10026-24-1) in the diet after a two to three month exposure (NICNASa).

In two separate non-guideline studies, 40 mg/kg bw/day of cobalt sulfate heptahydrate (CAS No. 10026-24-1) was administered in drinking water over 16 or 24 weeks in one study and 24 weeks in the other study. After the exposure period, animals in the first two groups (16 or 24 weeks) were euthanised and ventricular function was determined on a working-model Langendorff's circuit. In the first study, myocardial cobalt concentration was significantly increased in both exposure groups and there was a significant decrease in body weights of both groups compared with corresponding controls. The 24-week exposure in the first study resulted in left ventricular hypertrophy and impaired left ventricular systolic and diastolic function. In the second study, decreased enzyme activity in cardiac tissues (manganese-superoxide dismutase (Mn SOD), succinate-cytochrome C oxidase, NADH-cytochrome C reductase and decreased mitochondrial ATP production rate and a reduction in the capacity of the respiratory chain were observed (NICNASa).

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 cobalt has also been demonstrated to be relatively low (see **Toxicokinetics**).

Inhalation

As no data are available for the chemical or boric acid, the available information on soluble cobalt compounds has been used here for assessment. Inhalation could be possible in downstream processes where the chemical is included in mixtures and effectively acts as a soluble cobalt compound.

While it appears that the available bioaccessibility data on alveolar fluid do not correlate with acute inhalation toxicity and repeated dose toxicity, inhalation toxicity appears to correlate with the available bioaccessibility data on lysosomal fluid.

It has been postulated that phagocytosis followed by a release of solubilised Co^{2+} and macrophage contents (for components bioavailable in lysosomal fluid) may be a route for toxicity (Ortega et al., 2014). This can explain the lack of correlation between bioaccessibility in alveolar fluid and acute inhalation toxicity and repeated dose toxicity via inhalation. Considering that cobalt neodecanoate (CAS No. 27253-31-2) dissolves moderately in artificial alveolar fluid—26.1 %; and completely in artificial lysosomal fluid—100 % (Stopford et al., 2003), it is prudent to read-across data from soluble cobalt compounds.

Therefore, based on read across data on soluble cobalt chemicals (NICNASa), chemicals in this group are expected to cause serious damage to health by prolonged exposure via inhalation. A lowest observable adverse effect concentration (LOAEC) of 0.3 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) was identified for local effects on the larynx. The available data on the analogue chemical cobalt sulfate heptahydrate (CAS No. 10026-24-1), warrant hazard classification for the chemical (refer to **Recommendation** section).

The National Toxicology Program (NTP) conducted 13-week and two-year studies in male and female Fischer 344/N (F344/N) rats and B6C3F1 mice using cobalt sulfate heptahydrate (CAS No. 10026-24-1).

In the 13-week study, rats and mice (10 animals/sex/species) were exposed to aerosols containing 0, 0.3, 1, 3, 10 or 30 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) for six hours/day, five days/week for the duration of the study. Male rats exposed to any concentration of the chemical showed a significant increase in relative kidney weights. Even though the renal histopathology did not indicate any increase in kidney lesions in rats or mice, there was a concentration-related increase in epithelial cells and granular casts observed in the urine of male rats, suggesting slight kidney toxicity. There was also a significant increase in the relative lung weights of rats exposed to >0.3 mg/m^3 for males, and >1 mg/m^3 for females. In mice, this

was observed in both sexes from >10 mg/m^3. Absolute and relative testis weights and epididymal weight were significantly decreased in male mice at 30 mg/m^3. Polycythaemia was observed in rats at >3 mg/m^3. Histopathological lesions were observed in the respiratory tract of both rats and mice at all exposure levels from the chemical. A LOAEC of 0.3 mg/m^3 was determined, based on squamous metaplasia in the larynx (NICNASa).

In the two-year NTP study, rats and mice (50 animals/sex/species) were exposed to 0, 0.3, 1, 3 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) for six hours/day, five days/week for the duration of the study. Exposure to cobalt sulfate heptahydrate (CAS No. 10026-24-1) at all exposure levels caused inflammation, fibrotic and proliferative lesions in the respiratory tract of male and female rats and mice, although the changes in mice was less severe (NICNASa).

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 symptoms including dermatitis, alopaecia, loss of appetite, nausea, vomiting, diarrhoea, and focal or generalised central nervous system (CNS) effects or convulsions (NICNASb).

With respect to cobalt, a read-across approach was taken from data available on analogue chemicals, cobalt sulfate heptahydrate (CAS No. 10026-24-1) and cobalt chloride (CAS No. 7646-79-9).

Cobalt-induced cardiac failure was attributed to 50 patients who had ingested, over a period of years, an average of 0.2 to 0.7 mg/kg bw/day of cobalt sulfate heptahydrate (CAS No. 10026-24-1) that was added to stabilise foam in beer. The first signs of beer–cobalt cardiomyopathy were gastrointestinal effects including nausea, vomiting and diarrhoea. Beer–cobalt cardiomyopathy and alcoholic cardiomyopathy have similar symptoms, although the onset of beer–cobalt cardiomyopathy was found to be very abrupt. These patients had protein-poor diets and consumed significant quantities of alcohol, which might affect the symptoms of cardiomyopathy, pulmonary rales and pulmonary oedema that were observed. In an occupational study of 237 workers from a cobalt refinery, no dose-effect relationships were observed between cobalt exposure and incipient signs of cardiomyopathy (NICNASa).

Polycythaemia (increase in erythrocytes) and an increase in haemoglobin levels were observed in all subjects in another study where six volunteers were exposed to a daily dose of 150 mg/day of cobalt chloride (CAS No. 7646-79-9) for up to 22 days. Erythrocyte counts returned to normal in all subjects 15 days after treatment (NICNASa).

As a result of the effects of cobalt which have potential to increase haemoglobin levels, it has been previously used therapeutically to treat anaemia. In a series of studies, anephric patients were treated with 0.65–4.0 mg/kg bw/day of cobalt chloride (CAS No. 7646-79-9), daily for 3–32 weeks. The increase in erythrocytes resulted in a decreased need for blood transfusions. In another series of studies, sickle-cell anaemia patients receiving cobalt therapy showed enlargement and hyperplasia of the thyroid gland, which were reversible upon cessation of cobalt therapy (NICNAS a). When pregnant women were treated for 90 days with 2–2.4 mg/kg/day of cobalt chloride (CAS No. 7646-79-9), it did not prevent the common occurrence of decreasing levels of haemoglobin and haematocrit levels observed during pregnancy. There were also no effects observed on the heart, in liver function or obvious birth defects (NICNASa).

Genotoxicity

Limited data available on the chemical and the available information on borates and soluble cobalt compounds indicate that the chemical is not likely to have mutagenic or genotoxic potential.

The chemical tested negative in several in vitro mammalian cell gene mutation (gene mutation) tests with mouse lymphoma L5178Y cells (REACH).

It was concluded that, as effective protective processes exist in vivo to prevent genotoxicity in humans, soluble cobalt compounds are not likely to have a mutagenic or genotoxic potential (NICNASa).

Boric acid (CAS No. 10043-35-3) tested 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 a

mutagenic or genotoxic potential (NICNASb).

Carcinogenicity

As no data are available for the chemical, the available information on borates and soluble cobalt compounds have been used here for assessment.

The available information on boric acid (CAS No. 10043-35-3) indicates that the chemical is not likely to have carcinogenic potential. Boric acid (CAS No. 10043-35-3) is also not considered to have mutagenic or genotoxic potential (see **Genotoxicity**) (NICNASa).

Data are also not available for the analogue chemical cobalt neodecanoate (CAS No. 27253-31-2). Although an inhalable atmosphere is not technically feasible with cobalt soaps (due to their waxy physical properties), inhalation could be possible in downstream processes where cobalt chemicals are included in mixtures and effectively acting like soluble cobalt compounds (NICNASa; NICNASb; NICNASc).

Cobalt acetate (CAS No. 71-48-7) and cobalt sulfate (CAS No. 10124-43-3) are classified as hazardous—Category 2 carcinogenic substance—with the risk phrase ‘May cause cancer by inhalation’ (T; R49) in the HSIS (Safe Work Australia). Therefore, read across data on the soluble cobalt analogue chemical cobalt sulfate heptahydrate (CAS No. 10026-24-1), warrant hazard classification for the present chemical (refer to **Recommendation** section) (NICNASa; NICNASb; NICNASc).

The International Agency for Research on Cancer (IARC) has classified cobalt sulfate and other soluble cobalt (II) salts as possibly carcinogenic to humans (Group 2B) (IARC, 2006).

In a two-year inhalation carcinogenicity study conducted by the NTP, rats and mice (50 animals/sex/species) were exposed to 0, 0.3, 1 or 3 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) for six hours/day, five days/week for the duration of the study. Female rats exposed to 1 mg/m^3 and higher, and male rats as well as both sexes of mice exposed to 3 mg/m^3, had significantly increased incidences of alveolar/bronchiolar neoplasms compared with controls. Marginal incidences of phaeochromocytoma of the adrenal medulla compared with controls were seen in males exposed to >1 mg/m^3. The NTP (1998) concluded that there is 'some evidence of carcinogenic activity' of cobalt sulfate heptahydrate (CAS No. 10026-24-1) in male F344/N rats and there was 'clear evidence of carcinogenic activity' in female F344/N rats exposed to 3 mg/m^3 of the chemical. The combined or single incidence of alveolar/bronchiolar adenoma or carcinoma in the male and female mice exposed to 3 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) exceeded the NTP historical control ranges for inhalation studies. It was concluded that there is 'clear evidence of carcinogenic activity' of the chemical in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms (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, 5000 ppm (equivalent to 0, 446, 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 tested dose. 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 were used for macroscopic and histopathological examination. Animals in the low and mid-dose groups were not examined (NICNASb).

No evidence of carcinogenicity was seen in two, two-year dietary studies in rats exposed to 81 mg boron/kg bw/day as boric acid, and dogs exposed to 6.8 mg boron/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 (NICNASb).

Reproductive and Developmental Toxicity

No data are available regarding the reproductive or developmental effects of the chemical and the analogue chemical, cobalt neodecanoate (CAS No. 27253-31-2). While there are several non-guideline studies on developmental toxicity for soluble cobalt compounds, it is difficult to draw firm conclusions about the developmental toxicity of these chemicals due to various methodological deficiencies (NICNASa).

It is noted that, based on cobalt chloride (CAS No. 7646-79-9) and cobalt sulfate heptahydrate (CAS No. 10026-24-1), the analogue chemical cobalt neodecanoate (CAS No. 27253-31-2) has been recommended for classification as a Category 2 substance toxic to reproduction—with the risk phrase 'May impair fertility' (T; R60). Therefore, read across data on cobalt neodecanoate (CAS No. 27253-31-2) also support hazard classification for the chemical (NICNASa; NICNASb; NICNASc) (refer to **Recommendation** section).

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 a hazardous, Category 2 substance toxic to reproduction, with the risk phrases 'May impair fertility' (T; R60) and 'May cause harm to the unborn child' (T; R61) in the HSIS (Safe Work Australia) (NICNAS b). Due to the low boron content of the chemical, the reproductive effects of the chemical due to its borate content are likely to occur only at doses where cobalt toxicity is expected.

In a 12-week oral fertility study, adult male Swiss mice were exposed to cobalt chloride (CAS No. 7646-79-9) in drinking water (average of 25, 47 or 93 mg/kg bw/day) and then mated with unexposed females. The number of pregnant females and implantation sites were significantly reduced in females mated with exposed males at the 47 and 93 mg/kg bw/day dose. At all doses, the incidence of resorption was significantly higher, whereas the number of viable foetuses decreased. Decreased relative testes weight, decreased sperm concentration, and testis necrosis and degeneration were observed (NICNASa).

In a 13-week study, rats and mice (10 animals/sex/species) were exposed to aerosols containing 0, 0.3, 1, 3, 10 or 30 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) for six hours/day, five days/week for the duration of the study. Absolute and relative testicular weights and the epididymis weight were significantly decreased, together with an increased number of abnormal sperm in male mice at 30 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1). Sperm motility was significantly reduced in mice exposed to >3 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1), but data were not collected on mice exposed to lower concentrations (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 include reduced organ weight and organ to body-weight ratio; atrophy and degeneration of the spermatogenic epithelium; impaired spermatogenesis; and reduced fertility. The developmental effects that have been reported included high prenatal mortality; reduced foetal body weight; and malformations and variations of the eyes, central nervous system (CNS), cardiovascular system, and axial skeleton. A 100 mg/kg bw/day NOAEL for fertility of boric acid (equivalent to 17.5 mg boron/kg bw/day) has been determined (based on testicular effects) from two and three-year 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 (NICNASb).

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 **Repeat 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 100 mg/kg bw/day NOAEL 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 (NICNASb).

In a developmental toxicity study, boric acid was fed in the diet to 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 (NICNASb).

Other Health Effects

Neurotoxicity

Information is not available on the chemical or on cobalt compounds. Information on borates is presented below.

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, the chemical is not likely to have neurotoxic properties (NICNASb).

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 concentrations of 470 mg boron oxide/m^3 (73 mg boron/m^3) as an aerosol 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 systemic long-term effects (reproductive and developmental toxicity), local long-term effects (carcinogenicity), systemic acute effects (acute toxicity by oral exposure) and acute local effects (skin sensitisation and respiratory sensitisation). The chemical can also cause harmful effects following repeated exposure through inhalation, and eye irritation.

Public Risk Characterisation

The chemical has no identified uses in Australia.

Even though the chemical has reported domestic uses overseas (see **Import, manufacture and use**), the available North American database does not give evidence for the chemical's use in consumer products. Therefore, use of the chemical in cosmetic and consumer products is not anticipated in Australia and the public risk is not considered to be unreasonable.

Occupational Risk Characterisation

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

Given the critical long-term systemic effect, local long-term effect, systemic acute effect and acute local health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise 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 (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

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

Considering the concentration of 0.3 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) identified in the inhalation repeated dose toxicity studies (NICNASb) at which adverse effects are observed, there is a concern that the absence of exposure controls in the HSIS might not adequately protect workers' health.

NICNAS Recommendation

Assessment of the chemical 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 chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

The classification proposed below is based on read across principles (see introductory section of **Health hazard information**) for some human health toxicological end-points. If empirical data become available for the chemical indicating that a lower (or higher) classification is appropriate, these may be used to amend the default classification.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity		Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	May cause sensitisation by inhalation (Xn, R42) May cause sensitisation by skin contact (Xi; R43)	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 2 - May cause cancer by inhalation (T; R49)	May cause cancer - Cat. 1B (H350i)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May impair fertility (T; R60)	May damage fertility - Cat. 1B (H360F)

[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 chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, ocular and inhalation exposure to the chemical 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 chemical is used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- 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 chemical.

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 chemical is 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 the chemical has not been undertaken as part of this assessment.

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