Beryllium metal and Beryllium oxide: Human health tier II assessment

18 September 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Beryllium oxide (BeO)	1304-56-9
Beryllium	7440-41-7

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 beryllium metal (Be) and beryllium oxide (BeO). Beryllium metal has a non-porous protective layer of the oxide (up to 100 Å in thickness) giving the metal its industrial properties (resistance to oxidation). These compounds have been included in this group as, for both substances, the surface of each particle is insoluble beryllium oxide, leading to similar toxicological properties and highly restricted use. In addition, information outlined in the Organisation for Economic Co-operation and Development's (OECD) *Guidance on grouping of chemicals* (OECD, 2014) provided guidance on grouping 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 metal, soluble beryllium compounds and beryllium oxide. This assessment is specifically for beryllium oxide and beryllium metal only.

Import, Manufacture and Use

Australian

The chemicals in this group were reported under previous mandatory and/or voluntary calls for information to have site limited use in military non-sparking abrasive applications.

The National Pollutant Inventory (NPI) has identified beryllium metal as having site limited use including:

- in structural material in space technology;
- as an additive of rocket fuels;
- as a moderator and reflector in nuclear reactors;

- in manufacturing aircraft disc brakes;
- in manufacturing X-ray transmission windows;
- in manufacturing missile parts;
- in manufacturing fuel containers;
- in navigational systems;
- in manufacturing heat shields; and
- in manufacturing alloys.

The NPI has also identified beryllium oxide as having site limited use including manufacturing:

- specialty electrical and high-technology ceramics;
- special glass;
- electronic heat sinks;
- electron tubes;
- electrical insulators;
- electronic components;
- nuclear moderators and fuels;
- military vehicle armour;
- rocket nozzles; and
- laser components.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was less than one tonne.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database and the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Beryllium oxide has reported site-limited use including:

- in manufacturing electron tubes;
- in resistor cores;
- in manufacturing windows in klystron tubes;
- on transistor mountings;
- in high temperature reactor systems;
- in nuclear reactor fuels and moderators;

- as an additive to glass, ceramics and plastics; and
- in preparing beryllium compounds.

Beryllium metal has reported site-limited use including in:

- alloying (beryllium–copper);
- gyroscopes;
- in inertial guidance systems; and
- as a structural material in space technology

Restrictions

Australian

Beryllium metal is listed in the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP, 2013) in Schedule 6. There are no specific restrictions on its use in Schedule 6.

Schedule 6 chemicals are labelled with 'Poison'. These are 'substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label'.

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):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist"); and
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II (Part 1)—List of substances which must not form part of the composition of cosmetic products.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') 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 (Repeated dose toxicity);
- T; R49 (Carcinogenicity Cat. 2);

- Xi; R36/R37/R38 (Irritation); and
- Xi; R43 (Sensitisation).

Exposure Standards

Australian

The chemicals in this group (listed under 'Beryllium and compounds') 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 standard (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

The existing classifications for beryllium metal and beryllium oxide in HSIS have been sourced from those listed in the European Union's Annex 1 of the EEC Council Directive 67/548/EEC (as updated by EEC Council Directive 2001/59/EC) (Safe Work Australia). Although the classification of 'beryllium and its compounds' has been separated into three different groups, it is noted that all three groups have the same risk phrases for human health. Further studies on chemicals in this group have indicated that existing classification of some toxicological end points require further consideration (Strupp, 2010; REACHa; REACHb), as indicated in this report.

Toxicokinetics

The major route of beryllium exposure is through inhalation.

Inhalation

Following accidental exposure to beryllium dust for 10–20 hours, 25 individuals had increased serum levels of beryllium (3.5 ppb compared with 1 ppb in non-exposed individuals) one day following exposure. As serum levels were reported to return to normal 2–8 weeks after exposure, the half-life was estimated to be in the range of 2–8 weeks (ATSDR, 2002).

In an experimental study, rats exposed to beryllium oxide did not have detectable systemic beryllium concentrations until 63 days after exposure when 1.7 % of the initial alveolar deposit was present in the pulmonary lymph nodes in rats. Beryllium oxide clearance was reported as bi-phasic. The first phase accounted for 30 % of the total lung burden of beryllium oxide with a half-life of 2.5 days. The second phase accounted for the remaining 70 % of beryllium oxide with a half-life of 833 days. Based on this, the biological half-life of beryllium oxide in the rat lung was estimated to be six months. The majority (95 %) of beryllium oxide was excreted through the faeces (ATSDR, 2002).

In another study, male beagle dogs were exposed to a single dose of beryllium oxide (28 μg/L) via inhalation for 5–42 minutes. The beryllium oxide administered was calcined (heated) at either 500 or 1000 °C and lung burdens were 17 and 50 μg/kg bw, respectively. The chemical was slowly cleared from the lung, with 24 and 18 % of the initial lung burden in the 500 or 1000 °C calcined groups, respectively, being excreted by 32 days after exposure. At 180 days, 42 and 19 % of the initial lung burden in the 500 or 1000 °C calcined groups, respectively, had been excreted. The highest levels of beryllium were detected in the

skeleton, tracheobronchial lymph nodes, liver and blood. As in rats, elimination was bi-phasic and the majority of excretion was through faeces (ATSDR, 2002).

Oral

Limited data are available for the chemicals in this group. A study reports that beryllium was detected in the liver, large intestine, small intestine, kidneys, lungs, stomach, and spleen of hamsters following dietary exposure to beryllium oxide for 3–12 months. In animal studies, the majority (up to 98 %) of orally administered beryllium or beryllium compounds is excreted through faeces (ATSDR, 2002).

Dermal

Beryllium compounds are poorly absorbed after dermal exposure. Occupational exposure to beryllium compounds is associated with skin ulceration, but this only occurred in workers with abraded or accidentally cut skin. 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

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') are classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). Although limited data are available, the available data (median lethal dose—LD50 of >2000 mg/kg bw) for beryllium and beryllium oxide support an amendment (removal) of the existing classification (REACHa; REACHb).

The chemicals in this group were assessed for acute oral toxicity by tests conducted according to OECD Test Guideline (TG) 423. For beryllium metal, female Wistar rats were administered (gavage) a single oral dose of beryllium metal (2000 mg/kg bw) in polyethylene glycol (PEG) vehicle and observed for 15 days. No mortalities were reported and the only adverse effect reported was grey stained faeces one day after oral gavage (REACHa). For beryllium oxide, female Wistar (SPF) rats were administered (gavage) a single oral dose of beryllium oxide (300 or 2000 mg/kg bw) in PEG vehicle and observed for 15 days. Adverse effects were only reported in the 2000 mg/kg bw group and included slight sedation and ruffled fur, which was reported as reversible within the observation period. No mortalities were reported (REACHb).

Dermal

No data are available.

Inhalation

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') are classified as hazardous with the risk phrase ‘Very toxic by inhalation’ (T+; R26) in HSIS (Safe Work Australia). The available data support this classification.

The lung is the primary target following inhalation exposure to chemicals in this group. Although guideline studies are not available for these chemicals, data from non-guideline studies and observations in humans indicate that inhalation exposure to the chemicals in this group results in serious adverse respiratory effects and mortality (ATSDR, 2002; REACHa; REACHb).

Exposure to 31 mg/m^3 beryllium oxide resulted in mortality in 2/20 rats (strain unspecified) and a 50 minute exposure to 0.8 mg/m^3 of beryllium metal resulted in mortality in 20/74 rats (male Fischer 344/N) 12–15 days after exposure (ATSDR, 2002). Gross pathology of the deceased rats (20) showed diffusely dark red lungs, with tracheas and major bronchi full of bloody, frothy, and red-tinged fluid (ATSDR, 2002).

Observation in humans

Studies of occupational exposure to beryllium or its compounds are the major source of information regarding adverse effects in humans from inhalation exposure. Acute occupational inhalation exposure to high concentrations of beryllium oxide 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). It is a pulmonary disease of less than a year's duration and is mostly due to direct toxic effect rather than any immune-associated mechanism. 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

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') are classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). Although specific animal data are not available to evaluate this classification, the available epidemiological data from observations in humans support this classification (see **Repeat dose toxicity: observation in humans**).

Skin Irritation

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') are classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). As beryllium metal and beryllium oxide have not been reported to be irritating to the skin, the available data support an amendment (removal) of the existing classification.

In a skin irritation study conducted according to the OECD TG 404, 0.5 g of beryllium metal was applied (semi-occlusive) to three New Zealand White rabbits for four hours. The chemical was not found to be irritating to the skin up to 72 hours following exposure (REACHa). In an in vitro skin irritation study conducted, similar to the OECD TG 439, 15 mg of beryllium oxide was applied to artificial human skin (EpiSkin kit) for 15 minutes. The chemical was concluded not to be a skin irritant, based on a cell viability assay (REACHb).

Eye Irritation

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') are classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). As beryllium metal and beryllium oxide have not been reported to be irritating to the eyes, the available data support an amendment (removal) of the existing classification.

In an eye irritation study conducted according to the OECD TG 405, instillation of 0.1 g of beryllium metal to one eye of three New Zealand White rabbits was not irritating to the eyes. Slight to moderate reddening of the conjunctivae was reported in all animals and this resolved by day seven of observation. Average Draize scores reported for the cornea, iris, conjunctivae and chemosis were 0, 0, 1, and 0 respectively (REACHa).

In an in vitro eye irritation study conducted according to OECD TG 437, 0.75 mL of a 20 % suspension of beryllium oxide was applied to freshly isolated bovine eyes for four hours. The chemical was reported to be mildly irritating, based on the proposed INVITOX (UK) protocol No. 98 irritation scale. The chemical was evaluated as a mild eye irritant, based on the average irritation score of 6.69 which lies in the mild eye irritant category (3.1–25) (REACHb).

Sensitisation

Respiratory Sensitisation

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

Skin Sensitisation

The chemicals in this group are classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in HSIS (Safe Work Australia). The available data in animals do not support this classification, but human data are consistent with skin sensitisation.

In a skin sensitisation study (maximisation test) carried our according to OECD TG 406, Dunkin Hartley guinea pigs were administered an intradermal injection of beryllium metal powder on day one (15 % in polyethylene glycol) and induced on day eight by a 48-hour occlusive application of 50 % of the chemical in polyethylene glycol. The challenge phase was conducted on day 22 by a single application of the chemical (10 % in polyethylene glycol) and reactions were evaluated at 24 and 48 hours. None (0/10) of the guinea pigs showed a positive reaction at 24 or 48 hours following challenge and the chemical was reported not to be sensitising (REACHa).

Observation in humans

Respiratory sensitisation

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-necrosing granulomas 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).

Skin sensitisation

Limited information is available on chemicals in this group. The main dermal adverse effects, reported in a case history of 42 workers exposed to airborne beryllium compounds, was oedematous papulovesicular dermatitis, which was considered most likely to be an inflammatory response to beryllium compounds. 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 (ATSDR, 2002).

A patch test study of beryllium oxide was conducted on 13 volunteers occupationally exposed to beryllium compounds (beryllium fluoride mainly) in the workplace and diagnosed with dermatitis. Also a control group of 16 subjects never exposed to beryllium compounds was included. The volunteers were exposed to a moistened patch of beryllium oxide on the skin for 48 hours and evaluated at 48 or 72 hours following exposure. No subjects or controls showed positive responses to beryllium oxide. Further testing with other soluble compounds showed positive responses of varying severity (REACHb).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') 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). Although limited data are available from animal studies, extensive data from human epidemiological studies support this classification (see **Repeat dose toxicity: observation in humans**).

The lung is the primary target following inhalation exposure to chemicals in this group. In a 40-day study conducted in rats and dogs, animals exposed to low-fired (400 °C) beryllium oxide (3.6 mg/m^3) showed pneumonitis, granulomatous lesions, fibrosis and hyperplasia in the lungs. It is also reported that high-fired (1150 or 1350 °C) beryllium oxide did not produce pulmonary damage following inhalation exposure at 32 mg/m^3 for 360 hours (15 days), possibly due to a larger particle size and greater degree of aggregation in the high-fired material (WHO, 2001). However, respiratory effects were not observed in rabbits, cats or monkeys exposed to beryllium oxide (30 mg/m^3) for 15 days. (ATSDR, 2002).

Cardiovascular and haematological effects have been reported in rabbits, dogs and rats exposed through inhaling beryllium oxide. Rabbits exposed to beryllium oxide (307 mg/m^3) for 60 days were reported to develop macrocytic anaemia. Erythrocyte counts were reported to decrease over time and there was a tendency to develop hypochromia (discoloured red blood cells). In dogs, exposure to 30 mg/m^3 beryllium oxide for 15 days resulted in progressive leucocytosis and, at a lower dose (3.6 mg/m^3), dogs developed macrocytic anaemia (ATSDR, 2002).

Observation in humans

The respiratory tract is the primary target for beryllium toxicity following inhalation exposure. Non-neoplastic respiratory toxicity of beryllium compounds is divided into two categories: ABD and chronic beryllium disease (CBD). ABD has been discussed in the **Acute toxicity—observation in humans** section. CBD (also referred as berylliosis or chronic berylliosis) results from chronic inhalation exposure to beryllium and involves a beryllium-specific immune response. It is defined as an inflammatory lung disease characterised by the formation of granulomas (pathologic clusters of immune cells) with varying degrees of interstitial fibrosis. 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; WHO, 2001; ATSDR, 2002).

The majority of epidemiological data does not always specify whether exposure to 'beryllium' was specifically to beryllium oxide and/or beryllium metal. Exposure to beryllium metal is largely though machining of beryllium, in alloying (production and fabrication) or the production of beryllium oxide. Exposure to beryllium oxide is largely through beryl ore processing, ceramic manufacture and alloy fabrication (Kreiss et al., 1997; IARC, 2012). Therefore, epidemiological evidence pertaining to the above activities is summarised below.

In a cross-sectional study, 136 workers in a beryllium ceramic plant were largely exposed to beryllium oxide powder. The median breathing zone measurement of beryllium ranged from 0.3 - 0.6 μg/m^3, with a maximal exposure concentration of 5 μg/m^3. BeLT tests conducted on the 136 employees yielded 5 positive results for CBD which were confirmed through duplicate testing and presence of granulomas in lung biopsy samples. A human equivalent lowest observed adverse effect level (LOAEL) adjusted based on occupational exposure was reported as 0.20 μg/m^3. Five similar cases were reported in a study of workers exposed to beryllium oxide fumes in a refinery plant. Four of the five cases of CBD were in workers exposed to 0.52 ± 0.44 μg/m^3 (maximum 1.7 μg/m^3) for 4-8 years. The fifth case of CBD was identified in a worker who was employed as a crusher and exposed to beryllium dust at a concentration of 2.7 ± 7.2 μg/m^3. All five cases showed classic signs of CBD including lung adenopathy (visible in X-rays), non-necrosing granuloma and pulmonary fibrosis (in biopsy samples). Although the authors noted concomitant exposure to arsenic, lead and nickel, exposure to these metals were all within acceptable exposure limits (US EPA, 1998). In a further study, the prevalence of CBD was reported as 4.6 % at a beryllium metal, alloy, and oxide production plant. The median beryllium exposure was reported as 1.0 μg/m^3 for the entire workforce and slightly elevated to 1.3 μg/m^3 for the identified cases of CBD identified (WHO, 2001).

Genotoxicity

The chemicals in this group tested negative in several in vitro (mammalian cell gene mutation assay, Ames test, DNA damage and repair test and mammalian cell transformation test) tests for gene mutation and clastogenicity. A two-fold increase in the transformation assay and a positive result in the DNA damage assay was noted with low-fired beryllium oxide at a 1 mg/mL concentration. There are no in vivo data available for chemicals in this group. Based on the weight of evidence, the chemicals in this group are not considered to have mutagenic or genotoxic potential.

In a study conducted according to OECD TG 471, beryllium metal powder (2.5, 10, 20, 40, 60, 80 or 100 % extract in 0.9 % saline solution) did not increase the number of mutations in an Ames test following incubation with *Salmonella typhimurium* strains (TA 1535, TA 1537, TA 98 and TA 100), with and without metabolic activation. In a further study conducted according to OECD TG 476, beryllium metal powder (3.1, 4.5 to 14.0 mg/L) did not induce mutations in the hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene following incubation with Chinese hamster lung fibroblasts (V79), with and without metabolic activation. Further tests carried out with beryllium metal powder in Syrian hamster embryonic cells, hepatocytes isolated from Wistar rats, and with human lymphocytes, were also negative for mutagenicity (REACHa).

In a study conducted according to OECD TG 471, a suspension of beryllium (in 0.9 % saline) at 10–100 % concentrations did not increase mutation frequencies in any of the *S. typhimurium* strains (TA 1535, TA 1537, TA 98 and TA 100), with and without metabolic activation. In a further study, the effect of three types of beryllium oxide dust (rocket exhaust dust, low-fired beryllium oxide and high fired beryllium oxide) were assessed in genotoxicity assays (transformation and damage) conducted in cultured respiratory epithelial cells. For both assays, the cultured cells were incubated with beryllium oxide at 0.3, 1, 3 10 or 30 mg/mL. Cells exposed to low-fired beryllium oxide at a concentration of 1 mg/mL showed a two-fold increase in the transformation assay and a positive result in the DNA damage assay (REACHb).

Carcinogenicity

The chemicals in this group (listed as 'Beryllium' and 'Beryllium oxide') are classified as hazardous—Category 2 carcinogenic substances—with the risk phrase ‘May cause cancer by inhalation’ (T; R49) in HSIS (Safe Work Australia). Sufficient information was available on the chemicals in this group in animal studies, and on beryllium and beryllium compounds in several epidemiological reports, to support this classification (WHO, 2001; ATSDR, 2002).

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)'. It was also concluded that the processes underlying beryllium-induced carcinogenesis are clearly complex, with several possible interactive mechanisms (IARC, 2012).

The majority of epidemiological data does not always specify whether exposure to 'beryllium' was specifically to beryllium oxide and/or beryllium metal. Exposure to beryllium metal is largely though machining beryllium, in alloying (production and fabrication) or producing beryllium oxide. Exposure to beryllium oxide is largely through beryl ore processing, ceramic manufacture and alloy fabrication (Kreiss et al., 1997; IARC, 2012). Therefore epidemiological evidence pertaining to the above activities is summarised below.

In a follow-up study of males employed in beryllium extraction, production and fabrication plants between 1942 and 1948, the standardised mortality ratio (SMR) for lung cancer was reported to be 1.8 and 1.2 in two different plants across a cohort of 1222 and 2044 men. In a further cohort study across seven beryllium plants (including the two previously mentioned), 9225 male workers were followed. The SMR for lung cancer in this cohort was 1.26. Lung cancer mortality was reported to increase with latency (time since exposure) but not with duration of employment (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 mostly due to 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 risk factor 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 was 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).

The US EPA also 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 soluble compounds) produced lung cancers in rats and monkeys. Inhaling beryllium oxide also induced lung cancers in rats. Studies with beryl ore have a degree of bias as beryl ore often contains high concentrations of crystalline silica (4.14 % beryllium, 63.6 % crystalline silica, 18.1 % aluminium oxide and lower concentrations of other metals) (RoC, 1999), which is a carcinogen on its own account (NICNASb). Rats (Charles River, Flora) exposed to beryl ore (15 mg/m^3) for six hours/day, five days/week for up to 17 months developed epidermoid tumours after 12 months (5/11), and lung tumours after 17 months (18 bronchiolar alveolar-cell tumours, seven adenomas, nine carcinomas and four epidermoid tumours) (RoC, 1999).

Further studies showed the development of lung tumours (at 14 months) following a single inhalation exposure to beryllium metal, with a lung burden of 40, 110, 360 or 430 mg. It is reported that 64 % of the population of rats developed lung tumours at some stage during the life-time study (RoC, 1999). In a further single-exposure study, female F344/N rats were exposed to a single inhalation exposure to beryllium metal leading to a lung beryllium burden of 50, 150 or 450 mg. Animals were euthanised between 8–450 days after exposure. It was concluded that a single exposure to beryllium metal led to the development of bronchiolar/alveolar adenocarcinomas and squamous cell carcinomas. Similar development of lung carcinoma have also been reported in other single exposure studies to metallic beryllium (RoC, 1999).

In another short-term study, female rats (strain unspecified) were exposed to beryllium oxide (0.8, 4, 30 or 400 mg/m^3) for one hour/day for five days/week for four months. A dose-dependent increase in malignant epithelial lung tumours was noted. No further details are available (RoC, 1999).

Other studies, using methods of chemical delivery not considered relevant to risk assessment (intratracheal instillation and intravenous or intraperitoneal injection), have also shown site-specific carcinomas. Rabbits developed osteomas, chrondosarcomas and chondromas following multiple injections (1–43) of 10 mg of beryllium oxide (1 % suspension) into the femur marrow (RoC, 1999).

Reproductive and Developmental Toxicity

Although limited data are available for the chemicals in this group, based on the available information, these chemicals are not considered to have specific reproductive or developmental toxicity, with any effects likely to be secondary to maternal toxicity.

Developmental and reproductive studies have been conducted using methods of beryllium administration (intratracheal or intraperitoneal injection) that are not considered physiologically relevant for human risk assessment. In a reproductive study, male and female rats were instilled with 0.6 mg/kg bw of radioactive beryllium oxide intratracheally and allowed to mate over a 15-month period. No effects on reproductive performance (pregnancies per female, lactation index or average weight of pups) were noted during the study. In a developmental study conducted in rats (strain unspecified), beryllium oxide (50 mg/kg bw) administered intratracheally on gestation days 3, 5, 8 or 20 resulted in an increase in foetal mortality, decreased foetal body weight and an increase in internal abnormalities (ATSDR, 2002).

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 inhalation exposure) and local effects (skin and respiratory sensitisation). The chemical can also cause harmful effects including carcinogenicity following a single exposure by inhalation.

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

Epidemiological studies have shown that exposure to these chemicals may occur during industrial use. 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 amendments to the hazard classification in HSIS (refer to the **Recommendation** section), with respect to respiratory sensitisation, acute oral toxicity, skin irritation, and eye irritation.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classifications are 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	Very toxic by inhalation (T+; R26)*	Fatal if inhaled - Cat. 1 (H330)
Irritation / Corrosivity	Irritating to respiratory system (Xi; R37)*	May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
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 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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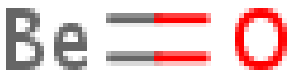
Last Update 18 September 2014

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Beryllium oxide (BeO)** beryllia beryllium monoxide thermalox 995 bromellete

CAS Number	1304-56-9
Structural Formula	
Molecular Formula	BeO
Molecular Weight	25

Chemical Name in the Inventory and Synonyms	**Beryllium** glucinium
CAS Number	7440-41-7
Structural Formula	

	
Molecular Formula	Be
Molecular Weight	9

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