Cobalt: Human health tier II assessment

27 November 2014

CAS Number: 7440-48-4

- Preface
- Chemical Identity
- Import, Manufacture and Use
- Restrictions
- Existing Work Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

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, elemental Cobalt metal
Structural Formula	
Molecular Formula	Co
Molecular Weight (g/mol)	58.93
Appearance and Odour (where available)	An odourless, metallic solid or powder.
SMILES	[Co]

Import, Manufacture and Use

Australian

The chemical cobalt metal (CAS No. 7440-48-4) has reported commercial use including in epoxy coating.

The chemical has reported site-limited use including, in nickel-metal hydride batteries.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; and Substances and Preparations in the Nordic countries (SPIN) database.

The chemical has reported domestic use. It is reported to be present in a range of domestic products including auto products and cleaning products (Household Products Database, US Department of Health and Human Services; HSDB).

The chemical has reported commercial use including:

- as a colourant or dye; and
- in pigments, paints and enamels.

The chemical has reported site-limited use including:

- as a component in alloys and carbides;
- as an intermediate for manufacture of electrical batteries and accumulators;
- in metal surface treatment and as a plating agent;
- in semiconductors; and
- in the manufacture of computer, electronic and optical products and electrical equipment.

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 for restricted use in abrasive blasting at a concentration of greater than 0.1 % of cobalt (WHS, 2014).

International

No international restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xn; R42 (Respiratory sensitisation); and

Xn; R43 (Skin sensitisation).

Exposure Standards

Australian

The chemical has an exposure standard of 0.05 mg/m^3 time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 0.02–0.1 mg/m^3 in different countries such as Germany (0.1 mg/m^3, inhalable fraction), Taiwan (0.05 mg/m^3, cobalt, metal fume and dust (as Co)), and Sweden (0.02 mg/m^3, cobalt and inorganic compounds, (as Co)- total dust).

Health Hazard Information

Toxicokinetics

Bioaccessibility data on elemental cobalt powder (7440-48-4) indicate that it is highly soluble at the low pH of artificial gastric fluid and artificial lysosomal fluid and show that cobalt metal releases the Co^{2+} cation at a similar rate to cobalt sulfate heptahydrate (CAS No. 1307-96-6) in acidic conditions, although low dissolution (3.7 - 11.3%) occurs in artificial alveolar (pH 7.4), interstitial (pH 7.4), intestinal (pH 7.4) fluids, and sweat (pH 5.5-6.5) (Stopford et al., 2003). 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.

The oral cobalt absorption in humans varies from 3-97 % depending on the type and dose of the cobalt compounds administered (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 (Firriolo 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; CDI, 2014). 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 of cobalt metal can be moved into the gastrointestinal tract by mucociliary action. Smaller particles are phagocytised by macrophages (ATSDR, 2004). Rats exposed to ultrafine metallic cobalt particles using a nebulizer producing droplets (with a mass median aerodynamic diameter (MMAD) of 0.76 µm), for five hours per day for four days, showed reversible lung lesions. Biphasic lung clearance occurred with 75% in the first three days, with the remainder cleared between three to 28 days (Kyono

et al., 1992; IARC, 2006). In another study, where cobalt metal was administered intratracheally to rats either alone (0.3 mg/kg bw) or mixed with tungsten carbide (5 mg/kg bw; WC-Co containing 6% of cobalt metal particles), retention of cobalt was longer in rats treated with cobalt alone (IARC, 2006).

Once absorbed, the cobalt ion is widely distributed in the body, including to 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 (ATSDR, 2004).

Acute Toxicity

Oral

The chemical had moderate acute toxicity in animal tests following oral exposure. The reported median lethal dose (LD50) in rats was 550 mg/kg bw and met the hazard classification between 300 - 2000 mg/kg bw. The chemical should be classified with the risk phrase 'Harmful if swallowed' (Xn; R22).

In a study carried out according to OECD Test Guideline (TG) 425, female Sprague Dawley rats were exposed to a single oral dose of cobalt powder ultrafine (CAS No. 7440-48-4) (175, 550,1750 and 5000 mg/kg) and observed for 14 days. Based on the results, the median lethal dose (LD50) in rats was reported as 550 mg/kg bw. Observed sub-lethal effects included hyperactivity, diarrhoea, nasal discharge, ano-genital staining and some facial staining (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

The chemical had very high acute toxicity in animal tests following inhalation exposure. The median lethal concentration (LC50) in rats was < 0.05 mg/L. Observed sub-lethal effects included slight ataxia and slight dyspnoea.

In the study carried out according to OECD TG 436, male and female Crj: CD (SD) rats were exposed to a single inhalation concentration of cobalt powder (CAS No. 7440-48-4) (mass median aerodynamic diameter (MMAD) ranging from 2.7 - 3.5 μm) of either 0.05, 0.51, 1.05 and 5.08 mg/L for four hours. At a concentration of 0.05 mg/L, all animals died prematurely by the 11th observation day. All animals exposed to concentrations ranging between 0.51 and 1.05 mg/L of the chemical died prematurely by test day four, or within 24 hours when exposed to the highest dose of 5.08 mg/L. At the 0.05 mg/L concentration, histopathology revealed perivascular inflammatory oedema in the lungs with neutrophilic granulocytes, lymphocytes and histiocytes and interstitial pneumonia in the animals that died prematurely. An LC50 value could not be determined due to the 100% mortality at all doses (REACH).

Corrosion / Irritation

Respiratory Irritation

Based on the available data, cobalt powder is a respiratory irritant in animal studies. Effects were sufficient to warrant a hazard classification. Refer to **Acute inhalation toxicity** and **Repeat dose inhalation toxicity**.

Skin Irritation

The chemical produced no skin irritation in a study performed in accordance with OECD TG 439.

In an in vitro study carried out according to OECD TG 439, cobalt powder (CAS No. 7740-48-4) was introduced for 15 minutes at a volume of 10 mg pre-wetted in 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. Each sample was performed in triplicate. 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 95.1 % for cell viability. As this value is above the 50 % viability threshold, the substance was not considered to be an irritant (REACH).

Eye Irritation

Based on the available data, cobalt powder is reported to be a slight eye irritant in animal studies but effects were not sufficient to warrant a hazard classification.

In an in vivo study carried out according to OECD TG 405, 0.1 g of cobalt powder / animal (CAS No. 7440-48-4) (median particle diameter of 2.3 μm) was applied to the eyes of three New Zealand White rabbits. Moderate reddening of the conjunctivae and slight to moderate reddening of the sclera was observed in all animals, one hour after treatment and this persisted as slight to marked reddening until 72 hours after treatment. Overall irritation results 24, 48 and 72 hours after application per animal were as follows: corneal opacity - 0.0, 0.0, 1.0; iritis - 0.0, 0.0, 0.0; conjunctival redness, 1.33, 2.33, 2.33 and conjunctival oedema - 0.0, 0.0 and 0.0. All eye reactions were reversible and no longer evident seven days after treatment. The responses do not met the criteria for classification (REACH).

In a further study, an in vitro experiment was carried out according to OECD TG 437. Cobalt powder (CAS No. 7440-48-4) (median particle diameter of 2.3 μm) was administered to bovine corneas for 240 minutes at a volume of 0.75 mL (20 % w/v in saline). The test was performed in triplicate. The mean in vitro score for the negative control, with no increase in opacity or permeability of the corneas, was approximately 1.22, whereas the mean in vitro score for the positive control was approximately 250.64, with clear observations of opacity and distinctive permeability of the cornea, corresponding to a corrosive effect. After exposure to cobalt metal, a mean in vitro score of 1.79 was determined. Under the experimental conditions reported, cobalt powder (CAS No. 7440-48-4) was not corrosive to the eye (REACH).

Sensitisation

Skin Sensitisation

The chemical is currently classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). No animal data are available for cobalt metal (CAS No. 7440-48-4); however, based on read across animal data available on the analogue chemical cobalt sulfate (CAS No. 10124-43-3), cobalt oxide (CAS No. 1307-96-6) and human data on cobalt chloride (CAS No. 7646-79-9) (refer to **Observations in humans**) hazard classification is supported.

The positive dermal sensitisation results from a non guideline adjuvant and patch test (APT) study with cobalt sulfate (CAS No. 10124-43-3) support this classification. In the study, five female Hartley guinea pigs were injected intradermally with 0.1 mL of Freund's complete adjuvant (FCA) and then induced with 3 % cobalt sulfate (CAS No. 10124-43-3). Induction exposure occurred four times via occlusive patches on days one, two, three and nine. Animals were then challenged with either 0.01, 0.03, 0.1, 0.3, 1 or 3 % cobalt sulfate (CAS No. 10124-43-3), 21 days after initial induction. A sensitisation rate of 40 % was seen at a concentration of 0.01 % (REACHb).

In a LLNA assay 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 (REACH).

Observation in humans

Respiratory sensitisation

The chemical is currently classified as hazardous with the risk phrase 'May cause sensitisation by inhalation' (R42) in HSIS (Safe Work Australia).

Several epidemiological studies conducted in cobalt-producing facilities support the findings that occupational exposure to inorganic cobalt compounds is associated with occupational asthma (ATSDR, 2004; WHO, 2006; CoRC 2014). Specifically, studies show that there was a significant correlation between decreasing lung function tests (FEV1/VC 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 (REACHc). 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 (REACHc). Furthermore, 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 (REACHc).

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. Bioaccessibility studies conducted with cobalt metal powder indicate that the Co^{2+} ion is released at moderate to high levels compared to soluble cobalt compounds (cobalt sulfate heptahydrate, CAS No. 10026-24-1) in artificial gastric fluid (Stopford et al., 2003; CDI, 2014). Data available from the NICNAS assessment of soluble cobalt compounds, 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 (NICNASa) do not meet the criteria for hazard classification.

Dermal

No data are available.

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

Inhalation

The chemical caused damage to health in animal tests following repeated inhalation exposure, at a level that met the classification criteria for GHS, although the severity of these effects was not sufficient to warrant hazard classification according to HSIS. The lowest observed effect concentration (LOAEC) in rats and mice was 0.61 mg/m³. Observed sub-lethal effects included histopathological changes observed in the lungs, nose and larynx. Human data suggest that repeated inhalation is harmful with debilitatory non-cancer outcomes (refer to **Observations in Humans**).

In an National Toxicology Program (NTP) 14 week repeat dose inhalation toxicity study carried out according to OECD TG 413, male and female Fischer 344 (F344) rats were exposed via whole body inhalation to 0.61, 1.23, 2.5 or 5 mg/m³ of aerosoled cobalt metal powder (for six hours per day, five days a week). The MMAD of the aerosol ranged between 1.61 - 1.96 μm. The lowest observed adverse effect concentration (LOAEC) for the chemical was reported to be 0.61 mg/m³. Absolute and relative lung weights of all exposed animals were significantly higher than control animals and lung weight changes were related to the histopathological changes. These included pale foci, chronic inflammation, alveolar proteinosis and bronchiolar epithelial hyperplasia. The severity of these lesions generally increased with increasing exposure concentration. Other changes were observed in the nose and included olfactory epithelial degeneration, respiratory epithelial hyperplasia, olfactory epithelial hyperplasia and turbinate atrophy. This study was repeated using B6C3F1/N mice for a duration of three months. The lowest observed adverse effect concentration (LOAEC) for the cobalt metal powder was reported to be 0.61 mg/m³. Predominant findings were increased lung weights and alveolar histiocytic cellular infiltration in the lung. Observations in the nose found chronic active inflammation, olfactory and respiratory epithelial degeneration and squamous metaplasia in the nose and larynx (NTP, 2013; REACH).

In an NTP 16 day repeated dose inhalation toxicity study carried out similarly to OECD TG 412, male and female F344 rats were exposed via whole body inhalation to an aerosol of 2.5, 4.9, 9.7, 19.7 or 40.1 mg/m³ of cobalt metal powder (for six hours plus T90 (12 minutes) per day, five days a week). The MMAD of the aerosol ranged between 1.79 - 1.94 μm. No NOAEC could be identified as the study was designed as a dose range finder with limited number of endpoints investigated; however, there was an increased incidence of non-neoplastic lesions of the lung including haemorrhage, acute inflammation, alveolar epithelial hyperplasia, histolytic cellular infiltration of the alveolar epithelium and increased incidences of non-neoplastic lesions of the nose including olfactory epithelial necrosis and epithelial atrophy. This study was repeated using B6C3F1/N mice for a duration of 17 days with similar results in increased incidences of non neoplastic lesions of the lung and nose (NTP, 2013; REACH).

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 have been 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).

As a result of the effects of cobalt, which have potential to increase haemoglobin levels, it has been previously used therapeutically to treat anaemia. In a series of studies, 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; these were reversible upon cessation of cobalt therapy (ATSDR, 2004). When pregnant women were treated for 90 days with 2 to 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 or liver function, or obvious birth defects (ATSDR, 2004).

Genotoxicity

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

In vitro studies

Several Ames studies have been reported with conflicting data. In a recent NTP in vitro bacterial mutagenicity test (Ames test), cobalt metal was incubated with *Salmonella typhimurium* strains TA 100 and TA 98 (100, 500, 1000, 2500, 5000 and 7500 μg/plate), as well as *Escherichia coli* pKM101 (5, 25, 50, 75, 100, 150, 200, 300 and 450 μg/plate) with and without S9 metabolic activation. Experiments were carried out in triplicate. An increase in revertant rate was reported in *S. typhimurium* strain TA 98, in the absence of metabolic activation but not with activation. The response was reported to be reproducible, although weak and not well correlated with dose level (100 - 3500 ug/plate). In strain TA 100, cobalt metal (100-5000 ug/plate) gave an equivocal response in the absence of S9 mix, and no mutagenic activity was observed with S9 mix. No mutagenicity was detected in *E. coli* pKM101, with or without S9 (NTP, 2013). However, in another recent Ames test carried out according to OECD TG 471 by different researchers, cobalt powder did not induce mutation in *S. typhimurium* TA 98 in the absence or presence of S9 metabolic activation at up to cytotoxic concentrations of 1000 μg/plate (REACH).

In an in vitro mammalian cell micronucleus study, extra fine cobalt powder (D50 of 4 μm) was incubated with human leukocytes at concentrations of 0.6, 1.2, 3.0 and 6.0 μg/ml) without metabolic activation. A significant induction (> 2 fold) in chromosome damage frequency was reported at the lowest concentration. At this concentration 19 % cytotoxicity was also observed (REACH). In a similar micronucleus study, extra fine cobalt metal was incubated with human osteosarcoma cells at test concentrations of 0.75, 1.0, 3.0 and 6 μg/mL. Significant increases in micronucleated cells at all concentrations were reported (REACH).

Furthermore, Anard et al. (1997) reported DNA breaks and/or alkali-labile sites in DNA purified from 3T3 mouse cells using alkaline single cell gel electrophoresis (SCGE) and modified alkaline elution (AE) assays following treatment with cobalt metal particles (D50 of 4 μm). The SCGE assay reported direct clastogenic effects in a dose dependent manner from the cobalt compound alone. AE experiments using human lymphocytes exposed to cobalt particles displayed a significant clastogenic potency, but significantly less than when mixed with WC particles (Anard et al., 1997; IARC, 2006).

In vivo studies

In an NTP study carried out according to OECD TG 474 (mammalian erythrocyte micronucleus test), B6C3F1 mice were exposed to a dust concentration of 0.625, 1.25, 2.5, 5 or 10 mg/m^3 for five days a week for 3 months. There was no increase in the frequencies of normochromatic erythrocytes observed in peripheral blood of male of female mice exposed to cobalt metal (0.625 - 10 mg/m^3) and the chemical was not mutagenic (REACH; NTP, 2013).

Human data

Occupational exposure to cobalt dust (average concentration 20 mg/m^3) in 35 workers from cobalt refineries reported no significant effects compared to matched controls for lymphocyte DNA damage using the comet assay or lymphocyte micronucleus frequencies (De Boeck et al., 2000; NTP, 2013; OECD, 2014a).

Carcinogenicity

The International Agency for Research on Cancer (IARC) classified cobalt metal without tungsten carbide as 'possibly carcinogenic to humans (Group 2B)' (IARC, 2006). Furthermore, a draft NTP report (2013) is considering that there is 'clear evidence of carcinogenic activity' of cobalt metal in both sexes of F344/N rats and B6C3F1 mice (NTP, 2013). Based on the weight of evidence from the draft NTP report and the similar bioavailablility of cobalt metal to soluble cobalt compounds once digested (NICNASa), the findings from the report on cobalt sulphate support the classification of the chemical.

In a draft report of a two-year inhalation carcinogenicity study conducted by the NTP, F344/Ntac rats and B6C3F1/N mice (50 animals/sex/species/dose) were exposed via whole body to an aerosol concentration of 0, 1.24, 2.49 or 5.01 mg/m^3 cobalt metal powder (MMAD of 1.4 - 2.0 μm) for six hours plus T90 (12 minutes) per day, five days per week for 105 weeks. A LOAEC of 1.24 mg/m^3 was reported for male and female rats based on the increased rates of alveolar/bronchiolar adenoma and carcinomas in the lungs at the lowest dose. In mice, a LOAEC of 1.24 mg/m^3 was reported based on increased incidences of alveolar/bronchiolar neoplasms of the lung, predominantly carcinoma, including multiple carcinomas. In rats and mice, the incidence of hyperplasia in the alveolar and bronchiolar epithelia was significantly increased. Systemic effects were only observed in rats and in both species; neoplasms that occurred in the lung were accompanied by a spectrum of similar inflammatory and nonneoplastic proliferative lesions of the respiratory tract. The draft NTP report (2013) concludes that there is 'clear evidence of carcinogenic activity' of cobalt metal in both sexes of F344/N rats and B6C3F1 mice (NTP, 2013).

The carcinogenic potential of cobalt compounds is also likely to be contributed to by the indirect genotoxic mechanisms previously mentioned (inhibition of DNA repair and generation of reactive oxygen species causing cellular oxidative stress) (ATSDR, 2004; IARC, 2006).

Several reports have provided evidence related to occupational exposure in hard-metal production facilities of an increased lung cancer risk with increasing duration of exposure to hard metal dust containing cobalt and tungsten carbide. However, data are confounded by smoking, other occupational carcinogens or limited by the number of workers in the study (IARC, 2006).

Reproductive and Developmental Toxicity

Limited data are available on the cobalt metal powder. Based on the similar bioavailablility of cobalt metal to soluble cobalt compounds once digested (NICNASa), the relevent data for oral exposure are read-across from the NICNAS assessment of soluble cobalt compounds (NICNASa; OECD, 2014b). Cobalt sulfate heptahydrate (CAS No. 10026-24-1) and cobalt dichloride (CAS No. 7646-79-9) are 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 the weight of evidence and read-across principles (OECD, 2014b), the data support a recommendation to classify this chemical.

Reproductive toxicity

In the draft three month NTP inhalation study in rats and mice, sperm motility was significantly decreased in male F344/Ntac rats exposed to 1.25, 2.5 or 5 mg/m^3 of cobalt metal powder. There were no cobalt related histopathological findings observed in female reproductive organs. Male and female B6C3F1/N mice were exposed to 2.5, 5 and 10 mg/m^3 of cobalt metal powder. Sperm motility was significantly decreased at all exposure concentrations. At the highest dose, males had decreased weights of cauda epididymis, epididymis and testis and marked degeneration of the germinal epithelium in the testes (NTP, 2013). In the draft report of the two year NTP inhalation study, male F344 rats exposed to 5 mg/m^3 had increased incidence of infarction recorded in the testes. Affected testes displayed complete effacement of the parenchyma due to necrosis with loss of differential staining and cellular detail (NTP, 2013).

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 testes 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 weights of testis and epididymis were significantly decreased, and 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 (carcinogenicity, mutagenicity and 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 acute ingestion and repeated exposure through inhalation.

Public Risk Characterisation

Although the public could come into contact with articles containing the chemical, it is expected that the chemical will be bound within the article 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 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, local long term, acute and local health 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 0.61 mg/m^3 cobalt metal (CAS No. 7440-48-4) identified in the inhalation repeated dose toxicity studies at which adverse effects are observed, there is a concern that the absence of exposure controls in the HSIS may not adequately protect workers' health.

NICNAS Recommendation

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 provided that the recommended amendment to the classification is adopted

and 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	Irritating to respiratory system (Xi; R37)	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		May cause damage to organs through prolonged or repeated exposure through inhalation - Cat. 2 (H373)
Carcinogenicity	Carc. Cat 2 - May cause cancer by inhalation (T; R49)	May cause cancer - Cat. 1B (H350i)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May impair fertility (T; R60)	May damage fertility - Cat. 1B (H360F)

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

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

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which 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.

References

Agency for Toxic Substances and Disease Registry (ATSDR) 2004. Toxicological Profile for Cobalt. Accessed July 2014 at http://www.atsdr.cdc.gov/toxprofiles/tp33.pdf

Anard D, Kirsch-Volders M, Elhajouji A, Belpaeme K& Lison D. In vitro genotoxic effects of hard metal particles assessed by alkaline single cell gel and elution assays. Carcinogenesis 18 (1) pp 177-184.

Cobalt Development Institute (CDI) 2014. Data on Cobalt (CAS No. 7740-48-4). Unpublished report submitted to National Industrial Chemicals Notification and Assessment Scheme under the Inventory Multi-tiered Assessment and Prioritisation framework. Generated by the Cobalt Development Institute, Guildford, Surrey, United Kingdom.

De Boeck M, Lardau S, Buchet JP, Kirsch-Volders M& Lison D (2000). Absence of Significant Genotoxicity in lymphocytes and urine from workers exposed to moderate levels of cobalt containing dust: A cross-sectional study (2000). Environmental and Molecular Mutagenesis 36 pp.151-160.

Elbetieha A, Al-Thani AS, Al-Thani RK, Darmani H& Owais W 2008. Effects of Chronic Exposure to Cobalt Chloride on the Fertility of Testes in Mice. Journal of Applied Biological Sciences 2(1) pp. 1-6.

Firriolo JM, Ayala-Fierro F, Sipes IG and Carter DE 1999. Absorption and disposition of cobalt naphthenate in rats after a single oral dose. Journal of Toxicology and Environmental Health, Part A. 58 (6) pp. 383-395.

Galleria Chemica. Accessed July 2014 at https://jr.chemwatch.net/galleria/

International Agency for Research on Cancer (IARC) 2006. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 86. Cobalt in Hard Metals and cobalt sulfate, gallium arsenide, idium phosphide and vanadium pentoxide. Accessed in March 2014 at http://monographs.iarc.fr/ENG/Monographs/vol86/mono86.pdf

International Programme on Chemical Safety (IPCS) 2006. Concise International Chemical Assessment Document 69. Cobalt and inorganic cobalt compounds. Accessed July 2014 at http://www.who.int/ipcs/publications/cicad/cicad69%20.pdf

Kyono H, Kusaka Y, Homma K, Kubota H& Endo-Ichikawa y 1992. Reversible lung lesions in rats due to short-term exposure to ultrafine cobalt particles. Industrial Health 30 pp. 103-118.

Lantin AC, Vermeulen J, Mallants A, Vanoverschelde JL, Speybroeck N, Swennen B, Hoet P& Lison D 2013. Occupational exposure to cobalt is not associated with incipient signs of dilated cardiomyopathy in a Belgian refinery. Occupational Enviromental Medicine 70 pp. 386-392.

Leggett RW 2008. The biokinetics of inorganic cobalt in the human body. Science of the Total Environment 389 pp. 259-269.

National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Inventory Multi-Tiered and Prioritisation (IMAP): Human Health Tier II Assessment for Cobalt oxide. Available at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Tier II Human health assessment for Soluble cobalt (II) and salts. Australian Government Department of Health. Accessed July 2014 at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=952

National Toxicology Program (NTP) 1991. Toxicity studies of cobalt sulfate heptahydrate in F344/N rats and B6C3F1 mice. NTP TOX 5. NIH Publication No. 91-3124. Accessed July 2014 at http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox005.pdf

National Toxicology Program (NTP) 2013 DRAFT. Toxicology studies of cobalt metal (CAS No. 7440-48-4) in F344/N rats and B6C3F1/N mice and toxicology and carcinogenesis studies of cobalt metal in F344/Ntac rats and B6C3F1/N mice. NTP TR 581. Accessed July 2014 at http://ntp.niehs.nih.gov/about/org/trpanel/meetings/docs/2013/10/index.html

OECD 2014b. Guidance on Grouping of Chemicals, Second Edition. Environment Directorate. Joint meeting of the Chemicals Committee and the Working party on Chemicals, Pesticides and Biotechnology. Series on Testing& Assessment No. 194. Accessed July 2014 at http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en

OECD 2014a. SIDS Initial Assessment Profile (SIAP) on soluble cobalt salts. Unpublished.

REACH Dossier (REACHb). Cobalt sulphate (CAS No. 10124-43-3). Accessed July at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c84b590-a1e1-7043-e044-00144f67d249/DISS-9c84b590-a1e1-7043-e044-00144f67d249_DISS-9c84b590-a1e1-7043-e044-00144f67d249.html

REACH Dossier (REACHc). Cobalt dichloride (CAS No. 7646-79-9). Accessed July at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c82ba1d-3983-63e3-e044-00144f67d249/DISS-9c82ba1d-3983-63e3-e044-00144f67d249_DISS-9c82ba1d-3983-63e3-e044-00144f67d249.html

REACH Dossier. Cobalt (CAS No. 7440-48-4). Accessed July 2014 at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c8246bc-6f29-126a-e044-00144f67d249/DISS-9c8246bc-6f29-126a-e044-00144f67d249_DISS-9c8246bc-6f29-126a-e044-00144f67d249.html

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed July 2014 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Stopford W, Turner J, Cappellini D& Brock T 2003. Bioaccessibility testing of cobalt compounds. Journal of Environmental Monitoring 5 (pp. 675-680).

Swennen B, Buchet J-P, Stanescu D, Lison D& Lauwerys R (1993). Epidemiological survey of workers exposed to cobalt oxides, cobalt salts and cobalt metal. British Journal of Industrial Medicine. 50: pp 835-842.

The Cobalt REACH Consortium Ltd. 2014 (CoRC). Chemical Safety Report for Cobalt, CAS RN 7440-48-4, EC Number 231-158-0. March 2014. Unpublished report submitted to National Industrial Chemicals Notification and Assessment Scheme under the Inventory Multi-tiered Assessment and Prioitisation framework.

Work Health and Safety (WHS) Regulations 2014. Schedule 10 - Prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals. Accessed May 2014 at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/model-whs-regulations

World Health Organisation (WHO) Concise International Chemical Assessment Document 69 (CICAD), 2006. Cobalt and Inorgainc Cobalt Compounds. Accessed July 2014 at http://www.who.int/ipcs/publications/cicad/en/

Last update 27 November 2014