Cobalt salts of organic acids: Human health tier II assessment

27 November 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Octanoic acid, cobalt salt	6700-85-2
Neodecanoic acid, cobalt salt	27253-31-2
tert-Decanoic acid, cobalt(2+) salt	84195-99-3
Isooctanoic acid, cobalt(2+) salt	84255-51-6

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 contain related cobalt salts of carboxylic acids and are members of the cobalt soap group. The chemicals within this group are expected to have similar toxicological effects given the health effects are primarily driven by the Co^{2+} ion. Therefore, these chemicals can be assessed together.

The dissociation of the chemicals is dependent on pH. A study on cobalt neodecanoate (CAS No. 27253-31-2) has shown a moderate dissociation at neutral pH (pH 7.4) and complete dissociation at low pH (pH 1.5 (Stopford et al, 2003). For example, in the stomach it is expected that cobalt neodecanoate complexes (CAS No. 27253-31-2) will completely dissociate into neodecanoic acid and cobalt(US EPA, 2008).

Considering the limited data on chemicals in this group, data from soluble cobalt compounds can be read-across from studies assessed by NICNAS on soluble cobalt compounds (NICNASa) according to the principles of OECD (2014). This is possible as the chemicals in this group are expected to have similar bioaccessibility and bioavailability in artificial gastric and lysosome fluids, and to some extent in alveolar, interstitial and serum fluids, as soluble cobalt compounds such as cobalt sulfate heptahydrate and cobalt chloride (Stopford et al, 2003).

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

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 the majority of chemicals in this group:

- as coating additive, driers or colouring agents in paint, lacquers and varnishes;
- in metal surface treatments;
- as plastic degradants; and
- as fillers and rubber adhesives in binding agents or construction material.

Site limited use as chemical intermediates has been identified for the majority of chemicals in this group.

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 the 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

Considering that toxicological data are only available for acute oral toxicity, skin and eye irritation for two of the chemicals in this group, the health effects from exposure to the dissociated Co^{2+} component of the metal fatty acids were read-across from studies assessed by NICNAS on soluble cobalt compounds (NICNASa).

The assessed soluble cobalt compounds (NICNAS) have been recommended for hazard classification for carcinogenicity, genotoxicity, reproductive toxicity and acute toxicity by the oral route of exposure, repeated dose toxicity via inhalation, skin and respiratory sensitisation, and eye irritation (NICNASa; NICNASb).

Toxicokinetics

This group of chemicals consists of closely related cobalt salts of C-8 or C-10 carboxylic acids and may also be referred to as cobalt soaps or cobalt salts of fatty acids. Studies have demonstrated that one of the chemicals from this group (cobalt neodecanoate (CAS No. 27253-31-2)) is dissolved in simulated human body fluids including: artificial gastric juice (pH 1.5)—100 %; artificial intestinal fluid (pH 7.4)—30.8 %; artificial interstitial fluid (pH 7.4)—43.1 %, artificial alveolar fluid (pH 7.4)—26.1 %, artificial serum (pH 7.4)—46.6 % 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 components 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). A study by Firrolo et al. (1999) demonstrated that upon oral administration; absorption, disposition and elimination of various cobalt salts were the same, and that the original identity of the salts do not affect cobalt ion absorption in vivo once the compounds have dissociated (Firrolo et. al., 1999).

Dermal absorption of cobalt has been demonstrated to be relatively low (NICNASa). In an in vitro study, percutaneous absorption of soluble cobalt through human skin was 1.08 % from a 100 mg/mL cobalt chloride hexahydrate (CAS No. 7791-13-1) (NICNASa; CDI, 2014). Absorption through intact skin of guinea pigs was very low (<1 %) while absorption through abraded skin was almost 80 % after a three-hour exposure (ATSDR, 2004).

Absorption following inhalation exposure to cobalt depends on the particle size. 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.

Acute Toxicity

Oral

The chemicals in this group were of moderate acute toxicity in animal tests following oral exposure. The data available for cobalt neodecanoate (CAS No. 27253-31-2) warrant hazard classification.

In a study carried out according to OECD Test Guideline (TG) 425, the median lethal doses (LD50) in female Crj:CD(SD) rats was 1098 mg/kg bw for cobalt neodecanoate (CAS No. 27253-31-2). Observed sub-lethal effects included ocular discharge, laboured breathing, diarrhoea, lethargy, ataxia, decreased muscle tone, brown discharge from the vulva and prostrate posture (REACH).

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), acute toxicity through the dermal route is not expected.

Inhalation

No data are available for 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. One of the chemicals in this group; cobalt neodecanoate (CAS No. 27253-31-2), was tested in accordance with OECD Test Guidelines (TG) 404, 431 and 439; the data available suggest that the chemicals are not skin irritants.

In a study carried out according to OECD TG 404, cobalt neodecanoate (CAS No. 27253-31-2) was applied to the dorsal trunk of three male New Zealand White rabbits for four hours as an 0.5 g aliquot, applied semi-occlusively. Very slight erythema (scores of 1, 2 and 1.33 from each animal) and oedema (scores of 0.67 for each animal) were reported from exposure to cobalt neodecanoate (CAS No. 27253-31-2), but this cleared within seven days after exposure and the chemical is not considered a skin irritant (REACH).

In a study carried out according to OECD TG 431, cobalt neodecanoate (CAS No. 27253-31-2) was added for three or 60 minutes, at a volume of 25 mg, to a cell culture of human-derived epidermal keratinocytes, cultured to form a multilayered, highly differentiated model of the human epidermis. Data available on REACH denotes that the highly viscous and sticky cobalt neodecanoate was stamped onto the tissue surface. Each sample was performed in duplicate. After exposure, a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed. Scores obtained after the three and 60 minute treatments were 108.1 % and 45.7 % for cell viability after exposure to cobalt neodecanoate (CAS No. 27253-31-2). As values for cobalt neodecanoate (CAS No. 27253-31-2) 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 neodecanoate (CAS No. 27253-31-2) was not considered to be corrosive (REACH).

In another similar study carried out according to OECD TG 439, cobalt neodecanoate (CAS No. 27253-31-2) was applied for 15 minutes at a volume of 10 mg, wetted with 15 μL of deionised water, to a cell culture of human-derived epidermal keratinocytes, cultured to form a multilayered, highly differentiated model of the human epidermis. The sample was tested in triplicate and after exposure, an MTT assay was performed. The score obtained after the 15-minute treatment was 11.7 % for cell viability. As this value was below the 50 % viability threshold, the substance was considered to have an irritant potential (REACH).

Eye Irritation

Chemicals in this group are not considered to be eye irritants. One of the chemicals in this group; cobalt neodecanoate (CAS No. 27253-31-2), was tested in accordance with OECD Test Guidelines (TG) 405 and 437.

In a study carried out according to OECD TG 405, 0.1 mL of cobalt neodecanoate (CAS No. 27253-31-2) was applied to the eyes of two male New Zealand White rabbits. Moderate conjunctival irritation was noted in both treated eyes one hour after treatment although this was transient and at the 24 hour observation period, minimal conjunctival irritation was observed. Slight chemosis was observed at the one hour observation in both treated eyes and at the 24 hour observation in one treated eye. The average scores for corneal, iris, conjunctivae (redness) and conjunctivae (chemosis) were given as 0.00, 0.00, 0.67 and 0.33 respectively for animal number one and 0.00, 0.00, 0.33 and 0.00 respectively for animal number two. All effects were reversible in both animals within 72 hours (REACH).

In another study carried out according to OECD TG 437 (in vitro), cobalt neodecanoate (CAS No. 27253-31-2) was administered to bovine corneas for 240 minutes at a volume of 0.75 mL (20 % w/v). The chemical test was performed in triplicate. After exposure, a mean in vitro score of 0.00 for cobalt neodecanoate (CAS No. 27253-31-2) was determined. The mean in vitro scores for the negative controls, with no increase in opacity or permeability of the corneas, was approximately 2.86, whereas the mean in vitro scores for the positive control was approximately 305.30, with clear observations of opacity of the cornea, corresponding to a corrosive effect. Under the experimental conditions reported cobalt neodecanoate (CAS No. 27253-31-2) was not considered corrosive to the eyes (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, based on read across from the human data available on the 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 for the chemicals in this group. However, based on read across animal data available on the analogue chemical cobalt sulfate (CAS No. 10124-43-3) and human data on cobalt chloride (CAS No. 7646-79-9) (refer to **Observations in humans**) hazard classification is warranted for these chemicals.

In a mouse LLNA carried out according to OECD TG 429, a volume of 25 μL of either 12.5 %, 25 % and 50 % solution of cobalt stearate (CAS No. 13586-84-0) diluted in acetone/olive oil was applied to groups of five female CBA mice for each dilution, at the dorsal surface of each ear, once daily over three consecutive days. The stimulation index was reported as 5.6, 9.7 and 8.1 for the 12.5 %, 25 % and 50 % concentrations of the chemical. Considering the stimulation indices at all three concentrations were above 3, the chemical cobalt stearate (CAS No. 13586-84-0) is considered as a skin sensitiser. (REACHd).

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

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

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

Repeated Dose Toxicity

Oral

No data are available 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 and cobalt sulfate, which have been established to be suitable analogues.

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 Sprague Dawley (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 on the chemicals in this group.

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

Inhalation

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 neodecanoate (CAS No. 27253-31-2) dissolves moderately in artificial alveolar fluid—26.1 % and completely in artificial lysosomal fluid—100 % (Stopford et al., 2003), it is prudent to read-across data from soluble cobalt compounds.

Therefore, 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 were observed in all subjects in another study where six volunteers were exposed to a daily dose of 150 mg/day of cobalt chloride (CAS No. 7646-79-9) for up to 22 days. Erythrocyte counts returned to normal in all subjects 15 days after treatment (ATSDR, 2004).

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

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

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 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 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 which conclude 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) and cobalt sulfate heptahydrate (CAS No. 10026-24-1), support hazard classification for reproductive toxicity for chemicals 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 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

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

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include a systemic long-term effect (reproductive toxicity), local long-term effect (carcinogenicity), systemic acute effect (acute toxicity by the oral route) and acute local effects (skin sensitisation and respiratory sensitisation). The chemical may also cause harmful 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 low 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, local long-term effect, systemic acute effect and acute local health 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 also 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]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
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, 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.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.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.

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

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

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at **http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_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**

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

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

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

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

OECD 2014b. 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 (REACH). Cobalt, neodecanoate complexes (CAS No. 27253-31-2). Accessed June 2014 at **http://apps.echa.europa.eu/registered/data/dossiers/DISS-dcebdeec-6d43-46ab-e044-00144f67d031/DISS-dcebdeec-6d43-46ab-e044-00144f67d031_DISS-dcebdeec-6d43-46ab-e044-00144f67d031.html**

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 Neodecanoate acid, cobalt salt, CAS RN 27253-31-2, EC Number 248-373-0. March 2014. Unpublished report submitted to National Industrial Chemicals Notification and Assessment Scheme under the Inventory Multi-tiered Assessment and Prioritisation framework.

UK Poisons Information Documents 1998. Cobalt chloride (7646-79-9). Accessed June 2014 at **http://www.inchem.org/documents/ukpids/ukpids/ukpid50.htm**

US EPA High Production Volume (HPV) Chemical Challenge Program (US EPA, 2008): Summary of existing data, proposed test plan and rational for cobalt salts of C8 to C13 carboxylic acids including neodecanoic acid, cobalt salt (CAS No. 27253-31-2), fatty acids, C9-C13 neo, cobalt salts (CAS No. 68955-83-9) and hexanoic acid, 2-ethyl, cobalt salt (CAS No. 136-52-7). Accessed June 2014 at **http://www.epa.gov/hpv/pubs/summaries/metalcarb/c14172rt9.pdf**

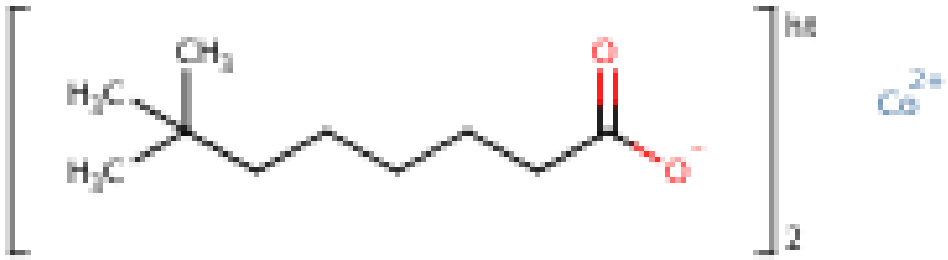
Last Update 27 November 2014

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Octanoic acid, cobalt salt** Cobalt octanoate cobalt caprylate
CAS Number	6700-85-2
Structural Formula	

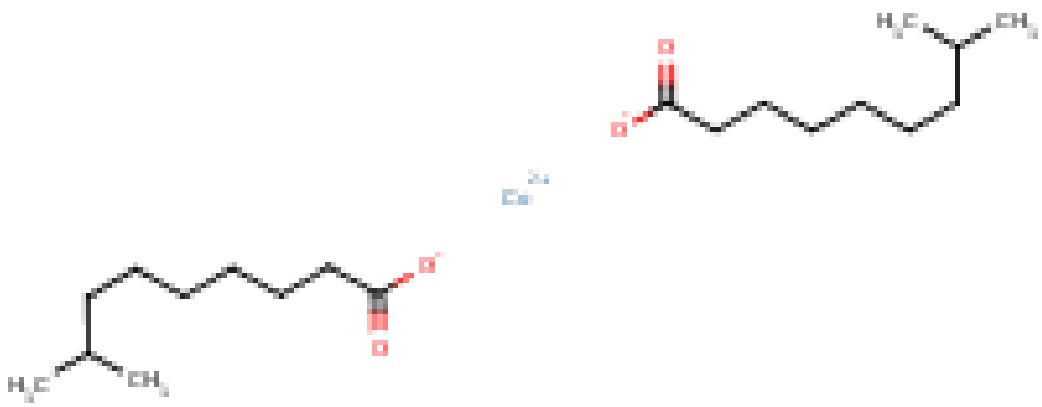
	
Molecular Formula	C8H16O2.xCo
Molecular Weight	202.14

Chemical Name in the Inventory and Synonyms	**Neodecanoic acid, cobalt salt** Cobalt neodecanoate
CAS Number	27253-31-2
Structural Formula	

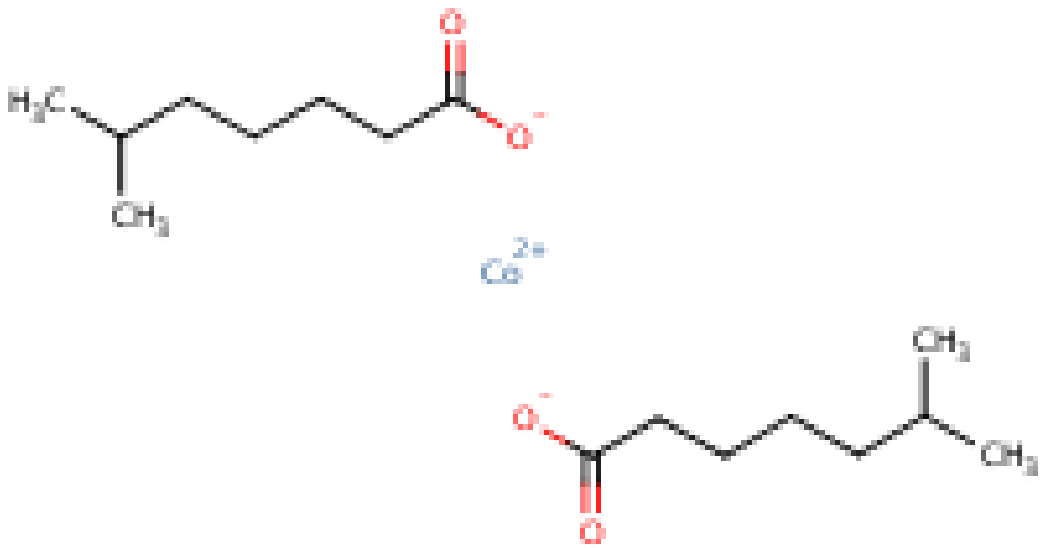


Molecular Formula	C10H20O2.xCo
Molecular Weight	401.45

Chemical Name in the Inventory and Synonyms	**tert-Decanoic acid, cobalt(2+) salt** Cobalt(2+) tert-decanoate
CAS Number	84195-99-3
Structural Formula	

	
Molecular Formula	C10H20O2.1/2Co
Molecular Weight	401.45

Chemical Name in the Inventory and Synonyms	**Isooctanoic acid, cobalt(2+) salt** Cobalt (II) isooctanoate
CAS Number	84255-51-6
Structural Formula	

	
Molecular Formula	C8H16O2.1/2Co
Molecular Weight	345.34

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