Cobalt chlorides and citrates: Human health tier II assessment

27 November 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, cobalt(2+) salt (2:3)	866-81-9
Cobalt chloride (CoCl2)	7646-79-9
Cobalt(II) chloride, hexahydrate	7791-13-1
Citric acid, cobalt(2+) salt (1:1)	18727-04-3

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 of chemicals contains 1,2,3-propanetricarboxylic acid, 2-hydroxy-, cobalt (2+) salt (cobalt citrate; CAS No. 866-81-9), citric acid, cobalt(2+) salt (cobalt hydrogen citrate; CAS No. 18727-04-3), cobalt chloride (CAS No. 7646-79-9) and cobalt chloride hexahydrate (CAS No. 7791-13-1). These compounds are soluble and upon dissolution the Co^{2+} cation is considered to be the moiety responsible for systemic toxicity. Local toxicity is expected to result from the combination of released ions (i.e. both the Co^{2+} cation and the anion) on exposure to lungs or skin (ATSDR, 2004; IARC 2006). These chemicals differ from the previously assessed soluble cobalt salts in the magnitude of their local effects. Stopford et al., (2003) have highlighted the importance of bioaccessibility of cobalt ions in different biological fluids (e.g. gastric fluid, interstitial fluid and lysosomal fluid).

Considering that cobalt sulfate heptahydrate (CAS No. 10026-24-1) and other soluble cobalt compounds (NICNASa) have similar bioaccessibility and bioavailability in biological fluids to chemicals in this group, data available for cobalt sulfate and other soluble cobalt compounds can be read across according to the principles of the OECD (2014a) when data are lacking for the chemicals in this group.

Import, Manufacture and Use

Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was less than 1000 tonnes for cobalt chloride (CAS No. 7646-79-9) and cobalt chloride hexahydrate (CAS No. 7792-13-1). Volume data

for other chemicals in this group were not available.

The following Australian industrial uses were reported for cobalt chloride (CAS No. 7646-79-9) and cobalt chloride hexahydrate (CAS No. 7792-13-1) under previous mandatory and/or voluntary calls for information:

The chemical has reported site-limited use including in metal treatment and plating.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Cobalt chloride (CAS No. 7646-79-9) and cobalt chloride hexahydrate (CAS No. 7792-13-1) have reported commercial use including as:

- a corrosion inhibitor;
- intermediates and colouring agents in textile dyes, inorganic pigments, frits, ceramic ware and glass;
- and as catalysts for oxidation; and
- an indicator in dessicants.

All the chemicals in this group have reported use as laboratory reagents.

The following non-industrial uses have been identified for all the chemicals in this group including:

- as fertilisers;
- in vitamin preparations and for therapeutic agents; and
- as animal food additives.

Cobalt chloride (CAS No. 7646-79-9) has also been reported to be used in tattoo ink.

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

The chemicals, cobalt chloride (CAS No. 7646-79-9) and cobalt chloride hexahydrate (CAS No. 7792-13-1) are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist") (Galleria Chemica).

The chemical, cobalt chloride (CAS No. 7646-79-9) is also listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and

- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

The chemical cobalt chloride (CAS No. 7646-79-9) is also restricted by Annex XVII to REACH Regulation (EU) No. 109/2012. The chemical cannot be placed on the market or used in substances, as constituents of other substances, or in mixtures for supply to the general public in individual concentration ≥ 0.01 %. This concentration is the percentage by weight of the metallic element calculated with reference to the total weight of the mixture. This concentration is the percentage by weight of the metallic element calculated with reference to the total weight of the mixture.

Existing Worker Health and Safety Controls

Hazard Classification

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

Cobalt chloride (CAS No. 7646-79-9)

Carc. Cat. 2; R49 (Carcinogenicity)

Muta. Cat. 3; R68 (Genotoxicity)

Repr. Cat. 2; R60 (Reproductive toxicity)

R22 (Acute toxicity)

R42/43 (Sensitisation)

Cobalt chloride hexahydrate (CAS No. 7791-13-1)

R42/43 (Sensitisation)

This substance has only been assessed against the endpoint of sensitisation and has not been subject to a complete assessment for hazard classification in accordance with the approved criteria.

Exposure Standards

Australian

No specific exposure standards are available for soluble cobalt compounds within this group.

International

The following exposure standards are identified (Galleria Chemica):

The chemicals cobalt citrate (CAS No. 866-81-9) and cobalt hydrogen citrate (CAS No. 18727-04-3) have exposure limits (time weighted average - TWA) of 0.05–0.1 mg/m^3 in different countries such as Switzerland, USA (Washington) and Ireland.

The chemicals cobalt chloride (CAS No. 7646-79-9) and cobalt chloride hexahydrate (CAS No. 7792-13-1) have exposure limits (TWA) of 0.01–0.1 mg/m^3 in different countries such as Denmark, USA (Washington), and Ireland.

Health Hazard Information

Toxicokinetics

The chemicals within this group are all soluble in water and highly bioavailable (IARC, 1997; Stopford et al., 2003; Government of Canada, 2010; CoRC, 2014a; CoRC, 2014b; CoRC, 2014c). Studies have also demonstrated that cobalt chloride (CAS No. 7646-79-9) is almost completely dissolved in simulated human body fluids including artificial gastric juice (pH 1.5)—100 %, artificial interstitial fluid (pH 7.4)—78.4 %, artificial alveolar fluid (pH 7.4)—100 %, and artificial lysosomal fluid (pH 4.5–5.0)—100 % (Stopford et al., 2003).

Oral administration of soluble cobalt salts leads to nearly complete dissociation into the hydrated Co^{2+} ion and the anionic component (NICNASa). The amount of cobalt absorption in humans varies from 3–97 % depending on the type and dose of cobalt compound given (Leggett, 2008). Females, as well as individuals with iron deficiencies, have higher cobalt absorption (ATSDR, 2004; IPCS, 2006).

Dermal absorption of cobalt has been demonstrated to be relatively low in human volunteers. In Leggett's study, urinary cobalt was increased by an order of magnitude and remained at an elevated level 48–60 hours after exposure (Leggett, 2008). In an in vitro study, percutaneous absorption of soluble cobalt through human skin was 1.08 %, using 100 mg/mL cobalt chloride hexahydrate (CAS No. 7791-13-1) (CDI, 2014). Absorption through the 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. Particles larger than 2 µm are deposited in the upper respiratory tract, whereas smaller particles are deposited into the lower respiratory tract. Larger particles can be absorbed into the blood after dissolution or can be moved into the gastrointestinal tract by mucociliary action. Smaller particles are either dissolved or phagocytised by macrophages (ATSDR, 2004).

Once absorbed, the cobalt ion is widely distributed in the body, including the skeleton, with the highest concentration found in the liver and kidney. After inhalation exposure, although there is a high initial excretion in faeces, the primary route of elimination is via the kidneys in urine (IPCS, 2006). Urinary excretion of cobalt from workers under experimental conditions was multiphased: 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

Cobalt chloride (CAS No. 7646-79-9) is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available data support the extension of this classification to other chemicals in this group.

Cobalt chloride hexahydrate (CAS No. 7791-13-1) had moderate acute toxicity in male and female Wistar rats following oral exposure. Male and female Wistar rats were administered 500, 600, 720, 864 or 1137 mg/kg bw of cobalt chloride hexahydrate (CAS No. 7791-13-1) by oral gavage. The median lethal dose (LD50) value was calculated to be 766 mg/kg bw for cobalt chloride hexahydrate (CAS No. 7792-13-1) and 418 mg/kg bw for the anhydrous compound. Reported signs of toxicity included sedation and diarrhoea at the highest dose levels, and rats displayed tremors and convulsions prior to death (Speijers et al., 1982).

Dermal

No data are available.

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

Inhalation

No data are available on chemicals in this group. Considering the physical properties of the chemicals in this group, the compounds are not able to be created into an inhalable atmosphere at high concentrations and testing is technically not feasible (CoRC, 2014a).

Observation in humans

The death of a 19-month-old male child was reported 6.5 hours after he swallowed an unknown amount of cobalt chloride solution, despite repeatedly induced vomiting and supporting therapy. Toxic effects included pale-blue discolouration, with oedematous lips and tongue, and respiratory distress. Cardiac arrest and death occurred 6.5 hours after ingestion. Autopsy revealed a blistered oesophageal mucosa and partially necrotic gastric mucosa, suggesting that the solution was highly concentrated and corrosive (UK PID, 1998; ATSDR, 2004).

Corrosion / Irritation

Skin Irritation

On the weight of evidence, chemicals in this group are not considered to be skin irritants. Cobalt chloride (CAS No. 7646-79-9) and cobalt citrate (CAS No. 866-81-9) were tested in accordance with OECD Test Guidelines (TG) 404 and 431; the data available suggest that the chemicals are not skin irritants.

In two studies carried out according to OECD TG 404, cobalt chloride (CAS No. 7646-79-9) and cobalt citrate (CAS No. 866-81-9) were applied to the dorsal trunk of three male New Zealand White rabbits for four hours as an 0.5 g aliquot, semi-occlusively. Cobalt chloride (CAS No. 7646-79-9) caused mild irritation reactions in all test animals, which cleared by the seventh day of observation and did not meet the criteria for classification of irritation (REACH). With cobalt citrate (CAS No. 866-81-9) neither erythema nor oedema was observed on the treated skin (REACH).

In another study carried out according to OECD TG 431, cobalt chloride (CAS No. 7646-79-9) was added for three or 60 minutes, at a volume of 25 mg, 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 duplicate. After exposure, a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed. Scores obtained after the three and 60 minute treatments were 78.7 % and 63.8 % for cell viability with exposure to cobalt chloride (CAS No. 7646-79-9). As values did not go below the threshold for corrosivity of less than 50 % cell viability for the three minute exposure, or less than 15 % cell viability for the 60 minute exposure, cobalt chloride (CAS No. 7646-79-9) was not considered to be corrosive (REACH).

Eye Irritation

The chemicals in this group cause serious damage to eyes and warrant hazard classification.

In a study carried out according to OECD TG 405, cobalt citrate (CAS No. 866-81-9) was applied to the eyes of three New Zealand White rabbits. Both oedema of the conjunctivae (chemosis) and redness of the conjunctivae had mean scores of two after exposure to the chemical. All effects were reversible in two out of three animals within the 21-day observation period; redness of the conjunctivae remained in one animal. Ocular lesions were noted as white spots on the nictitating membrane of two animals. In one animal, the lesion remained past the 21-day observation period (REACH).

In another study carried out according to OECD TG 405, cobalt chloride (CAS No. 7646-79-9) was applied to the eyes of three New Zealand White rabbits. Exposure to the chemical resulted in moderate reddening of the conjunctivae and moderate to marked chemosis, as well as slight to moderate ocular discharge one hour after administration in two out of three animals. In all

three animals, the signs of ocular irritation had not reversed within the 21-day observation period. No staining or corrosion of the cornea were observed (REACH).

Sensitisation

Respiratory Sensitisation

The chemicals, cobalt chloride (CAS No. 7646-79-9) and cobalt chloride, hexahydrate (CAS No. 7791-13-1) are classified as hazardous with the risk phrase ‘May cause sensitisation by inhalation’ (R42) in HSIS (Safe Work Australia).

Human data (refer to **Observations in humans**) support this classification.

Skin Sensitisation

Cobalt chloride (CAS No. 7646-79-9) and cobalt chloride, hexahydrate (CAS No. 7791-13-1) are classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). Animal data available on cobalt chloride hexahydrate (CAS No. 7791-13-1) and human data (refer to **Observations in humans**) available on cobalt chloride (CAS No. 7646-79-9) support this classification, and the extension of this classification to the other chemicals in this group.

In a non guideline guinea pig maximisation test, 15 female Dunkin Hartley guinea pigs per dose were injected intradermally with Freund's complete adjuvant (FCA) and induced with 1 % cobalt chloride hexahydrate (CAS No. 7791-13-1). Animals were then challenged with either 0.1 % or 0.3 % cobalt chloride hexahydrate (CAS No. 7791-13-1). The study resulted in 11/15 animals sensitised when challenged with 0.3 % cobalt chloride hexahydrate (CAS No. 7791-13-1), 48 hours after challenge (REACH).

Observation in humans

Respiratory

Occupational inhalation exposure to cobalt chloride (CAS No. 7646-79-9) present in aerosols can produce an asthmatic response in sensitised individuals, based on evaluation for specific Immunoglobulin E (IgE) and Immunoglobulin A (IgA) antibodies to cobalt (ATSDR, 2004; Government of Canada, 2010).

Skin

In a study conducted in human volunteers, skin patch tests showed a positive reaction in 286/4034 patients with 1 % cobalt chloride (CAS No. 7646-79-9) in petroleum jelly 24 hours after exposure (REACH). In another two patch test studies, 225/1415 patients and 24/373 patients showed a positive reaction to cobalt chloride when applied to the upper back using occlusive patches (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).

Repeated Dose Toxicity

Oral

The main effect of the chemicals in this group from repeated oral exposure is polycythaemia (increased erythrocytes), which is reversible after the exposure ceases.

Some effects of cobalt administration are the promotion of polycythaemia, increased haematocrit and increased haemoglobin levels, all of which are reversible shortly after exposure ceases. In a short-term repeated oral dose study of Sprague Dawley (SD) rats administered with 0, 2.5, 10 and 40 mg/kg bw/day of cobalt chloride hexahydrate (CAS No. 7791-13-1) for six weeks,

seven days a week in gelatine capsules, the no observed adverse effect level (NOAEL) was 2.5 mg/kg bw/day. The lowest observed adverse effect level (LOAEL) was 10 mg/kg bw/day based upon dose- and time-related increases in haemoglobin content and numbers of erythrocytes (ATSDR, 2004). In another longer-term study over seven months, oral doses of 0.2 and 10 mg/kg bw/day of cobalt chloride hexahydrate (CAS No. 7791-13-1) administered to rats by gavage six times a week, stimulated polycythaemia and decreased leukocyte function in rats. The NOAEL in this study was 0.2 mg/kg bw/day (Government of Canada, 2011).

Increased heart weight was reported in male rats exposed to 122 mg/kg bw/day of cobalt chloride hexahydrate (CAS No. 7791-13-1) in drinking water. Degenerative heart lesions were observed after administration of 124 mg/kg bw/day of cobalt sulfate heptahydrate (CAS No. 10026-24-1) in the diet after a two to three month exposure (ATSDR, 2004).

Dermal

No data are available.

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

Inhalation

Chemicals in this group cause serious damage to health by prolonged exposure through inhalation. A lowest observable adverse effect concentration (LOAEC) of 0.3 mg/m^3 of the analogue chemical cobalt sulfate heptahydrate (CAS No. 10026-24-1) was identified as having local effects on the larynx. The available data on an analogue chemical, cobalt sulfate heptahydrate (CAS No. 10026-24-1), warrant hazard classification for chemicals in this group.

The National Toxicology Program (NTP) conducted 13-week (NTP, 1991) and two-year studies (NTP, 1998) in male and female 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. Histopathology 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 kidney toxicity. There was also a significant increase in the relative lung weights of rats exposed to $\geq$0.3 mg/m^3 for males, and $\geq$1 mg/m^3 for females. In mice, this was observed in both sexes from $\geq$10 mg/m^3. Absolute and relative testis weights and the epididymal weight were significantly decreased in male mice at 30 mg/m^3. Polycythaemia was observed in rats at $\geq$3 mg/m^3. Histopathological lesions were observed in the respiratory tract of both rats and mice at all exposure levels from the chemical. An LOAEC of 0.3 mg/m^3 was determined based on squamous metaplasia in the larynx (NTP, 1991).

In the two-year NTP study, rats and mice (50 animals/sex/species) were exposed to 0, 0.3, 1.0, 3.0 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. Exposure to cobalt sulfate heptahydrate at all exposure levels caused inflammation, fibrotic and proliferative lesions in the respiratory tract of male and female rats and mice, although the changes in mice were less severe (NTP, 1998).

Observation in humans

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 cobalt's effects which have potential to increase haemoglobin levels, it has been previously used therapeutically to treat anaemia. In a series of studies, anephric patients were treated with 0.65–4.0 mg/kg/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 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, in liver function or obvious birth defects (ATSDR, 2004).

Genotoxicity

The chemical cobalt chloride (CAS No. 7646-79-9) is classified as hazardous: Category 3 mutagenic substance, with the risk phrase 'Possible risk of irreversible effect' (R68) in HSIS (Safe Work Australia). However, a recent review concluded that effective protective processes exist in vivo to prevent genotoxicity in humans (OECD, 2014b). The available data support a removal of this classification from the current HSIS (refer to **Recommendation** section).

Data from the analogue chemicals cobalt sulfate (CAS No. 10124-43-3) and cobalt acetate (CAS No. 71-48-7) are read across according to the principles of the OECD (2014) considering the similar bioaccessibility of these chemicals to cobalt chloride in artificial fluids (Stopford et al., 2003).

In vitro

Point mutation studies conducted in bacteria with cobalt chloride (CAS No. 7646-79-9) (Ames test in *Salmonella typhimurium* and *Escherichia coli*) and cobalt chloride hexahydrate (CAS No. 7791-13-1) (Ames test in *Salmonella typhimurium*) were predominantly negative with and without metabolic activation (IARC, 2006). However, clastogenicity studies conducted in human white blood cells, mononuclear leukocytes, lymphocytes and mammalian cell cultures (Chinese hamster ovary and mouse lymphoma) showed that cobalt chloride heptahydrate is clastogenic and induces chromosomal effects (DNA-protein cross-linkage, DNA strand breakage and sister chromatid exchange) in most studies (IARC, 2006).

For cobalt sulfate (CAS No. 10124-43-3) both positive and negative results were obtained in Ames tests in *Salmonella typhimurium* (strain TA100, TA98 and TA1535). Positive results were obtained for chromosomal aberrations and aneuploidy in plant cells, in producing reactive oxygen species (ROS) (by degradation of 2-deoxyribose), and malondialdehyde assay. Positive results were seen for chemical changes in DNA bases in the calf thymus DNA (IARC, 2006).

Cobalt acetate (CAS No. 71-48-7) inhibited the repair of UV-induced pyrimidine dimers in human HeLa cells and enhanced cell transformation by simian adenovirus SA7 in Syrian hamster embryo cells (IARC, 2006).

These genotoxic effects observed in vitro are consistent with a reactive oxygen mechanism (OECD, 2014b).

In vivo

Genotoxicity studies conducted using cobalt chloride (CAS No. 7646-79-9) injected intraperitoneally into Syrian hamsters showed aneuploidy, pseudodiploidy and hyperploidy in the bone marrow and testes (IARC, 2006). Enhanced micronucleus formation in male BALB/c AnNCrj mouse bone marrow was observed 30 hours after a single intraperitoneal injection of 50 or 200 mg/kg, but not at 25 mg/kg of cobalt chloride (CAS No. 7646-79-9) (IARC, 2006). Dose-dependent chromosomal aberrations were observed in the bone marrow of male Swiss mice given single oral doses of 0, 20, 40 or 80 mg/kg bw cobalt chloride (CAS No. 7646-79-9) (ATSDR, 2004). However, in a study similar to TG 474 and 475, a single oral dose of 50, 200 or 600 mg/kg cobalt chloride hexahydrate (CAS No. 7791-13-1) did not induce a significant increase in cells with structural and numerical chromosome aberrations or micronucleated polychromatic erythrocytes using SD rats (REACH).

Cobalt acetate (CAS No. 71-48-7) caused DNA base damage (products of hydroxyl radical attack) in the liver, kidney and lung in male and female Fischer 344/NCr rats after a single intraperitoneal injection of 50 μM/kg, indicating an increased incidence of oxidative stress (IARC, 2006).

In a study similar to OECD TG 475, but with some deviations, cobalt sulfate heptahydrate (10026-24-1) had no genotoxic effect in a mammalian bone marrow chromosome aberration test, in four SD rats administered a single oral gavage dose of 80, 160 or 320 mg/kg bw (REACH).

In an occupational study in 35 workers in a cobalt refinery, there was no indication of increased DNA strand breaks or micronuclei in blood lymphocytes compared with 27 unexposed workers (Government of Canada, 2011; OECD, 2014).

Carcinogenicity

Cobalt chloride (CAS No. 7646-79-9) is classified as hazardous: Category 2 carcinogenic substance, with the risk phrase ‘May cause cancer by inhalation’ (T; R49) in HSIS (Safe Work Australia). The available data on the analogue chemical, cobalt sulfate heptahydrate (CAS No. 10026-24-1), support this classification and the extension of this classification to other chemicals in the group.

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

In a two-year inhalation carcinogenicity study conducted by the National Toxicology Program (NTP), rats and mice (50 animals/sex/species) were exposed to 0, 0.3, 1.0 or 3.0 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. Female rats exposed to 1.0 mg/m^3 and higher, and males rats as well as both sexes of mice exposed to 3 mg/m^3, had significantly increased incidences of alveolar/bronchiolar neoplasms compared with controls. Marginal incidences of phaeochromocytoma of the adrenal medulla compared with controls were seen in males exposed to $\geq$1.0 mg/m^3. The NTP (1998) concludes that there is 'some evidence of carcinogenic activity' of cobalt sulfate heptahydrate (CAS No. 10026-24-1) in male F344/N rats and there was 'clear evidence of carcinogenenic activity' in female F344/N rats exposed to 3.0 mg/m^3 of the chemical. The combined or single incidence of alveolar/bronchiolar adenoma or carcinoma in the male and female mice exposed to 3.0 mg/m^3 exceeded the NTP historical control ranges for inhalation studies and it concludes that there is 'clear evidence of carcinogenic activity' of the chemical in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms (NTP, 1998).

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).

Reproductive and Developmental Toxicity

Cobalt chloride (CAS No. 7646-79-9) is classified as hazardous: Category 2 substance toxic to reproduction, with the risk phrase ‘May impair fertility’ (T; R60) in HSIS (Safe Work Australia). The available data on cobalt chloride and the analogue chemical, cobalt sulfate heptahydrate (CAS No. 10026-24-1), support this classification and the extension of this classification to other chemicals in the group.

Reproductive toxicity

In a 12-week oral fertility study, adult male Swiss mice were exposed to cobalt chloride (CAS No. 7646-79-9) in drinking water (average of 25, 47 or 93 mg/kg bw/day) and then mated with unexposed females. The number of pregnant females and implantation sites were significantly reduced in females mated with exposed males at 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 testis necrosis and degeneration were observed (Elbetieha et al., 2008).

In the 13-week NTP 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 testis weights and the epididymis weight were significantly decreased, together with the number of abnormal sperm 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, 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.

Other Health Effects

Neurotoxicity

In one clinical case, a 35-year-old woman who was treated for six months with 25 mg of cobalt chloride (CAS No. 7646-79-9) a day for anaemia developed clinically confirmed bilateral nerve deafness, absent ankle reflexes and impaired vibration sense, all of which resolved after treatment ceased (UK National Poisons Information Services, 1998).

Endocrine Disruption

Histological examination of 11/14 thyroids that were available for examination from patients who died from beer–cobalt myocardosis showed irregular follicle morphology and decreased follicular size (ATSDR, 2004).

In many case studies where cobalt chloride (CAS No. 7646-79-9) has been used to treat sickle cell anaemia, treatment with cobalt resulted in an enlargement of the thyroid, which was reversible when cobalt therapy ceased (ATSDR, 2004). In one study where a four-year-old boy was treated for seven months with 60–80 mg cobalt chloride (CAS No. 7646-79-9) daily for sickle cell anaemia, the thyroid was bilaterally and asymmetrically enlarged, firm and nodular (goitre). The goitre disappeared one month after cobalt therapy ceased (UK National Poisons Information Services, 1998). However, in an occupational study of 249 Belgian males in a cobalt refinery, no effects were observed on the thyroid or red blood cells when occupational exposure to cobalt was kept below the recommended biological limit of occupational exposure (15 $\mu gCo/g_{creatine}$ in urine) (Lantin et al. 2011).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include a systemic long-term effect (reproductive toxicity), local long-term effect (carcinogenicity), systemic acute effect (acute toxicity from oral exposure) and local effects (skin sensitisation and respiratory sensitisation). The chemicals may also cause toxic effects following repeated exposure through inhalation and serious eye irritation.

Public Risk Characterisation

No cosmetic or domestic uses of the chemicals in this group have been identified in Australia. Therefore, it is unlikely that the public will be exposed to chemicals of this group. Although the public could 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 the use of chemicals in this group, oral, dermal, ocular and inhalation exposure of workers to the chemical could occur, particularly where manual or open processes are used. These might include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could 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 chemicals in this group may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemicals are implemented. These chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

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

The classification proposed below is based on read across principles (refer to section on **Grouping rationale**). It should be used as a default for all members of the group. If empirical data become available for any member of the group indicating that a lower (or higher) classification is appropriate for the specific chemical, these may be used to amend the default classification for that chemical.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)

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 - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 2 - May cause cancer by inhalation (T; R49)	May cause cancer - Cat. 1B (H350i)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May impair fertility (T; R60)	May damage fertility - Cat. 1B (H360F)

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

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

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- 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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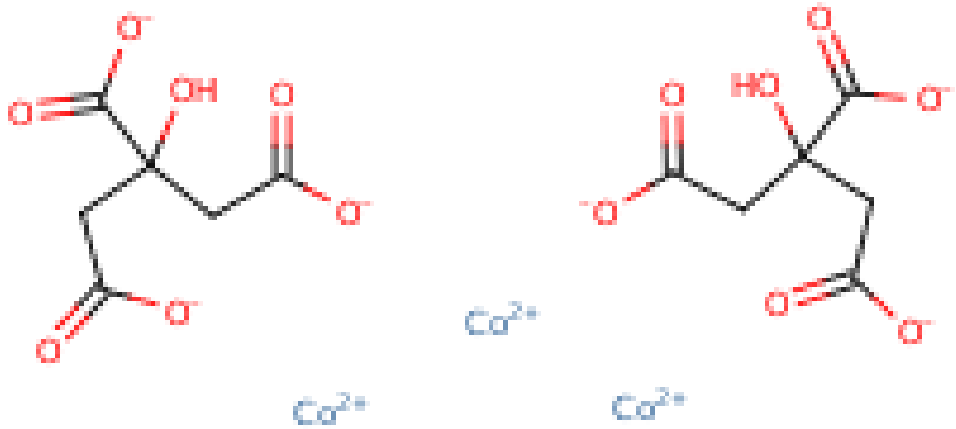
Last Update 27 November 2014

Chemical Identities

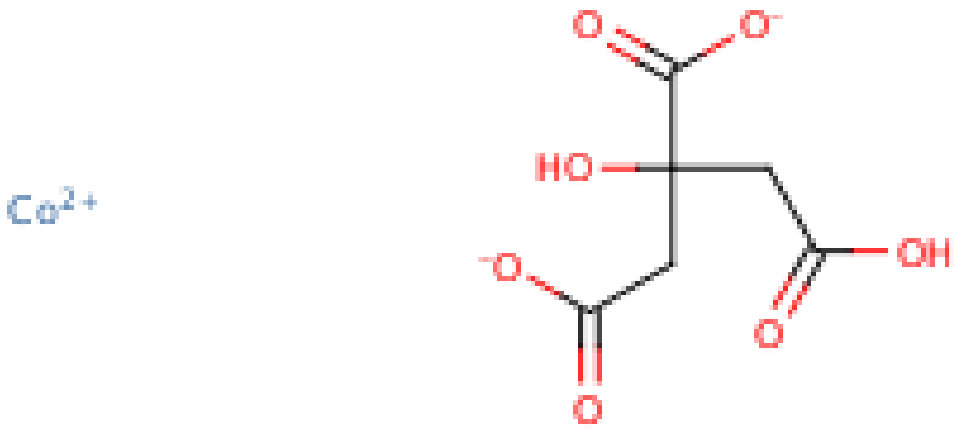
Chemical Name in the Inventory and Synonyms	**1,2,3-Propanetricarboxylic acid, 2-hydroxy-, cobalt(2+) salt (2:3)** Cobalt citrate Cobaltous citrate Citric acid, cobalt(2+) salt (2:3) Tricobalt dicitrate
CAS Number	866-81-9
Structural Formula	
Molecular Formula	C6H8O7.3/2Co
Molecular Weight	554.996

Chemical Name in the Inventory and Synonyms	**Cobalt chloride (CoCl2)** Cobaltous chloride Cobalt(II) chloride Cobaltous dichloride Dichlorocobalt Cobalt muriate
CAS Number	7646-79-9

Structural Formula	
Molecular Formula	Cl2Co
Molecular Weight	129.84

Chemical Name in the Inventory and Synonyms	**Cobalt(II) chloride, hexahydrate** Cobaltous chloride, hexahydrate Cobalt dichloride hexahydrate
CAS Number	7791-13-1
Structural Formula	
Molecular Formula	Cl2Co.6H2O
Molecular Weight	237.93

Chemical Name in the Inventory and Synonyms	**Citric acid, cobalt(2+) salt (1:1)** Cobalt(2+) hydrogen citrate

CAS Number	18727-04-3
Structural Formula	
Molecular Formula	C6H8O7.Co
Molecular Weight	249.039

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