Cobalt nitrate: Human health tier II assessment

27 November 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Nitric acid, cobalt(2+) salt, hexahydrate	10026-22-9
Nitric acid, cobalt(2+) salt	10141-05-6

Preface

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

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

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

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

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

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

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

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of chemicals contains cobalt dinitrate (CAS No. 10141-05-6) and its hydrated salt: cobalt dinitrate hexahydrate (CAS No. 10026-22-9). 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). Stopford et al., (2003) has highlighted the importance of the 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), cobalt chloride (CAS No. 7646-79-9) and other soluble cobalt compounds (NICNASa and b) have similar bioaccessibility and bioavailability in biological fluids to chemicals in this group, data available for these 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 calls for information, was less than 1000 tonnes for cobalt nitrate, hexahydrate (CAS No. 10026-22-9).

No specific Australian use information has been identified.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers; Galleria Chemica; and eChemPortal: OECD High Production Volume chemical program—OECD

HPV, the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported commercial use including:

- for preparation of catalysts;
- in metal surface treatments (e.g. galvanising and electroplating);
- in pigments; and
- as a corrosion inhibitor and anti-scaling agent.

The chemical has reported site-limited use including:

- as an intermediate for manufacturing computer, electronic and optical equipment, electrical batteries and accumulators; and
- as chemical intermediates.

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 chemical, cobalt dinitrate (CAS No. 10141-05-6) is listed on the EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; Article 15/Carcinogen, Mutagen, Reproductive toxicity (CMR).

The chemical cobalt nitrate (CAS No. 10141-05-6) 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.

Existing Worker Health and Safety Controls

Hazard Classification

The chemical cobalt nitrate (CAS No. 10141-05-6) is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Carc. Cat. 2; R49 (Carcinogenicity)

Muta. Cat. 3; R68 (Genotoxicity)

Repr. Cat. 2; R60 (Reproductive toxicity)

R42/43 (Sensitisation)

Exposure Standards

Australian

No specific exposure standards are available for chemicals in this group.

International

The following exposure standards are identified (Galleria Chemica).

The chemicals in this group have exposure limits (time weighted average -TWA) of 0.01–0.1 mg/m^3 in different countries such as USA (Washington), Canada (Alberta), Denmark and Ireland.

Health Hazard Information

Limited data are available for cobalt dinitrate (CAS No. 10141-05-6) and cobalt dinitrate hexahydrate (CAS No. 10026-22-9). Data are available for acute oral toxicity, skin and eye irritation and genotoxicity. In the absence of further toxicological data for these chemicals, it is expected that these will dissociate into the Co^{2+} ion in solution and have a similar hazard profile to soluble cobalt compounds due to high water solubility (REACH) of the chemicals.

The soluble cobalt compounds (NICNASa) were assessed under the IMAP Framework and are currently recommended for classification for carcinogenicity, genotoxicity and reproductive toxicity. In addition, soluble cobalt compounds (NICNASa, 2014) are classified for acute toxicity from oral exposure, skin and respiratory sensitisation and eye irritation. Also, these compounds are classified for repeated dose toxicity via inhalation.

Considering that cobalt sulfate (CAS No. 10124-43-3) and cobalt chloride (CAS No. 7646-79-9) have similar bioaccessibility and bioavailability in biological fluids to chemicals in this group (Stopford et al., 2003; CoRC, 2014a; CoRC, 2014b; CoRC, 2014c), these chemicals were used as analogue chemicals to assess the systemic hazards of chemicals in this group where there are data gaps, by reading across according to the principles of the OECD (2014).

Toxicokinetics

The chemicals cobalt dinitrate (CAS No. 10141-05-6) and cobalt dinitrate hexahydrate (CAS No. 10026-22-9) are soluble in water and are highly bioavailable (IARC, 1997; Stopford et al., 2003; Government of Canada, 2010; CoRC, 2014a).

Oral administration of soluble cobalt salts leads to nearly complete dissociation into the Co^{2+} ion and the anionic component. The amount of cobalt absorption in humans varies from 3–97 % depending on the type and dose of the cobalt compound given (Leggett, 2008). Women, as well as individuals with iron deficiencies, have increased 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 % of 100 mg/mL cobalt chloride hexahydrate (CAS No. 7791-13-1) (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 nitrate labelled with cobalt-57 (^{57}Co) was investigated in male beagle dogs. Dissolution of the inhaled particles was the primary mode of clearance. Particle size varied from 0.3 to 2.7 microns. The rate of dissolution was inversely proportional to particle size and ranged from six to 80 days. After initial inhalation, ^{57}Co was found predominately in the lungs, followed by muscles, bone and skin. After 400 days (biological half life), less than 10% of the initial

lung burden was present, although the presence of high concentrations of ^{57}Co in the trachea and upper respiratory tract at the time the animals died confirmed the long-term retention of cobalt in some tissues (Kreyling et al. 1986; ECHA, 2010)

Once absorbed, the cobalt ion is widely distributed in the body, including the skeleton, with the highest concentration found in the liver and kidney. Following intracardiac injection of cobalt dinitrate in rats, accumulation was found in the liver, kidneys and intestines (29 %, 10 % and 4.6 % of the dose, respectively) (ATSDR, 2001). After inhalation exposure, there is a high initial excretion in faeces but the primary route of elimination is via the kidneys in 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 orally administered cobalt sulfate (CAS No. 10124-43-3) results in a dose-dependent increase in cobalt levels in foetal blood and amniotic fluid (ATSDR, 2004).

Acute Toxicity

Oral

The chemicals, cobalt dinitrate (CAS No. 10141-05-6) and cobalt dinitrate hexahydrate (CAS No. 10026-22-9), have moderate acute toxicity in rats following oral gavage exposure. The available data warrant hazard classification.

The chemical cobalt dinitrate hexahydrate (CAS No. 10026-22-9) was tested through oral gavage exposure in a study similar to OECD Test Guideline (TG) 401 in male and female Wistar rats. The median lethal dose (LD50) value in rats was 691 mg/kg bw and was calculated for the anhydrous cobalt dinitrate as 434 mg/kg bw. Reported signs of toxicity included sedation and diarrhoea at the highest dose levels (Speijers et al., 1982).

In another study similar to OECD TG 401, cobalt dinitrate (CAS No. 10141-05-6) had an LD50 value of 978 mg/kg bw in male and female Sprague Dawley rats (CoRC, 2014a).

Dermal

No data are available for the chemicals in this group.

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

Inhalation

No data are available on chemicals in this group. Considering 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 (CDI, 2014).

Observation in humans

Human data are available for the analogue chemical cobalt chloride, which was established to be a suitable analogue (See **Category justification**).

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 repeated 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, cobalt dinitrate and cobalt dinitrate hexahydrate (CAS No. 10026-22-9) are considered to be corrosive to the skin.

The chemical cobalt dinitrate (CAS No. 10141-05-6) was tested in accordance with OECD TG 404. While the data available for the pure solid substance showed it to be only slightly irritating, when completely dissolved in water, it was found to have more severe effects, such as necrosis. Considering the high solubility of the chemicals in this group, contact with the skin as a solution could result in corrosive effects.

In a non guideline study, a 15 % solution of cobalt dinitrate (CAS No. 10141-05-6) was applied to the dorsal trunk of six rabbits for four hours as an 0.5 mL aliquot. After the four-hour exposure, residual sample was removed and observations were recorded immediately after removal of the patch, at 24 hours and 48 hours after the initial application. At the initial reading immediately after patch removal, 4/6 animals exhibited corrosive effects, which included spotted thickening and necrosis, which remained unchanged at the 48-hour reading. Spotted erythema was also noted (REACH).

In one study carried out according to OECD TG 404, solid cobalt dinitrate (CAS No. 10141-05-6) was applied to the dorsal trunk of three male New Zealand White rabbits for four hours as an 0.5 g aliquot of the test material slightly moistened with water, semiocclusively. According to the Draize scale, mean erythema and oedema scores at time points of 24, 48 and 72 hours were reported as 2, 1.67, and 1 (reversible within seven days) and 0.67, 0.33, and 0.33 (reversible within 72 hours), respectively. These cleared by the seventh day of observation and do not meet the criteria for classification (REACH).

Eye Irritation

On the weight of evidence, the chemical cobalt dinitrate (CAS No. 10141-05-6) was reported to irritate the eyes when tested according to OECD Test Guidelines (TG). Effects were sufficient to warrant hazard classification (refer to **Recommendation** section).

In a study carried out according to OECD TG 405, 95 mg of cobalt dinitrate (CAS No. 10141-05-6) was applied to the eye of one male New Zealand White rabbit. Moderate conjunctival redness (score of two) and moderate chemosis (score of three) were observed throughout the whole observation period and were not reversible within 21 days. Slight corneal opacity was observed one hour after administration, and was not reversible within 21 days. An iris score of one was obtained for slight inflammation, which was reversible within 14 days. The persistence of effects in the treated eye at the 21-day observation was considered to be indicative of irreversible ocular damage (REACH).

In studies carried out according to OECD TG 437 (in vitro), cobalt dinitrate (CAS No. 10141-05-6) was administered to bovine corneas for 240 minutes at a volume of 0.75 mL (20 % w/v). Each chemical test was performed in triplicate. After exposure, mean in vitro scores of 3.58 were determined for cobalt dinitrate (CAS No. 10141-05-6). The mean in vitro score for the negative control, with no increase in opacity or permeability of the corneas, was approximately 2.17, whereas the mean in vitro score for the positive control was approximately 156.46, with clear observations of opacity of the cornea, corresponding to a corrosive effect. Under the experimental conditions reported, cobalt dinitrate (CAS No. 10141-05-6) was not considered an eye irritant (REACH).

Sensitisation

Respiratory Sensitisation

Cobalt dinitrate (CAS No. 10141-05-6) is 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**) are available for the analogue chemical cobalt chloride, which was established to be a suitable analogue (see **Category justification**).

Skin Sensitisation

The chemical cobalt dinitrate (CAS No. 10141-05-6) is 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 cobalt sulfate (CAS No. 10124-43-3), and human data (refer to **Observations in humans**) available for cobalt chloride (CAS No. 7646-79-9) (NICNASa and b) support this classification, and the extension to the other chemical in this group.

A sensitisation rate of 40 % was seen at a challenge concentration of 0.01 % in an adjuvant and patch test (APT) study in female Hartley guinea pigs injected with Freund's complete adjuvant and induced using 3 % cobalt sulfate (CAS No. 10124-43-3) (NICNASa, REACH).

In another study using the guinea pig maximisation test, 11/15 Dunkin Hartley guinea pigs were sensitised when challenged with 0.3 % cobalt chloride hexahydrate (CAS No. 7791-13-1), 48 hours after challenge (NICNASb, REACH).

Observation in humans

Respiratory

Occupational inhalation exposure to cobalt chloride (CAS No. 7646-79-9) 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 study, 225/1415 patients and 24/373 patients showed a positive reaction to cobalt chloride when applied to the upper back using occlusive patches (REACH). There appears to be an increased incidence of positive testing in females compared with males in all tests (REACH). In an occupational study with 853 hard metal workers patch tested with an initial test of 1 % cobalt chloride (CAS No. 7646-79-9), 62 % showed a positive sensitisation reaction (REACH).

In another study, flaring of eczema was observed following oral administration of 1 mg of cobalt sulfate (CAS No. 10124-43-3) to cobalt-sensitised people, with exposure once a week for a duration of three weeks. The reported allergic dermatitis was considered a positive allergic response to cobalt (ATSDR, 2004).

Repeated Dose Toxicity

Oral

No data are available for oral repeated dose toxicity for chemicals in this group. Reading across from soluble cobalt compounds (NICNASa), the main effect of the chemicals in this group with repeated oral exposure is polycythaemia (increased erythrocytes), which is reversible after the exposure ceases.

This is based on high quality data for cobalt chloride, which has been established to be a suitable analogue (See **Category justification**).

Some effects of cobalt administration are the promotion of polycythaemia, increased haematocrit and increased haemoglobin levels which are all 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 NOAEL was 2.5 mg/kg bw/day and the LOAEL was 10 mg/kg bw/day based upon dose- and time-related increases in haemoglobin content and numbers of erythrocytes (ATSDR, 2004; US HPV, 2005). In another longer-term study over seven months, oral doses of 0.2 and 10 mg/kg bw/day 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).

The available data on a analogue chemical, cobalt chloride hexahydrate (CAS No. 7791-13-1), reported increased heart weight in male rats exposed to 122 mg/kg bw/day of the chemical in drinking water and 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).

In two separate non-guideline studies by the same research group, 40 mg/kg bw/day of cobalt sulfate heptahydrate (CAS No. 10026-24-1) was administered in drinking water over 16 or 24 weeks in one study and 24 weeks in the other study. After the exposure period, animals in the first two groups (16 or 24 weeks) were euthanised and ventricular function was determined on a working-model Langendorff's circuit. In the first study, myocardial cobalt concentration was significantly increased in both exposure groups and there was a significant decrease in body weights of both groups compared with corresponding controls. Only the 24-week exposure in the first study resulted in left ventricular hypertrophy and impaired left ventricular systolic and diastolic function (Haga et al., 1996). In the second study, decreased enzyme activity in cardiac tissues (manganese-superoxide dismutase, succinate-cytochrome C oxidase, NADH-cytochrome C reductase), decreased mitochondrial ATP production rate and a reduction in the capacity of the respiratory chain were observed (Clyne et al., 2001; ATSDR, 2004).

In another study designed to simulate alcohol-related cobalt cardiomyopathy, 95 mg/kg bw/day of cobalt sulfate heptahydrate (CAS No. 10026-24-1) was administered to guinea pigs by gavage either alone or in combination with ethanol for five weeks. Although there was clear cardiomyopathy, alcohol did not intensify the cardiac effects (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 the dermal route 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.

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 post treatment (ATSDR, 2004).

As a result of cobalt's effects which have the 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 2–2.4 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 dinitrate (CAS No. 10141-05-6) is classified as hazardous: Category 3 mutagenic substance, with the risk phrase ‘Possible risk of irreversible effects’ (Xn; 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).

Limited genotoxicity data are available for this group of chemicals. Based on the high solubility of the chemicals in this group, genotoxicity data will be read-across from the NICNAS assessment of soluble cobalt compounds (NICNASa).

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 *S. 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 *S. typhimurium* (strain TA100, TA98 and TA1535). Positive results were obtained for chromosomal aberrations and aneuploidy in plant cells, in production of reactive oxygen species (ROS) (observed as degradation of 2-deoxyribose), 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).

Negative results were obtained for cobalt dinitrate (CAS No. 10141-05-6) in test systems for chromosomal aberrations (numerical) in two human cell lines (diploid fibroblasts with a dose of 0.08 μM and mononuclear leucocytes with a dose of 0.8 μM) without metabolic activation (IARC, 2006).

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

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 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 a single oral dose 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 significant increases in cells with structural and numerical chromosome aberrations or micronucleated polychromatic erythrocytes in SD rats (REACH).

Cobalt acetate (CAS No. 71-48-7) caused DNA base damage (attributed to products of hydroxyl radical attack) in the liver, kidney and lung in male and female Fischer 344/NCr rats following 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 (CAS No. 10026-24-1) did not cause genotoxic effects in a mammalian bone marrow chromosome aberration test, in groups of four SD rats administered a single oral gavage dose of 80, 160 or 320 mg/kg bw (REACH).

Positive results were obtained from the *Drosophila* wing somatic mutation and recombination test (SMART) which induced loss of heterozygosity in *D. melanogaster* after treatment with 1 mM cobalt dinitrate hexahydrate (CAS No. 10026-22-9). Defective meiotic recombination and disjunction, DNA repair and cell proliferation were observed (IARC, 2006).

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, 2014b).

Carcinogenicity

The chemical cobalt dinitrate (CAS No. 10141-05-6) is classified as hazardous: Category 2 carcinogenic substance, with the risk phrase ‘May cause cancer by inhalation’ (T; R49) in HSIS (Safe Work Australia). Based on the high solubility of the chemicals in this group, carcinogenicity data will be read-across from the NICNAS assessment of soluble cobalt compounds (NICNASa). 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 the other chemical 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 dinitrate (CAS No. 10141-05-6) is classified as hazardous: Category 2 substance toxic to reproduction, with the risk phrase ‘May impair fertility’ (T; R60) in HSIS (Safe Work Australia). Based on the high solubility of the chemicals in this group, reproductive and developmental toxicity data will be read-across from the NICNAS assessment of soluble cobalt compounds (NICNASa). The available data on analogue chemicals, cobalt chloride (CAS No. 7646-79-9) and cobalt sulfate heptahydrate (CAS No. 10026-24-1), support this classification and the extension of this classification to the other chemical in this 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 administered 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

Male Wistar rats were exposed to 0.01 % of cobalt dinitrate (CAS No. 10141-05-6) in drinking water, resulting in a dose of 20 mg/kg bw/day. Treatment resulted in increased sensitivity and decreased maximal response to a cholinergic agonist, which blocks the actions of acetylcholine, a neurotransmitter found at neuromuscular junctions and many sites in the central nervous system (Vassilev et al., 1993; ATSDR, 2004).

Based on the high solubility of the chemicals in this group, neurotoxicity data will be read-across from the NICNAS assessments of soluble cobalt compounds (NICNASa).

Endocrine Disruption

Based on the high solubility of the chemicals in this group, endocrine disruption data will be read-across from the NICNAS assessments of soluble cobalt compounds (NICNASa, 2014).

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 (corrosivity, 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 use of chemicals in this group, 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 could 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 might 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 burns (C; R34)	Causes serious eye damage - Cat. 1 (H318) Causes severe skin burns and eye damage - Cat. 1B (H314)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	May cause sensitisation by inhalation (Xn, R42) May cause sensitisation by skin contact (Xi; R43)	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 2 - May cause cancer by inhalation (T; R49)	May cause cancer - Cat. 1B (H350i)
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, 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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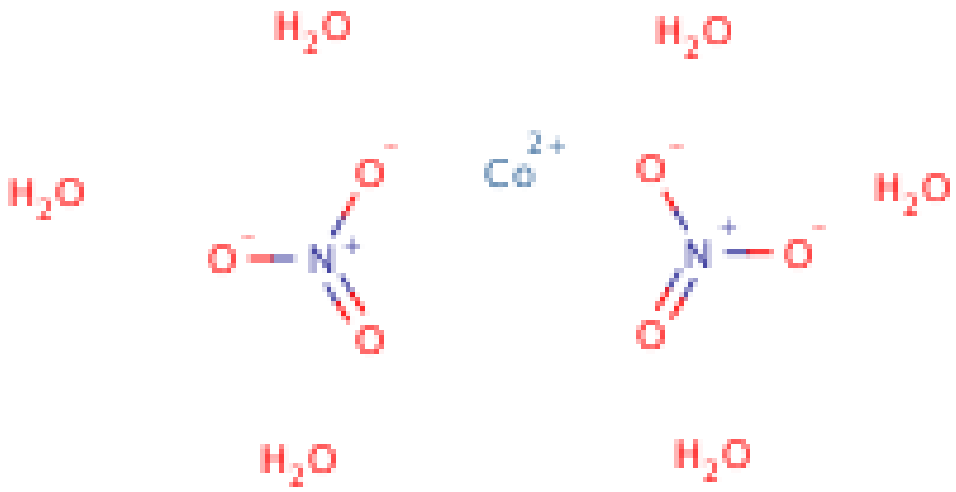
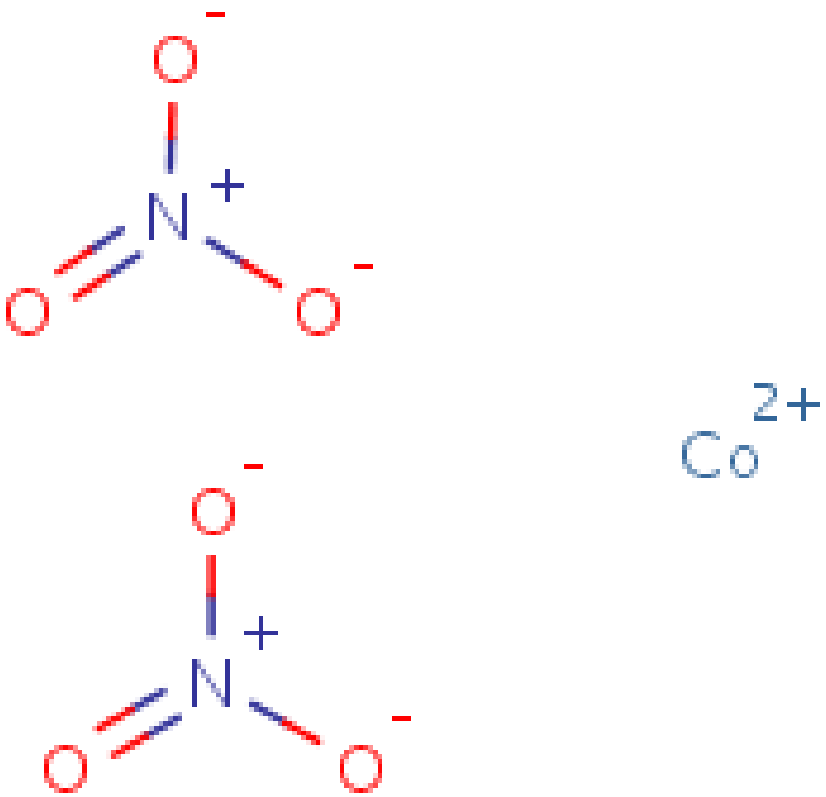
Last Update 27 November 2014

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Nitric acid, cobalt(2+) salt, hexahydrate** Cobalt(II) dinitrate, hexahydrate Cobaltous nitrate hexahydrate

CAS Number	10026-22-9
Structural Formula	
Molecular Formula	Co.6H2O.2HNO3
Molecular Weight	291.03

Chemical Name in the Inventory and Synonyms	**Nitric acid, cobalt(2+) salt** Cobalt(II) nitrate Cobalt dinitrate Cobalt bis(nitrate) Cobaltous nitrate
CAS Number	10141-05-6
Structural Formula	

	
Molecular Formula	Co.2HNO3
Molecular Weight	182.94

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