Soluble beryllium salts: Human health tier II assessment

04 July 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Nitric acid, beryllium salt, tetrahydrate	13510-48-0
Beryllium chloride (BeCl2)	7787-47-5
Sulfuric acid, beryllium salt(1:1), tetrahydrate	7787-56-6

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

Grouping Rationale

This group consists of soluble salts of beryllium. These compounds have been included in this group due to the expectation that the physico-chemical properties will not vary greatly, leading to the compounds within this group having related end uses. In addition, information outlined in the Organisation for Economic Co-operation and Development's (OECD) guideline on Grouping of Chemicals (OECD, 2014) provided guidance on the grouping of chemicals based on physico-chemical or toxicological criteria.

The majority of data available for human health assessment are taken from reports titled 'Beryllium and beryllium compounds' (WHO, 2001; ATSDR, 2002), which encompass beryllium, soluble beryllium compounds and beryllium oxide. This assessment is specifically about soluble beryllium compounds only.

Import, Manufacture and Use

Australian

The National Pollutant Inventory (NPI) holds data for all sources of beryllium compounds. Beryllium chloride (CAS No. 7787-56-6) has site-limited use in refining beryllium ores and as a chemical reagent.

International

The following international uses have been identified through Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals in this group have reported site-limited use including:

- in alloys to strengthen other metals;
- in beryllium metal extraction; and
- as catalysts.

Restrictions

Australian

Beryllium and its compounds are listed in Schedule 10 (prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals) of the Work Health and Safety Regulations (WHS) for restricted use. The Schedule 10 entry states the restriction as 'for abrasive blasting at a concentration of greater than 0.1% as beryllium' (WHS, 2011).

International

The following international restrictions are identified (Galleria Chemica):

- European union: EU Cosmetics directive 74/768/EEC Annex II: list of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group (listed by SWA as 'Beryllium compounds, with the exception of aluminium beryllium silicates, and those elsewhere specified') are classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- T; R25/26 (Acute toxicity);
- T; R48/23 (Repeat dose toxicity);
- Xn; R49 (Carcinogenicity Cat. 2);
- Xi; R36/R37/R38 (Irritation); and
- Xi; R43 (Sensitisation).

Exposure Standards

Australian

The chemicals in this group fall under the Safe Work Australia (SWA) group entry 'Beryllium and compounds', which have an exposure standard of 0.002 mg/m^3 time weighted average (TWA) (Safe Work Australia).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit (TWA) of 0.001–0.002 mg/m^3 and a short-term exposure limit (STEL) of 0.01–0.005 mg/m^3 in different countries such as the USA (Washington, TWA = 0.002 mg/m^3, STEL = 0.005 mg/m^3), Canada (Ontario, STEL = 0.01 mg/m^3) and Denmark (TWA = 0.001 mg/m^3).

Health Hazard Information

Toxicokinetics

The major route of beryllium exposure is through inhalation.

Inhalation

Rats (unspecified strain) exposed to 0.034 mg/m^3 of beryllium as beryllium sulfate (aerosol) for seven hours a day, five days a week for 72 weeks reached steady state concentration in the lungs at 36 weeks of exposure. The beryllium concentration in tracheobronchial lymph nodes peaked in weeks 36–52 and then decreased for the duration of the study (ATSDR, 2002).

In another study, radioactive beryllium sulfate and beryllium chloride were reported to be widely distributed as a result of pulmonary absorption. Immediately after a three-hour exposure, the percentage of radioactivity was distributed across the lungs (60 %), liver (0.9 %), kidneys (1.9 %), muscles (9.5 %), skeleton (13.5 %), blood (5 %) and excrement (10 %) (ATSDR, 2002).

In another study conducted in rats and guinea pigs, animals exposed to 2–40 mg/m^3 beryllium as beryllium nitrate for 16 hours reported 60–70 % of beryllium bound to proteins (prealbumins and γ–globulins) in the blood (ATSDR, 2002). ATSDR (2002) reported that soluble beryllium compounds are partially converted to less soluble forms in the lung. The excretion of soluble beryllium compounds is described as bi-phasic. Excretion follows an initial rapid phase (half-life 1–60 days in rats) due to mucociliary transport of the particles from the tracheobronchial area to the gastrointestinal tract, followed by a slow (0.6 weeks to 2.3 months) clearance of the chemicals into the tracheobronchial lymph nodes and uptake by alveolar macrophages (WHO, 2001).

Oral

Gastrointestinal absorption is reported as <1 %, resulting in most of the beryllium compound being excreted unchanged in the faeces. Data show that rats orally gavaged with radioactive beryllium (unknown dose) excreted all the administered compound unchanged in the urine and faeces (0.11 and 104.7 % respectively). Even though soluble beryllium compounds are poorly absorbed, there is a trend for beryllium compounds to accumulate over time with repeated exposure, especially in bones. With respect to excretion, analysis of excreta from rats administered 0.019 and 0.19 mg/kg as beryllium sulfate in drinking water showed that 99 and 0.5 % of the doses were excreted unchanged in the faeces and urine respectively (ATSDR, 2002).

Dermal

Soluble beryllium compounds are poorly absorbed after dermal exposure. Occupational exposure to beryllium compounds was associated with skin ulceration, but this only occurred in workers with abraded or accidentally cut skin (ATSDR, 2002). One animal study reported that a 'small' amount of beryllium from an aqueous solution of beryllium chloride was absorbed through the tail skin of rats, but no further data were provided. A study in guinea pigs reported that beryllium can bind alkaline phosphatase and nucleic acids in the guinea pig epidermis in vitro, thus accounting for the inefficient transfer to the blood (ATSDR, 2002).

Acute Toxicity

Oral

Beryllium compounds are classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). The available data (median lethal dose (LD50) ≤200 mg/kg bw) support this classification (WHO, 2001; ATSDR, 2002). No further information on sub-lethal effects are available.

The reported LD50 in rats is 120 mg/kg bw for beryllium sulfate (CAS No. 13510-49-1) and 200 mg/kg bw for beryllium chloride (CAS No. 7787-47-5). The reported LD50 in mice is 18–20 mg/kg for beryllium chloride and 140 mg/kg bw for beryllium sulfate (WHO, 2001).

Dermal

No data are available.

Inhalation

Beryllium compounds are classified as hazardous with the risk phrase ‘Very toxic by inhalation’ (T+; R26) in HSIS (Safe Work Australia). The available data (median lethal concentration (LC50) 0.15 mg/m^3) support this classification (WHO, 2001; ATSDR. 2002). No further information on sub-lethal effects is available

Observation in humans

Studies of occupational exposure to beryllium or its compounds are the major source of information regarding adverse effects in humans after inhalation exposure. Acute occupational inhalation exposure to high concentrations of soluble beryllium compounds is associated with symptoms of nasal and pharyngeal mucous membrane irritation, sore nose and throat, weight loss, laboured breathing, decreased vital capacity, anorexia and increased fatigue. These symptoms are collectively defined as acute beryllium disease (ABD) and have been associated with soluble beryllium concentrations as low as 0.1 mg/m^3 of beryllium as beryllium sulfate or beryllium fluoride. The incidence of ABD has essentially been eliminated (due to workplace exposure limits and mandatory personal protective equipment introduction) except in cases of accidental acute exposure (ATSDR, 2002).

Corrosion / Irritation

Respiratory Irritation

Beryllium compounds are classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). No animal data are available to evaluate this classification, although the available epidemiological data from observations in humans support this classification (refer to **Irritation: Observation in humans**).

Skin Irritation

Beryllium compounds are classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). No animal data are available to evaluate this classification, although the available epidemiological data from observations in humans support this classification (refer to **Irritation**: **Observation in humans**).

Eye Irritation

Beryllium compounds are classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). No animal data are available to evaluate this classification, although the available epidemiological data from observations in humans support this classification (refer to **Irritation: Observation in humans**).

Observation in humans

It is reported that the soluble salts of beryllium cause allergic dermatitis. Direct contact with soluble beryllium compounds is reported to cause local irritation (reddened, elevated, or fluid-filled lesions on exposed body surfaces) in workers exposed to beryllium sulfate and other soluble beryllium compounds (beryllium fluoride or beryllium oxyfluoride). Chronic ulceration with granuloma has also been noted in workers after soluble or insoluble beryllium compounds are introduced into or under the skin as a result of abrasions or cuts. Conjunctivitis has also been reported in cases of accidental splash injuries, and has often been associated with severe periorbital oedema. With respect to the respiratory system, ABD is clinically associated with symptoms of rhinitis, pharyngitis, tracheobronchitis and pneumonitis (Homayoun, 2011).

The characteristics, severity and the time to symptom onset for skin, eye and respiratory sensitisation described above, are dependent on the quality and quantity of exposure, and are reported to subside 1–4 weeks after the individual has been removed from further exposure (Homayoun, 2011). Occupational exposure to soluble beryllium compounds was associated with skin ulceration, but this only occurred in workers with abraded or accidentally cut skin (ATSDR, 2002).

Sensitisation

Respiratory Sensitisation

Based on the available epidemiological data (see **Sensitisation: Observation in humans** and **Repeat dose toxicity: Observation in humans**), it is recommended to classify this group of chemicals as respiratory sensitisers (refer to **Recommendation** section).

Skin Sensitisation

Beryllium compounds are classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). The available data from animal studies and case reports in humans (refer to **Sensitisation: Observation in humans**) supports this classification.

Rats and guinea pigs exposed to 0.5 mg/m^3 beryllium salts as beryllium nitrate for 10 weeks developed a delayed allergic skin reaction 24–48 hours following challenge (ATSDR, 2002). In a further skin sensitisation study, guinea pigs became sensitised to beryllium through 12 twice-weekly intradermal injection of beryllium sulfate or beryllium fluoride (0.0018 or 0.0005 mg) and developed skin reactions 6–8 hours following challenge. The adverse effects were noted to last for up to three weeks (WHO, 2001; ATSDR, 2002). Similar studies conducted in guinea pigs have shown that the sensitising potential of beryllium compounds depends on the solubility of the sensitiser (beryllium fluoride > beryllium sulfate > beryllium oxide) and the anion of what the test agent was bound to (beryllium-albuminate > beryllium sulfate > beryllium-hydrogen citrate > beryllium-aurin-tricarboxylate) (WHO, 2001; ATSDR, 2002).

Observation in humans

Dermal exposure to soluble beryllium salts has been associated with beryllium sensitisation. The main dermal adverse effects, reported in a case history of 42 workers exposed to airborne soluble beryllium compounds, was oedematous papulovesicular dermatitis, which was considered most likely an inflammatory response to beryllium compounds. Ulceration was reported in cases where workers were exposed to soluble beryllium chemicals after accidental skin abrasion. A delayed, hypersensitive reaction in the skin has also been noted in workers following exposure to beryllium, as the same mononuclear infiltrates were detected in the biopsied skin as in the lungs. Patch tests in humans confirmed that soluble beryllium compounds, particularly the fluoride salt, produced allergic contact dermatitis (ATSDR, 2002).

Inhalation exposure to beryllium compounds can induce chronic beryllium disease (CBD) in humans with symptoms increasing in severity over time. CBD is an inflammatory disease of the lung, characterised by the presence of non-caseating granulomas (without necrosis) in a person known to be sensitised to beryllium. It is a well described Type IV, delayed hypersensitivity, cell-mediated immune response characterised by weight loss, a non-productive cough, fatigue, chest pain, anorexia, and weakness. The latency period for developing clinical CBD can be more than 20 years (ATSDR, 2002).

Repeated Dose Toxicity

Oral

The available data from non-guideline studies indicate that the chemicals in this group can cause serious damage to health in dogs, but the observed effects are secondary to the local effects, rather than the result of direct systemic toxicity following absorption.

In a repeated dose oral toxicity study, male and female Wistar rats were fed beryllium as beryllium sulfate tetrahydrate at 0, 5, 50 or 500 ppm (0, 0.36, 3.6 or 37 mg/kg bw/day in males, 0, 0.42, 4.3 or 43 mg/kg bw/day in females) from four weeks of age through to maturation, mating and gestation. Fifty male and 50 female offspring (F1 generation) were then placed on the same diet for 104 weeks. While no data are reported for the parental animals (Po), data available for the offspring indicate that beryllium sulfate tetrahydrate did not affect mortality. Growth was not affected for the first 40–50 weeks of the study, but was decreased (non-significant) in the 500 ppm group (males and females). No further signs of toxicity were reported under gross or histopathological examination (WHO, 2001).

In another study conducted in Long–Evans rats, beryllium in the form of beryllium sulfate tetrahydrate (0 or 5 mg/L) was administered through drinking water from weaning until natural death. No gross or histopathological changes in toxicity were reported (WHO, 2001).

In a long-term study conducted in beagle dogs, five male and five female dogs were fed diets containing 0, 5, 50, or 500 ppm beryllium as beryllium sulfate tetrahydrate (equivalent to 0, 0.12, 1.1 and 12.2 mg/kg bw/day in males and 0.029, 0.15, 1.3 and 17.4 mg/kg bw/d in females) for 172 weeks. Due to excessive toxicity (indicated by death, anorexia, weight loss, blood in faeces and associated anaemia) in the 500 ppm group after 33 weeks, this group was euthanised. Further investigation showed that 9/10 dogs in the 500 ppm group had extensive ulcerative inflammatory lesions in the gastrointestinal tract. A new group of dogs was entered into the study that were administered 1 ppm beryllium as beryllium sulfate tetrahydrate (equivalent to 0.023 mg/kg bw/day) for 143 weeks. No toxic effects associated with beryllium exposure were reported at the lower doses (1–50 ppm) (WHO, 2001).

Dermal

No data are available.

Inhalation

Beryllium compounds are classified as hazardous with the risk phrase ‘Toxic: danger of serious damage to health by prolonged exposure through inhalation’ (T; R48/23) in HSIS (Safe Work Australia). Available data from animal studies and from human epidemiological studies (see **Repeat dose toxicity: observation in humans**) support this classification.

The respiratory system is the primary target for inhalation exposure to beryllium in animals. Chronic exposure to beryllium and its compounds causes similar health effects as those observed after shorter exposure durations. Rabbits, dogs, cats and monkeys exposed to 0.04 mg/m^3 beryllium as beryllium sulfate through inhalation for 100 days caused distorted lung structure, which appeared to be severely inflamed and emphysematous. In further studies, Sprague Dawley (SD) rats exposed to 0.034 mg/m^3 of beryllium as beryllium sulfate through inhalation for 72 weeks showed inflamed lungs, emphysema, arteriolar wall thickening, granulomas, fibrosis and proliferative responses within the alveoli (ATSDR, 2002).

Sherman rats exposed to 0.0547 mg/m^3 beryllium as beryllium sulfate via inhalation for 6–18 months also showed signs of inflamed lungs and fibrosis (ATSDR, 2002).

Observation in humans

The respiratory tract is the primary target for beryllium toxicity. Non-neoplastic respiratory toxicity of beryllium compounds is divided into ABD and CBD (WHO, 2001; ATSDR, 2002). ABD has been discussed in the **Acute toxicity—Observation in humans** section.

The majority of epidemiological data does not specify whether exposure to 'beryllium' was specifically to soluble beryllium compounds. As soluble beryllium compounds are key intermediaries in the process of beryllium extraction, the available epidemiological evidence from beryllium extraction plants will be taken as weight of evidence in this assessment. Data mentioning the use of beryllium oxide or beryllium oxide fumes have been excluded.

CBD, also referred to as berylliosis, is defined as an inflammatory lung disease resulting from inhalation exposure to beryllium. Pathological features characteristic of a beryllium-induced immune response include granulomas (pathologic clusters of immune cells) and varying degrees of interstitial fibrosis (US EPA, 1998). Several criteria have been developed to establish CBD in patients, and include incidence of respiratory disease, X-rays with evidence of interstitial fibronodular disease, a positive blood or broncheoalveolar lavage lymphocyte transformation test or a positive beryllium lymphocyte transformation test (BeLT) (US EPA, 1998).

In a study conducted in beryllium extraction and processing plant workers, 214 full-time workers (employed 1–14 years) were exposed to beryllium concentrations ranging from 0.31–1310 μg/m^3. In 1971, radiographic findings showed 31 workers with interstitial disease, 20 workers with reduced arterial oxygen tension (hypoxaemia), 11 workers with both, and two workers with CBD. A re-evaluation following-up workers in 1974, after exposure levels had been reduced to 2–15 μg/m^3, showed a significant improvement in hypoxaemia and reversed interstitial disease as shown by clinically normal chest radiographs (US EPA, 1998).

Genotoxicity

The chemicals in this group produced inconsistent results in genotoxicity assays conducted in vitro (Ames assay, chromosomal aberration test, DNA repair test), with and without metabolic activation. Limited data from in vivo genotoxicity studies indicate that soluble beryllium compounds do not induce mutations (US EPA, 1998; WHO, 2001). Based on the weight of evidence, the chemicals in this group are not considered to have mutagenic or genotoxic potential.

Ames assays conducted with beryllium sulfate in two bacterial species (*Escherichia coli* and *Saccharomyces cerevisiae*) were negative, with and without metabolic activation. Positive results were reported using *Escherichia coli* in the *Bacillis subtilis* rec assay (DNA repair test). Further studies showed that beryllium sulfate did not induce unscheduled DNA synthesis in primary rat hepatocytes and was not mutagenic in vivo (host-mediated assay) when injected into adult mice (US EPA, 1998). Similarly, genotoxicity studies conducted with beryllium nitrate reported that the chemical tested negative in several studies using the Ames assay, but tested positive in studies using the *Bacillus Subtilis* rec assay (US EPA, 1998). Soluble beryllium compounds cultured with mammalian cells were reported to induce clastogenic alterations (US EPA, 1998).

Beryllium sulfate (1.4 or 2.3 g/kg bw) administered to CBA mice by oral gavage did not induce micronuclei formation in the bone marrow, even though a depression in erythropoiesis (indicative of bone marrow toxicity) was reported 24 hours after dosing (US EPA, 1998).

Carcinogenicity

Beryllium compounds are classified as hazardous—Category 2 carcinogenic substances—with the risk phrase ‘May cause cancer by inhalation’ (T; R49) in HSIS (Safe Work Australia). While the appropriate data are limited for chemicals in this group, sufficient information was available from several epidemiological reports for 'Beryllium and beryllium compounds' (WHO, 2001; ATSDR, 2002) (refer to **Recommendation** section).

Epidemiological evidence

The International Agency for Research on Cancer (IARC), has concluded that there is sufficient evidence in humans and experimental animals for the carcinogenicity of beryllium and beryllium compounds. Consequently, the IARC has classified beryllium and beryllium compounds as '*carcinogenic to humans (Group 1)*'. While several molecular mechanisms (possibly interrelated) could possibly operate in beryllium-induced carcinogenesis, it was concluded that the processes underlying this are clearly complex, with several possible interactive mechanisms (IARC, 2012).

Although specific epidemiological evidence for the chemicals in this group has not been stated, the risk of developing cancer following occupational exposure to beryllium and beryllium compounds during processing or extracting beryllium has been suspected (IARC, 2012). As soluble beryllium compounds are used during processing or extracting beryllium, these studies in particular have been discussed below.

A study of workers at seven beryllium processing plants across the USA reported to be exposed to 'many forms of beryllium and beryllium compounds', had an elevated risk of developing lung cancer, the standardised mortality ratio (SMR) being 1.26. The SMR was particularly high (1.69) in older plants (IARC, 2012). A further cohort study conducted in over 3000 men employed in two beryllium extraction, production and fabrication facilities in the USA between 1942–1948, reported a combined SMR of 1.45 for lung cancer. It was also noted that the SMR for lung cancer was higher before 1949, when the levels of exposure to beryllium and beryllium compounds were highest. In addition, patients followed up for 15 years after the last exposure had a higher SMR of 1.5–2 for lung cancer (RoC, 1999).

However, public comments received for the *10th Report on Carcinogens* (RoC, 1999) by the National Toxicology Program, suggest that certain aspects of the epidemiological data might need further evaluation. Brush Wellman INC. highlighted a number of factors that should be re-considered for the classification of beryllium and beryllium compounds as a carcinogen. One of the main reasons is that the majority of risk for lung cancer is not attributed to the study of seven plants, but in fact a single beryllium extraction and processing plant: the Lorain plant. Also, it is reported that workers at this plant could have been occupationally exposed to mists of sulfuric acid which, on its own, is a significant bias for lung cancer and not considered in the report. A further point raised by Brush Wellman INC. is that the smoking status of workers was not adjusted or inadequately adjusted for in the epidemiological studies evaluated by the RoC (NTP, 2000). However, the results of these studies have been re-assessed, taking into consideration smoking status, exposure duration (maximum annual and cumulative beryllium exposure) and other confounding factors with the conclusion that occupational exposure to beryllium compounds is associated with an elevated risk of lung cancer (Schubauer-Berigan et al., 2008; Couch et al., 2011; Schubauer-Berigan et al., 2011a; Schubauer-Berigan et al., 2011b).

Also, in 2008, the US EPA revised the carcinogenicity section of its toxicological report on beryllium and compounds and released it for peer review. Comments from the peer reviewers consistently agreed that even though smoking could have been a confounder in the epidemiological studies, consistent epidemiologic literature and animal data across a host of species indicate that beryllium and beryllium compounds fall into the classification of 'carcinogenic to humans' (US EPA, 2008). The revisions to the toxicological report on beryllium and compounds by the US EPA are currently archived in draft stage; to be followed up (currently defined as 'To be determined') by the Integrated Risk Information System (IRIS) (US EPA, 2014).

Laboratory animal data

There is clear evidence in animal studies that inhaling beryllium (metal, ore and sulfate) produced lung cancers in rats and monkeys. Inhaling beryllium oxide also induced lung cancers in rats. Male and female rats (Wistar and Sherman strains) were exposed through aerosol exposure to beryllium sulfate tetrahydrate at a beryllium concentration of 35.8 $\mu g/m^3$ for eight hours/day, 5.5 days/week for up to 180 days. Animals exposed to the chemical developed pulmonary tumours (adenomas, squamous carcinomas, acinous adenocarcinomas, papillary adenocarcinomas, alveolar cell adenocarcinomas and metastases), while neoplastic changes were not reported in the control animals (RoC, 1999).

In a similar study conducted with beryllium sulfate tetrahydrate, SD rats (75 animals/sex) were exposed to the chemical (34.25 ± 23.66 $\mu g/m^3$) for seven hours/day, five days/week for 72 weeks. All surviving rats (43/sex) in the treatment group were reported to have alveolar adenocarcinomas at the end of the study. No tumours were reported in the control rats. Similarly, female rats (strain unspecified) exposed to 0, 0.8, 4, 30 or 400 $\mu g/m^3$ of beryllium chloride for one hour/day, five days/week for four months, were reported to have developed epithelial cell lung tumours in a dose-dependent manner. Lung tumours were not observed in control animals (RoC, 1999).

In a study conducted in rhesus monkeys (*Macaca mulatta*), exposure to beryllium sulfate aerosol with a beryllium concentration of 35 μg/m^3 (length of exposure unspecified) resulted in primary anaplastic pulmonary tumours with adenomatous and epidermoid patterns in three animals, six months to eight years after the exposure began. No further details are available (RoC, 1999).

Reproductive and Developmental Toxicity

Limited data are available for the chemicals in this group, although, based on the available information, the chemicals in this group are not considered to have specific reproductive or developmental toxicity.

In a combined repeated dose and reproductive/developmental toxicity study (see **Repeat dose toxicity: oral**), beagle dogs (five/sex) were used to assess the reproductive and/or developmental effects of oral exposure to beryllium sulfate in the diet. It was concluded that oral exposure to beryllium sulfate did not adversely affect reproductive or developmental outcomes such as the number of pregnancies, number of pups, number of live pups, pup weight, skeletal abnormalities or post-natal survival (WHO, 2001).

Developmental effects (increased foetal mortality, decreased foetal body weight, internal abnormalities and delayed neurodevelopment) have been reported after using methods of beryllium administration (intracheal or intraperitoneal injection), but are not considered physiologically relevant for human risk assessment. In a study conducted in rats (strain unspecified), 0.021 mg/kg bw beryllium as beryllium nitrate was administered via intravenous injections on one of post-mating days 1, 11, 12, 13, 15 or 17. All pups were reported to die within 2–3 days of birth. Also, in mothers injected on post-mating day 11, all pups died in utero. The authors note that these effects could have been due to repeated surgeries on the mothers (US EPA, 1998).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are those following inhalation exposure. Both short- and long-term effects occur, with debilitating chronic berylliosis and long-term carcinogenicity being the main effects seen in epidemiological studies. The chemicals can also cause systemic acute effects (acute toxicity by the oral and inhalation exposure) and local effects (skin sensitisation and respiratory sensitisation). The chemical can also cause harmful effects following a single exposure through skin, eye and respiratory irritation.

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, dermal, ocular and inhalation exposure of workers to the chemicals may occur, given the low levels at which effects, particularly by inhalation, have been observed. These can include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations might 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 systemic long-term, acute and local health effects, the 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 HSIS (refer to the **Recommendation** section).

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Very toxic by inhalation (T+; R26)*	Toxic if swallowed - Cat. 3 (H301) Fatal if inhaled - Cat. 1 (H330)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
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)

[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 industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular 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 chemical is used. Examples of control measures which may 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;
- 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 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 assist with meeting 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 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 the chemicals has not been undertaken as part of this assessment.

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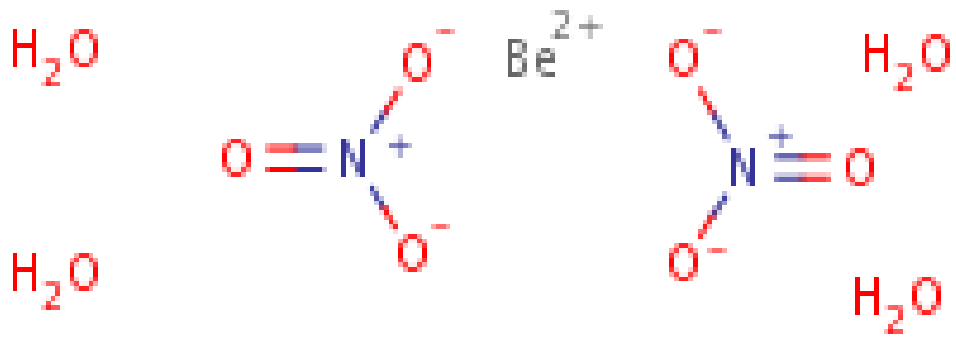
Last Update 04 July 2014

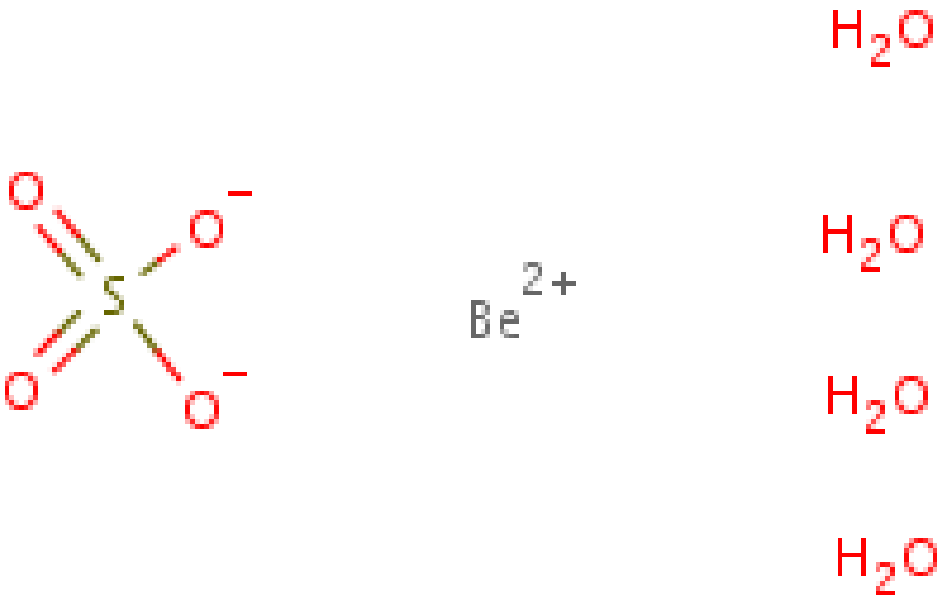
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Nitric acid, beryllium salt, tetrahydrate** Beryllium nitrate, tetrahydrate Beryllium dinitrate tetrahydrate
CAS Number	13510-48-0
Structural Formula	
Molecular Formula	Be.4H2O.2HNO3
Molecular Weight	250.1

Chemical Name in the Inventory and Synonyms	**Beryllium chloride (BeCl2)** Beryllium dichloride
CAS Number	7787-47-5
Structural Formula	

	
Molecular Formula	BeCl2
Molecular Weight	79.9

Chemical Name in the Inventory and Synonyms	**Sulfuric acid, beryllium salt(1:1), tetrahydrate** Beryllium sulfate, tetrahydrate
CAS Number	7787-56-6
Structural Formula	

	
Molecular Formula	Be.H2O4S.4H2O
Molecular Weight	177.1

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