Cobalt(II) hydroxide: Human health tier II assessment

27 November 2014

CAS Number: 21041-93-0

Preface

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

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

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

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

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

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

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

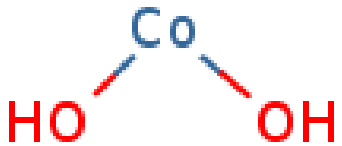
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	cobalt dihydroxide Cobaltous hydroxide
Structural Formula	
Molecular Formula	CoH2O2
Molecular Weight (g/mol)	92.95
Appearance and Odour (where available)	A blue-green to rose-red powder.
SMILES	O{-}.[Co]{2+}.O{-}

Import, Manufacture and Use

Australian

Safety data sheets have identified the following use:

- in nickel-cadmium batteries (rechargeable batteries) as an electrochemical ingredient.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; Galleria Chemica and Substances and Preparations in the Nordic countries (SPIN) database.

The chemical has reported commercial use including:

- as a coating additive, drier or colouring agent in paint, lacquers and varnishes;
- in metal surface treatments including galvanic and electroplating products; and
- as a filler in rubber adhesives, binding agents or construction materials.

The chemical has reported site-limited use including:

- as a chemical intermediate.
- as an intermediate for computer, electronic and optical products and electrical equipment; and
- as an intermediate for manufacture of electrical batteries and accumulators.

The following non-industrial uses have been identified internationally:

- in formulation of fertiliser.

Restrictions

Australian

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.

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):

The chemical has exposure limits (time weighted average–TWA) of 0.01–0.1 mg/m^3 in different countries such as Denmark, US (Washington), Ireland and Greece.

Health Hazard Information

Limited data are available for specific toxicological endpoints (repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity). Unpublished bioaccessibility data suggest that cobalt dihydroxide releases Co^{2+} cation at the same levels as soluble cobalt compounds and cobalt oxide in artificial gastric and lysosomal fluids (CDI, 2014). In the absence of animal studies, considering the high level of Co^{2+} ion release expected through the oral route, cobalt dihydroxide (CAS No. 21041-93-0), following oral exposure, will have a similar hazard profile to other soluble cobalt compounds, which have previously been assessed under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework (NICNASa, NICNASb).

Toxicokinetics

The bioavailability of the chemical varies in simulated human body fluids. The chemical freely dissociates into the divalent cobalt species in artificial gastric fluid (pH 1.5) and artificial lysosomal fluid (pH 4.5–5.0), although low dissociation occurs in artificial alveolar (pH 7.4), interstitial (pH 7.4), intestinal (pH 7.4) fluids, and sweat (pH 5.5-6.5) (CDI, 2014). Based on this information, the chemical is likely to have a toxicokinetic profile similar to soluble cobalt compounds (NICNASa) and cobalt oxide (NICNASb) for oral and inhalation exposure, respectively.

Oral administration of the chemical leads to nearly complete dissociation into the Co^{2+} ion. The amount of cobalt absorption in humans varies from 3-97 % depending on the administered type and dose of the cobalt compounds (Leggett, 2008). A study by Firrolo et al. (1999) demonstrated that, upon oral administration, absorption, disposition and elimination of various cobalt salts were the same, and that the original identity of the salts do not affect cobalt ion absorption in vivo once the compounds have dissociated (Firrolo et. al., 1999).

Dermal absorption of cobalt has been demonstrated to be relatively low (NICNASa). In an in vitro study, percutaneous absorption of soluble cobalt through human skin was 1.08 % from 100 mg/mL cobalt chloride hexahydrate (CAS No. 7791-13-1) (NICNASa; REACH). Absorption through intact skin of guinea pigs was very low (<1 %) while absorption through abraded skin was almost 80 % after a three-hour exposure (ATSDR, 2004).

Absorption following inhalation exposure to cobalt depends on the particle size and solubility. Particles larger than 2 µm are deposited in the upper respiratory tract, whereas smaller particles are deposited into the lower respiratory tract. Larger particles that are more soluble can be absorbed into the blood after dissolution or similar to cobalt hydroxide, can be moved into the gastrointestinal tract by mucociliary action and have similar absorption to orally administered particles. Smaller particles are phagocytosed by macrophages that contain abundant lysosomes (pH 4.5–5.0)(ATSDR, 2004). Considering low dissociation

occurs in artificial alveolar (pH 7.4), interstitial (pH 7.4), intestinal (pH 7.4) fluids, and sweat (pH 5.5-6.5), the chemical is likely to have a toxicokinetic profile similar to cobalt oxide (NICNASb) for inhalation exposure (CDI, 2014).

Once absorbed, the cobalt ion is widely distributed in the body, including the skeleton, with the highest concentration found in the liver and kidneys. After inhalation exposure, although there is a high initial excretion in faeces, the primary route of elimination is via urine (IPCS, 2006). Urinary excretion of cobalt from workers under experimental conditions was multiphasic: an initial rapid elimination ($T_{1/2}$ = 44 hours), a second slower elimination ($T_{1/2}$ = 10 days) and a third long-term retention ($T_{1/2}$ in the order of years) (Leggett, 2008). The estimated long-term half life of cobalt after oral intake by a female volunteer was 625 days (Leggett, 2008). 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 (IPCS, 2006). Although the liver and kidneys had the highest initial cobalt concentrations after exposure, concentrations were considered low at 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.

Acute Toxicity

Oral

The chemical had moderate acute toxicity in an animal test following oral exposure. The median lethal doses (LD50) in rats was 1060 mg/kg bw. Observed sub-lethal effects included diarrhoea, ruffled fur and debilitation (REACH). The data available warrant hazard classification.

In a study carried out similarly to OECD Test Guideline (TG) 401, cobalt hydroxide (250, 500, 1000, 2000, 4000 and 8000 mg/kg bw) was administered via a single oral gavage to five female and five male Wistar rats which were then observed for 14 days. Mortality was reported to be zero at 250 and 500 mg/kg bw, three out of five at 1000 mg/kg bw, four out of five at 2000 mg/kg bw and 100% at 4000 mg/kg bw and above. Based on these data, the LD50 was reported to be 1060 mg/kg bw in male and female rats (REACH).

Dermal

No data are available.

Given that the toxicokinetics data show low dermal absorption (ATSDR, 2004; Leggett, 2008; CDI, 2014), acute toxicity via the dermal route is not expected.

Inhalation

No data are available on chemicals in this group. Considering that the chemicals in this group have similar bioaccessibility to cobalt oxide in artificial alveolar fluid, the chemicals in this group should be classified for acute inhalation toxicity, similarly to cobalt oxide (NICNASb) (refer to **Regulatory Control–Occupational Health and Safety**).

In a study conducted according to OECD TG 436, male and female Crj: CD(SD) rats were exposed to single exposures at inhalation concentrations of 0.11 and 0.53 mg/L of cobalt oxide (CAS NO. 1307-96-6) (mass median aerodynamic diameter (MMAD) ranging from 3.3–3.7 μm) in the main study group for four hours, and then observed for 14 days. A satellite group was exposed at 0.05, 0.11, 0.53, 1.07 or 5.06 mg/L cobalt oxide, for four hours and observed for 24 hours. In the main study group, all animals exposed to concentrations of 0.11 and 0.53 mg/L died prematurely on days four and three of the observation period, respectively. In the satellite group, observation only occurred for 24 hours and during this time mortality was reported at all concentrations above 0.05 mg/L (0.11 mg/L—2/3 males and 0 females, 0.53mg/L—3/3 males and 1/3 females, 1.07 mg/L—2/3 males and 3/3 females, 5.06 mg/L—3/3 males and 1/3 females). Sub-lethal effects reported in the main study included ataxia, tremor and dyspnoea in all exposure groups. In the satellite group, sub-lethal effects of ataxia, tremor, reduced muscle tone and dyspnoea were reported in animals exposed to the two highest concentrations (1.07 and 5.06 mg/L). Based on this study the LC50 was calculated to be 0.06 mg/L (NICNASb).

Corrosion / Irritation

Skin Irritation

The chemical showed no irritation potential in a study performed in accordance with OECD TG 439; the data available suggest the chemical is not a skin irritant.

In a study carried out according to OECD TG 439, 10 mg of the chemical was applied for 15 minutes, wetted with 15 μL of deionised water, to a cell culture of human-derived epidermal keratinocytes, cultured to form a multilayered, highly differentiated model of the human epidermis. The sample was tested in triplicate and after exposure, a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed. The score obtained after the 15-minute treatment was 110.1 % for cell viability (maximum score of 113.4 %). As this value was above the 50 % viability threshold, the substance was considered to not have irritant potential (REACH).

Eye Irritation

The chemical was reported to irritate the eyes when tested according to OECD TG 405; the available data suggest the chemical warrants hazard classification. The severity of the effect only met the classification criteria under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and not the Approved Criteria (HSIS).

In a study similar to OECD TG 405, 0.1 g of the chemical as a powder, was applied to the eyes of six New Zealand White rabbits. In three out of the six rabbits, the chemical was left in the eye for 30 seconds and then washed out; for the remaining three rabbits, the eyes were not washed. In the unrinsed eye, corneal opacity or iritis was not noted at any time during the study. Moderate to severe conjunctivitis was noted in all three rabbits without rinsing and blistering of the lower lids was recorded in two rabbits at the 24 and 48 hour reading after exposure. Mild to moderate conjunctivitis was recorded in all rabbits at the 72 hour reading. The average scores for conjunctival redness and chemosis were given as 1.67 and 0.33 respectively for animal number one; 2.00 and 0.67 respectively for animal number two; and 2.67 and 1.00 respectively for animal number three (REACH). Lesser but non-zero conjunctival effects were seen in rinsed eyes. Considering two out of three animals showed a mean conjunctival redness score after 24, 48 and 72 hours of 2.0 and above, the classification criteria under the GHS are met, although the severity is not sufficient to warrant classification under the HSIS.

Sensitisation

Respiratory Sensitisation

The chemical is considered a respiratory sensitiser based on epidemiological studies. Refer to section **Observations in Humans**.

Skin Sensitisation

No animal data are available for the chemical. Considering that the chemical has similar bioaccessibility to cobalt oxide in artificial sweat, data on sensitisation will be read across from cobalt oxide (NICNASb; OECD 2014).

In a local lymph node assay (LLNA) conducted according to OECD TG 429, 25 μL of a suspension of cobalt oxide (CAS No. 1307-96-6) (50, 25 or 12.5 %) in acetone/olive oil was applied to the dorsal area of each ear of CBA female mice once daily for three consecutive days. Based on the LLNA study results, stimulation indexes of 1.8, 2.6 and 3.4 were reported for 12.5, 25 and 50 % suspensions of the chemical. After linear interpolation of the results, an EC3 (estimated concentration needed to produce a stimulation index of three) value of 37.5 % was reported. Based on the results of this study, cobalt oxide is classified as a skin sensitiser (NICNASb).

Observation in humans

Respiratory sensitisation

Several epidemiological studies conducted in cobalt-producing facilities support the findings that occupational inhalation exposure to inorganic cobalt compounds is associated with occupational asthma (ATSDR, 2004; WHO, 2006; CoRC, 2014) and provide the basis of classification for sensitisation via the inhalation route of exposure. Specifically, studies have shown that there was a significant correlation between decreasing lung function tests (FEV1/FVC ratio) and increasing concentrations of cobalt in the air and in the urine of occupationally exposed workers (CoRC, 2014).

Skin sensitisation

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 (REACH). In another two patch test study, 225/1415 patients and 24/373 patients showed a positive reaction to cobalt chloride when applied to the upper back using occlusive patches (REACH). There appears to be an increased incidence of positive testing in females compared with males in all tests (REACH). 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 (REACH).

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 a duration of three weeks. The allergic dermatitis reported was considered a positive allergic response to cobalt (ATSDR, 2004).

Repeated Dose Toxicity

Oral

No data are available. As unpublished data show moderate to high bioaccessibility and bioavailability in artificial gastric fluid, data from soluble cobalt compounds are read-across (NICNASa; OECD, 2014a). Data available from the NICNAS assessment of soluble cobalt compounds (NICNASa), particularly data available for cobalt sulfate heptahydrate (CAS No. 10026-24-1) and cobalt chloride hexahydrate (CAS No. 7791-13-1) show that the main effect after repeated oral exposure to soluble compounds is polycythaemia (increased erythrocytes). However, this effect is reversible after cessation of exposure (NICNASa). The severity and/or reversibility of effects seen in these studies do not meet the criteria for hazard classification.

Dermal

No data are available.

Given that the toxicokinetic data show low dermal absorption (ATSDR, 2004: Leggett, 2008; CDI, 2014), repeated dose toxicity via the dermal route is not expected.

Inhalation

No data are available. Unpublished bioaccessibility studies conducted with cobalt hydroxide indicate that while the Co^{2+} ion is released at low levels in artificial alveolar fluid, it is released at similar rates to soluble cobalt compounds (cobalt sulfate heptahydrate, CAS No. 10026-24-1) in artificial lysosomal fluid (Stopford et al., 2003). As a result, systemic toxicity may be read across from soluble cobalt compounds after the chemical is phagocytosed, while local toxicity can be read across from cobalt oxide, for repeated dose toxicity via the inhalation route. Human data from occupational studies, suggest the chemical causes serious damage to health by prolonged expsoure through inhalation. Refer to section **Observations in Humans**.

Cobalt oxide

A study conducted in Syrian Golden hamsters evaluated the effect of lifetime exposure to cobalt oxide (CAS No. 1307-96-6) at10 mg/L (seven hours a day, five days a week). Compared with controls, lifetime exposure to cobalt oxide did not affect survival, but induced pneumoconiosis (emphysema) (WHO, 2006).

Cobalt sulfate heptahydrate

The National Toxicology Program (NTP) conducted 13-week (NTP, 1991) and two-year studies (NTP, 1998) in male and female Fisher 344/N (F344/N) rats and B6C3F1 mice. In the 13-week study, rats and mice (10 animals/sex/species) were exposed to aerosols containing 0, 0.3, 1.0, 3.0, 10 or 30 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) for six hours a day, five days a week for the duration of the study. Male rats exposed to any concentration of the chemical showed a significant increase in relative kidney weights. Histopathological examination of the kidneys did not indicate any increase in kidney lesions in rats or mice in the 13-week study, although in male rats there was a concentration-related increase in epithelial cells and granular casts observed in the urine, suggesting slight renal toxicity. There was also a significant increase in the relative lung weights of rats exposed to 0.3 mg/m^3 and higher for males, and 1 mg/m^3 and higher for females. In mice, this was observed in both sexes from 10 mg/m^3 and higher. Absolute and relative testicular and epididymal weights were significantly decreased in male mice at 30 mg/m^3. Polycythaemia was observed in rats at 3 mg/m^3 and higher. 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 (NTP, 1991).

Observation in humans

A survey conducted in workers exposed to 'cobalt dusts' consisting of cobalt oxides, cobalt salts or cobalt metal (average concentration of 0.125 mg/m^3) concluded that exposure to these compounds interfered with thyroid metabolism and induced respiratory disorders. In particular, workers exposed to 'cobalt dusts' frequently complained of difficulty in breathing (dyspnoea and wheezing), compared with the control group. This was supported by a statistically significant relationship (logistic regression analysis) between the dustiness of the workplace, the level of cobalt in the urine and symptoms of dyspnoea in the workers. Also, there was a significant dose-effect relationship between a reduction in measures of lung function (FEV1/FVC ratio) to the intensity of 'cobalt dust' exposure as measured in the air and measured as cobalt in the urine of workers (Swennen et al., 1993). Further data on the risk of lung cancer and cobalt exposure are summarised in the **Carcinogenicity** section of this report.

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 (ATSDR, 2004). 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 (Lantin et al., 2013).

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 (ATSDR, 2004).

Cobalt has been previously used therapeutically to treat anaemia due to its ability to increase haemoglobin levels. In a series of studies, patients with impaired kidney function were treated with 0.65–4.0 mg/kg/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 (ATSDR, 2004). 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 (ATSDR, 2004). 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 (ATSDR, 2004).

Genotoxicity

Limited data are available on the chemical. Data on the in vitro genotoxicity for the chemical itself are of limited relevance due to its low solublility in culture medium. Under in vivo conditions, solublisation of the chemical in biological fluids, including acidic gastric juices, precedes the delivery of cobalt to the cells. Based on the high solubility of the chemical after ingestion, genotoxicity data can be read-across from the NICNAS assessment of soluble cobalt compounds (NICNASa; NICNASb). It was concluded that effective protective processes exist in vivo to prevent genotoxicity in human (OECD, 2014b) and hence, no classification is required (NICNASa; NICNASb).

In vitro

In a mammalian cell gene mutation assay carried out according to OECD TG 476, cobalt dihydroxide (CAS No. 21041-93-0) was incubated with mouse lymphoma L5178Y cells up to a range of 40 μg/mL with and without S9 metabolic activation. The chemical was not mutagenic when tested up to toxic concentrations in the absence of S9 metabolic activation, however in two out of three experiments where tested up to cytotoxic concentration with S9 mix, mutagenic activity was reported. The increases in mutation frequency were not concentration related and in one case, did not lead to a significant increasing linear trend. The results indicate that the data may be considered to have questionable biological relevance (REACH).

Carcinogenicity

No data are available. Considering that the chemicals in this group have similar bioaccessibility to cobalt oxide (NICNASc; OECD, 2014a) in artificial alveolar and lysosomal fluid, data on carcinogenicity could be read across from cobalt oxide. However, the available carcinogenicity data for cobalt oxide are inappropriate for interpreting the hazard classification due to the non-physiologically relevant exposure routes used, absence of guideline laboratory studies and confounding in epidemiological studies arising from mixed exposure to cobalt oxide with other cobalt compounds and metals (nickel, arsenic, tungsten carbide). The mechanisms of carcinogenicity for cobalt compounds found to be carcinogenic by IARC (IARC, 2006) have not been clearly identified, making read across for compounds of different solubility difficult. Further studies are required to investigate the specific mode of action prior to hazard classification (NICNASc).

Reproductive and Developmental Toxicity

No data are available. Based on data that indicate moderate bioaccessibility and bioavailability in artificial gastric fluid, data are read-across from the NICNAS assessment of soluble cobalt compounds (NICNASa; OECD, 2014a). Data available for cobalt sulfate heptahydrate (CAS No. 10026-24-1) and cobalt chloride (CAS No. 7646-79-9) indicate that there is a concern for reproductive toxicity. Cobalt sulfate heptahydrate is classified as hazardous, a Category 2 substance toxic to reproduction, with the risk phrase ‘May impair fertility’ (T; R60) in HSIS (Safe Work Australia). Based on read-across principles (OECD, 2014a), the data for cobalt chloride and cobalt sulfate heptahydrate support a recommendation to classify this chemical.

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 numbers of pregnancies and implantation sites were significantly reduced in unexposed females mated with exposed males at 47 and 93 mg/kg bw/day. At all doses, the incidence of resorption was significantly higher, whereas the number of viable foetuses decreased. Decreased relative testicular weight, decreased sperm concentration, and testicular necrosis and degeneration were observed (Elbetieha et al., 2008).

In a 13-week NTP inhalation study, rats and mice (10 animals/sex/species) were exposed to aerosols containing 0, 0.3, 1.0, 3.0, 10 or 30 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) for six hours a day, five days a week for the duration of the study. Absolute and relative testicular weights and the epididymal weight were significantly decreased, and an increased number of abnormal sperm were seen in male mice at 30 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1). Data were not collected on mice exposed to lower concentrations. Sperm motility was significantly reduced in mice exposed to $\geq$3 mg/m^3, but data were not collected on mice exposed at lower concentrations (NTP, 1991).

Developmental toxicity

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. Testing is currently underway for this endpoint.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity), systemic acute effects (acute toxicity by the inhalation route of exposure) and local effects (skin sensitisation and respiratory sensitisation). The chemical may also cause harmful effects following ingestion and repeated exposure through inhalation. There are insufficient data to enable classification for carcinogenicity, although it would be prudent to treat the chemical as a potential carcinogen.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Although the public may come into contact with articles/coated surfaces containing the chemical, it is expected that the chemical will be bound within the article/coated surface and hence will not be bioavailable. Therefore, the risk to the public is not considered to be unreasonable.

Occupational Risk Characterisation

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

Given the critical systemic long-term effects, systemic acute effects and local effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalational exposure to the chemical are implemented. The chemical 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 **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 where adverse effects were observed, there is a concern that the absence of exposure controls in the HSIS might not adequately protect workers' health.

NICNAS Recommendation

A Tier III assessment may be required to assess the relationship between cobalt oxide exposure and carcinogenicity should relevant data become available.

A Tier III assessment may be necessary to provide further information to determine the adequacy of protection to workers under the current exposure control framework.

All other risks are considered to have been sufficiently assessed at the Tier II level, subject to implementing any risk management recommendations, and provided that all 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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Very toxic by inhalation (T+; R26)	Harmful if swallowed - Cat. 4 (H302) Fatal if inhaled - Cat. 1 (H330)
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)
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 industry

Control measures

Control measures to minimise the risk from oral, dermal 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 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;
- 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 chemical has not been undertaken as part of this assessment.

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