Cobalt salts of 2-ethylhexanoic acid and related compounds: Human health tier II assessment

27 November 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Hexanoic acid, 2-ethyl-, cobalt(2+) salt	136-52-7
Hexanoic acid, 2-ethyl-, cobalt salt	13586-82-8
Cobalt, 2-ethylhexanoate, isononanoate complexes	68478-57-9

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 consists of cobalt salts of 2-ethylhexanoic acid (2-EHA) and may also be referred to as cobalt soaps or cobalt salts of fatty acids. Cobalt salts with unspecific oxidation states are expected to be predominantly in the Co^{2+} state. The toxicological effects are distinct from other metal salts due to the toxic effects of the 2-EHA anion. The chemicals within this group are expected to have similar toxicological effects given the health effects are driven by both the Co^{2+} ion and the fatty acid component of these chemicals, 2-EHA.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the chemicals in this group.

International

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

The following commercial uses have been identified for cobalt 2-ethylhexanoate (CAS No. 136-52-7):

- as a corrosion inhibitor;
- as a preservative;
- as a coating additive, drier or colouring agent in paint, lacquers and varnishes;
- in metal surface treatments; and
- as a filler, adhesive in binding agents or construction material.

The following site limited use has been identified for cobalt 2-ethylhexanoate (CAS No. 136-52-7):

- as a chemical intermediate.

The following non-industrial uses have been identified for cobalt 2-ethylhexanoate (CAS No. 136-52-7):

- as agricultural pesticide.

Restrictions

Australian

Cobalt and its compounds are listed in Schedule 10 (prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals) of the Work Health and Safety Regulations (WHS, 2014) for restricted use in abrasive blasting at a concentration of greater than 0.1 % cobalt.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals in this group are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

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 0.05–5 mg/m^3 in different countries such as USA (Washington), Canada (Yukon), Ireland and Russia.

Health Hazard Information

The health hazards associated with the chemicals in this group are predominately driven by the Co^{2+} ion. The fatty acid component of these chemicals, in this case 2-ethylhexanoate (2-EHA) (CAS No. 149-57-5), has been assessed by NICNAS. The chemical 2-EHA is classified for skin irritation and reproductive and developmental toxicity (refer to **Recommendation section**) (NICNASa). The skin irritation effects of 2-EHA are associated with the acidity of this chemical, and are not expected to be manifested by salts of 2-EHA. The branched nonanoic acid (C9) in the other chemical (CAS No. 84215-43-0) is closely related to 2-ethylhexanoic acid. As both have branching at the second position and a longest chain length of six, it is considered that 2-EHA would be a worst case analogue for this acid.

The Co^{2+} cation is considered to be the moiety responsible for the majority of the 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). Cobalt 2-ethylhexanoate (CAS No. 136-52-7) has similar bioaccessibility and bioavailability in biological fluids to soluble cobalt compounds and is expected to readily release Co^{2+} in aqueous solutions (Stopford et al, 2003).

Considering that toxicological data are only available for acute oral toxicity, skin and eye irritation for one of the chemicals in this group, the health effects from exposure to the Co^{2+} component of the metal fatty acids were read-across from studies assessed by NICNAS on soluble cobalt compounds (NICNASb) and the chemical, 2-EHA (NICNASa). The assessed soluble cobalt compounds (cobalt chloride and cobalt sulfate) are currently classified for carcinogenicity, genotoxicity, reproductive toxicity, acute toxicity by the oral route of exposure, repeat dose toxicity via inhalation, skin and respiratory sensitisation, and eye irritation (NICNASb; NICNASc).

Toxicokinetics

This group of chemicals consists of cobalt salts of 2-ethylhexanoic acid, which may also be referred to as cobalt soaps. Studies have demonstrated that one of the chemicals from this group (cobalt 2-ethylhexanoate, CAS No. 136-52-7) is almost completely dissolved in simulated human body fluids including: artificial gastric juice (pH 1.5)—100 %, artificial interstitial fluid (pH 7.4)—50.8 %, artificial alveolar fluid (pH 7.4)—100 %, artificial serum (pH 7.4)—100 % and artificial lysosomal fluid (pH 4.5–5.0)—100 % (Stopford et al., 2003).

Oral administration of soluble cobalt soaps leads to nearly complete dissociation into the Co^{2+} ion and the fatty acid component of these chemicals. The amount of cobalt absorption in humans varies from 3-97 % depending on the type and dose of the cobalt compounds given (Leggett, 2008).

Dermal absorption of cobalt has been demonstrated to be relatively low (NICNASb).

In an in vitro study, percutaneous absorption of soluble cobalt through human skin was 1.08 % from a 100 mg/mL cobalt chloride hexahydrate (CAS No. 7791-13-1) (NICNASb; 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. 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 phagocytosed 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 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

Chemicals in this group have low acute toxicity in animal tests following oral exposure.

In a study carried out according to OECD Test Guideline (TG) 425, the median lethal dose (LD50) in female Sprague Dawley (SD) rats is > 2000 mg/kg bw of cobalt 2-ethylhexanoate (CAS No. 136-52-7). Observed sub-lethal effects included nasal and mouth discharge, irregular respiration, hyperactivity, hunched posture, anogenital staining and diarrhoea (REACH).

Dermal

No data are available.

Given that the toxicokinetics 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. It has been reported that due to the physical properties of the chemicals in this group being predominantly waxy solids, the compounds are not able to be created into an inhalable atmosphere and testing is considered to not be technically feasible (CoRC, 2014).

Corrosion / Irritation

Skin Irritation

On the weight of evidence, chemicals in this group are not considered to be skin irritants. Two in vitro studies performed in accordance with OECD TG 439 and 431, using cobalt 2-ethylhexanoate (CAS No. 136-52-7) suggest that the chemicals are not skin irritants.

In an in vitro study carried out according to OECD TG 439, cobalt 2-ethylhexanoate (CAS No. 136-52-7) was introduced for 15 minutes at a dose of 11 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 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 88 % for cell viability. As this value is above the 50 % viability threshold, the substance was not considered to be an irritant (REACH).

In another in vitro study carried out according to OECD TG 431, cobalt 2-ethylhexanoate (CAS No. 136-52-7) was introduced for three or 60 minutes, at a dose 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 MTT assay was performed. Scores obtained after the three and 60 minute treatments were 106.9 % and 80.7 % for cell viability. 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 2-ethylhexanoate (CAS No. 136-52-7) was not considered to be corrosive (REACH).

Eye Irritation

The chemicals in this group are considered to be eye irritants based on in vivo data for one chemical. However, the severity of the effects only met the classification criteria under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and not the Approved Criteria (HSIS).

In an in vivo study carried out according to OECD TG 405, cobalt 2-ethylhexanoate (CAS No. 136-52-7) was applied to the eyes of three New Zealand White rabbits. Marked reddening of the conjunctivae were observed in two female animals one hour after treatment and slight reddening was observed in the male animal 24 hours after treatment. Overall irritation results 24, 48 and 72 hours after application per animal are as follows: corneal opacity - 0.0, 1.0, 1.0; iritis - 0, 0, 0; conjunctival redness - 1.0, 3.0, 2.33 and conjunctival oedema - 0.0, 1.33 and 1.33. Slight chemosis and ocular discharge were observed in two female animals, these effects were transient and resolved during the 14 day study. (REACH).

In an in vitro study carried out according to OECD TG 437, cobalt 2-ethylhexanoate (CAS No. 136-52-7) 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, a mean in vitro score of 0 was determined. 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 250.6, with clear observations of opacity and distinctive permeability of the cornea, corresponding to a corrosive effect. Under the experimental conditions reported, cobalt 2-ethylhexanoate (CAS No. 136-52-7) was not considered an eye irritant (REACH).

Sensitisation

Respiratory Sensitisation

No data are available on the chemicals in this group. Although an inhalable atmosphere is not technically feasible with cobalt soap complexes (due to their waxy physical properties), in downstream processes where these chemicals are included in mixtures and effectively acting like soluble cobalt compounds, inhalation could be possible. Therefore, using a read across approach from human data available on analogue chemical, cobalt chloride hexahydrate (CAS No. 7791-13-1) (refer to **Observations in humans**), hazard classification is warranted for these chemicals.

Skin Sensitisation

No animal data are available on the chemicals in this group. However, based on read across animal data on the soluble cobalt chemical, cobalt sulfate (CAS No. 10124-43-3) and human data on cobalt 2-ethylhexanoate (CAS No. 136-52-7) and cobalt chloride hexahydrate (CAS No. 7791-13-1) (refer to **Observations in humans**), hazard classification is warranted for these chemicals.

In a non guideline adjuvant and patch test (APT) 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 % (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, 2011).

Skin

A case report of occupational allergic contact dermatitis caused by cobalt 2-ethylhexanoate (CAS No. 136-52-7) was reported in a 52 year old man who worked as an offset printer for 35 years. The patient displayed hand eczema for 12 years. Patch testing revealed an allergic reaction in the standard series to cobalt chloride. Two ink driers from work containing 5% and 2% cobalt 2-ethylhexanoate (CAS No. 136-52-7), respectively, elicited allergic reactions in a dilution series (Kanerva et al, 1996).

In a study conducted in human volunteers, skin patch tests showed a positive reaction in 286/4034 patients to 1 % cobalt chloride (CAS No. 7646-79-9) in petroleum jelly 24 hours after exposure (REACH). In another two patch test study, 225/1415 patients and 24/373 patients showed a positive reaction to cobalt chloride when applied to the upper back using occlusive patches (REACH). There appears to be an increased incidence of positive testing in females compared with males in all tests (REACH). In an occupational study with 853 hard metal workers patch tested with an initial test of 1 % cobalt chloride (CAS No. 7646-79-9), 62 % showed a positive sensitisation reaction (REACH).

In another study, flaring of eczema was observed following an oral administration of 1 mg of cobalt sulfate (CAS No. 10124-43-3) to cobalt-sensitised people, with exposure to the chemical 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 on the chemicals in this group. Reading across from the soluble cobalt compounds (NICNASa), the main effect of the chemicals in this group with repeated oral exposure is expected to be 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.

Some effects of cobalt administration are the promotion of polycythaemia, increased haematocrit and increased haemoglobin levels which are reversible shortly after exposure ceases. In a short-term repeated dose oral dosing study of SD rats administered with 0, 2.5, 10 and 40 mg/kg bw/day 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). 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 per 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 cobalt chloride hexahydrate (CAS No. 7791-13-1) 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 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. 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 (Mn SOD), succinate-cytochrome C oxidase, NADH-cytochrome C reductase and 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 for chemicals in this group.

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

Inhalation

No data are available on the chemicals in this group. Although an inhalable atmosphere is not technically feasible with cobalt soap complexes (due to their waxy physical properties), in downstream processes where these chemicals are included in mixtures and effectively acting like soluble cobalt compounds, inhalation could be possible.

While it appears that the available bioaccessibility data on alveolar fluid do not correlate with acute inhalation toxicity and repeated dose toxicity via the inhalation route, inhalation toxicity appear to correlate with the available bioaccessibility data on lysosomal fluid. It has been reported by Ortega et al., (2014) that phagocytosis followed by release of solubilised Co^{2+} and macrophage contents (for components bioavailable in lysosomal fluid) may be a route for toxicity, which can explain the lack of correlation between bioaccessibility in alveolar fluid and acute inhalation toxicity and repeated dose toxicity via the inhalation route. Considering that cobalt 2-ethylhexanoate (CAS No. 136-52-7) is almost completely dissolved in both artificial alveolar fluid and artificial lysosomal fluid (Stopford et al., 2003) similarly to cobalt sulfate, it is prudent to read-across data from soluble cobalt compounds.

Based on read across data on soluble cobalt chemicals (NICNASb), chemicals in this group are expected to cause serious damage to health by prolonged exposure via inhalation. A lowest observable adverse effect concentration (LOAEC) of 0.3 mg/m^3 cobalt sulfate heptahydrate (CAS No. 10026-24-1) was identified for local effects on the larynx. The available data on the 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 on 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 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 was less severe (NTP, 1998).

Observation in humans

A read-across approach was taken from data available on analogue chemicals, cobalt sulfate heptahydrate (CAS No. 10026-24-1) and cobalt chloride (CAS No. 7646-79-9).

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 2–2.4 mg/kg/day of cobalt chloride (CAS No. 7646-79-9), it did not prevent the common occurrence of decreasing levels of haemoglobin and haematocrit levels observed during pregnancy. There were also no effects observed on the heart, in liver function or obvious birth defects (ATSDR, 2004).

Genotoxicity

Limited data are available on one of the chemicals in this group. Based on the high solubility of the chemicals in this group, genotoxicity data can be read-across from the NICNAS assessment of soluble cobalt compounds (NICNASb; NICNASc). It was concluded that effective protective processes exist in vivo to prevent genotoxicity in human (OECD, 2014) and hence, no classification is required (NICNASb; NICNASc).

In vitro

In a study carried out according to OECD TG 476, cobalt 2-ethylhexanoate (CAS No. 136-52-7) did not induce mutation at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus of L5178Y mouse lymphoma cells when tested at concentrations of 10 to 150 μg/ml (up to toxic concentrations) for three hours in the absence and presence of a rat liver metabolic activation system (S9) in a single experiment (REACH).

Carcinogenicity

No data are available on the chemicals in this group. Although an inhalable atmosphere is not technically feasible with cobalt soap complexes (due to their waxy physical properties), in downstream processes where these chemicals are included in mixtures and effectively acting like soluble cobalt compounds, inhalation could be possible. Therefore, read across data on the soluble cobalt analogue chemical cobalt sulfate heptahydrate (CAS No. 10026-24-1), support hazard classification for chemicals in this 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 per day, five days per 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 1.0 mg/m^3 and higher. 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 carcinogenic 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.

The NTP study 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).

Reproductive and Developmental Toxicity

No data are available on the chemicals in this group. However, the available data on the analogue chemicals cobalt chloride (CAS No. 7646-79-9), cobalt sulfate heptahydrate (CAS No. 10026-24-1) and hexanoic acid, 2-ethyl (CAS No. 149-57-5) support hazard classification for chemicals in this group.

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 increased 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

The chemical, hexanoic acid, 2-ethyl (CAS No. 149-57-5) was reported to cause developmental toxicity in several studies in rats following exposure via the oral route (REACH; NICNASa). These effects were noted in the absence of signs of maternal toxicity. The lowest developmental toxicity LOAEL was reported to be 100 mg/kg bw/day.

In a developmental toxicity study, pregnant female Wistar rats were administered the chemical on gestation days 6–19 via drinking water at 0, 100, 300 or 600 mg/kg bw/day (REACH; NICNASa). Skeletal variations in foetuses were observed at the lowest dose. A dose-dependent increase in club foot was observed in foetuses of the treatment group (statistically significant at the highest and intermediate dose); this anomaly was not observed in any foetuses of the control group. A statistical increase in wavy ribs was also observed in the foetuses of all treatment groups compared to controls. A dose-dependent increase in malformation of the legs, reported as 'flabby legs (external, slightly paralysed)' was also observed in foetuses of all treatment groups; this was not observed in any foetuses of the control group. The maternal toxicity LOAEL was reported as 300 mg/kg bw/day (REACH), and a developmental toxicity LOAEL of 100 mg/kg bw/day was reported (REACH; NICNASa).

Foetal skeletal variations, malformations, reduced foetal body weights and early foetal deaths have also been reported in several other developmental toxicity studies in rats following oral exposure to the chemical (REACH; NICNASa). For each of these studies, developmental effects were observed in the absence of maternal toxicity.

While maternal effects are expected from the Co^{2+} ion at a dose (10 mg/kg bw/day) an order of magnitude below the dose (100 mg/kg bw/day) resulting in developmental toxicity, these effects are not considered adverse (refer **Repeated dose toxicity - Oral** section). Therefore, based on read-across data on hexanoic acid, 2-ethyl (CAS No. 149-57-5), developmental effects are expected from chemicals in this group that are not secondary to maternal toxicity.

While there are several non-guideline studies on developmental toxicity with soluble cobalt chemicals, it is difficult to draw firm conclusions about the developmental toxicity of these chemicals due to various methodological deficiencies. Testing is underway for this endpoint.

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) and local effects (skin sensitisation and respiratory sensitisation). The chemicals may also cause toxic effects following repeated exposure through inhalation and eye irritation.

Public Risk Characterisation

The chemicals in this group have no identified uses in Australia. Overseas, it has been indicated that metal soaps are used as coating additives, driers or colouring agents in paints, lacquers and varnishes. Although the public could come into contact with articles/coated surfaces containing chemicals in this group, it is expected that the chemicals will be bound within the article/coated surface and hence will have reduced bioavailability. Therefore the risk to the public is not considered to be unreasonable.

Occupational Risk Characterisation

Based on overseas use, it is possible that the chemicals in this group may be used commercially. During use of chemicals in this group, dermal, ocular and inhalation exposure of workers to these chemicals may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemicals at lower concentrations may also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical long-term systemic effect and local long-term effects, these chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemicals are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

The data available support 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 (NICNASb) 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

Should information become available that identifies use of these chemicals in Australia, a Tier III assessment may be necessary to determine whether exposure controls are required to offer adequate protection to workers.

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 chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

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]
Irritation / Corrosivity		Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	May cause sensitisation by inhalation (Xn, R42) May cause sensitisation by skin contact (Xi; R43)	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
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) Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)	May damage fertility. Suspected of damaging the unborn child - Cat. 1B (H360Fd)

[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.

References

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

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.nohsc.gov.au/pdf/Standards/approved_criteriaNOHSC1008_2004.pdf

Clyne N, Hofman-Bang C, Haga Y, Hatori N, Marklund SL, Pehrsson SK and Wibom R. 2001. Chronic cobalt exposure affects antioxidants and ATP production in rat myocardium. Scandinavian Journal of Clinical and Laboratory Investigation 61 (8) pp 609-614.

Cobalt Development Institute 2014. The In Vitro Percutaneous Absorption of Cobalt Through Human Skin. Testing facility: Charles River, Tranent Edinburgh. Testing Facility Study No. 785464, Report No. 30161. An unpublished report to the Cobalt Development Institute, Guildford, Surrey, United Kingdom. CDI/37.

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.

Galleria Chemica. Accessed May 2014 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2013. Fifth edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html

Government of Canada 2011. Cobalt (7440-48-4), Cobalt chloride (7646-79-9), Sulfuric acid, cobalt (2+) salt (1:1) (10124-43-3) & Sulfuric acid, cobalt salt (10393-49-4). Batch 10 Challenge Substances. Accessed May 2014 at http://www.ec.gc.ca/ese-ees/8E18277B-457E-4073-8F27-EF5878648820/batch10_4substances%281%29_en.pdf

Haga Y, Clyne N, Hatori N, Hoffman-Bang C, Pehrsson SK and Ryden L 1996. Impaired myocardial function following chronic cobalt exposure in an isolated rate heart model. Trace Elements and Electrolytes 13 (2) pp 69-74.

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 March 2014 at http://www.who.int/ipcs/publications/cicad/cicad69%20.pdf

Kanerva L, Jolanki R & Estlandre T 1996. Offset printer's occupational allergic contact dermatitis caused by cobalt-2-ethyhexanoate. Contact Dermatitis 34 (6) pp. 390 - 396.

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

National Industrial Chemical Notification and Assessment Scheme (NICNASa). Tier II Human health assessment for hexanoic acid, 2- ethyl-. Australian Government Department of Health. Accessed May 2014 at http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=787

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

National Industrial Chemicals Notification and Assessment Scheme (NICNASc). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for Cobalt chloride and citrates. Available at http:www.nicnas.gov.au

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

Ortega R, Bresson C, Darolles C, Gautier C, Roudeau S, Perrin L, Janin M, Floriani M, Aloin V, Carmona A, Malard V. (2014) Low-solubility particles and a Trojan-horse type mechanism of toxicity: the case of cobalt oxide on human lung cells. Part Fibre Toxicol. 11:14.

REACH Dossier. Cobalt bis(2-ethylhexanoate) (CAS No. 136-52-7). Accessed May 2014 at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c842f34-96e1-0c52-e044-00144f67d249/AGGR-55af2dc9-30e4-45c2-a97f-6aead3967721_DISS-9c842f34-96e1-0c52-e044-00144f67d249.html#section_1.1

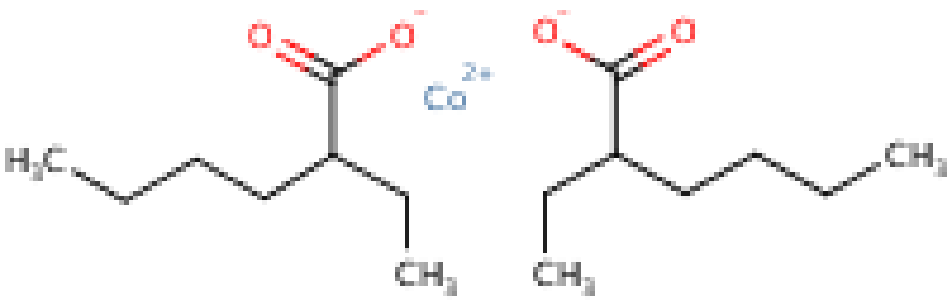
Stopford W, Turner J, Cappellini D & Brock T 2003. Bioaccessibility testing of cobalt compounds. Journal of Environmental Monitoring 5 (pp. 675-680).

The Cobalt REACH Consortium Ltd. 2014. Chemical Safety Report for Cobalt bis(2-ethylhexanoate), CAS RN 136-52-7 EC Number 205-250-6. March 2014. Unpublished report submitted to National Industrial Chemicals Notification and Assessment Scheme under the Inventory Multi-tiered Assessment and Prioritisation framework.

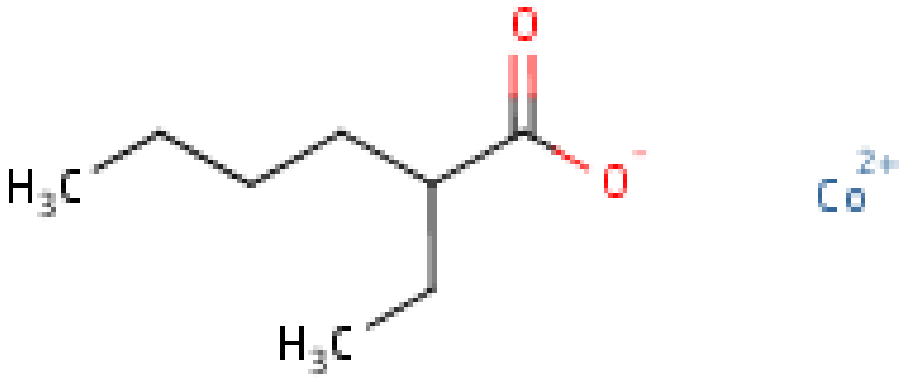
Work Health and Safety (WHS) Regulations 2011. Schedule 10 - Prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals. Accessed May 2014 at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/616/Model-WHS-Regulations-January-2014.pdf Last Update 27 November 2014

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Hexanoic acid, 2-ethyl-, cobalt(2+) salt** Cobalt octoate 2-Ethylhexanoic acid, cobalt salt Cobalt bis(2-ethylhexanoate) Cobalt 2-ethyl hexanoate Hexanoic acid, 2-ethyl-, cobalt(2+) salt (2:1)
CAS Number	136-52-7
Structural Formula	

	
Molecular Formula	C8H16O2.1/2Co
Molecular Weight	345.34

Chemical Name in the Inventory and Synonyms	**Hexanoic acid, 2-ethyl-, cobalt salt** Cobalt 2-ethyl hexanoate 2-Ethylhexanoic acid, cobalt salt Hexanoic acid, 2-ethyl-, cobalt salt (1:?)
CAS Number	13586-82-8
Structural Formula	

	
Molecular Formula	C8H16O2.xCo
Molecular Weight	202.14

Chemical Name in the Inventory and Synonyms	**Cobalt, 2-ethylhexanoate, isononanoate complexes** Cobalt, 2-ethylhexanoate, branched nonanoate
CAS Number	68478-57-9
Structural Formula	**No Structural Diagram Available**

Molecular Formula	Unspecified
Molecular Weight	Unspecified

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