SIDS INITIAL ASSESSMENT PROFILE

Category Name	Soluble cobalt salts
Chemical Name(s) and CAS No(s).	Cobalt sulfate CAS 10124-43-3 (anhydrous) CAS 10026-24-1 (heptahydrate) Cobalt dinitrate CAS 10141-05-6 (anhydrous) CAS 10026-22-9 (hexahydrate) Cobalt dichloride CAS 7646-79-9 (anhydrous) CAS 7791-13-1 (hexahydrate) Cobalt diacetate CAS 71-48-7 (anhydrous) CAS 6147-53-1 (tetrahydrate)
Molecular Formula(s)	$CoSO_4$ $Co(NO_3)_2$ $CoCl_2$ $Co(C_2H_3O_2)_2$

SUMMARY CONCLUSIONS OF THE SIAR

RATIONALE FOR THE SOLUBLE COBALT SALTS CATEGORY

Category Assessments:

The category is based on a common moiety of concern, the divalent cobalt cation. All category members are potential contributors of this moiety. The counter ions of the cobalt salts (i.e. sulfate, nitrate, chloride, acetate), due to their ubiquitous presence in biota and/or their essential role in physiology, are not addressed further as they are not considered to contribute to toxicity of the cobalt salts.

In addition to the common moiety of concern (divalent cobalt cation), and toxicological inertness of the counter ion, the following inclusion criteria relevant to human health were applied: extreme water solubility (approx. 350-670 g/L) which is also reflected in the high bioaccessibility (>400 µg/mL) and significant oral bioavailability (approx. 30%). .

In the context of ecotoxicity, a read-across approach was adopted based on the assumption that the toxic agent released from the dissolution of the cobalt containing substances is the divalent cobalt cation. The cobalt salts included here are representative of substances that release divalent cobalt ions under environmentally relevant conditions. In order to provide a means to evaluate those substances for which little or no ecotoxicity information is available, and to reduce the need to test each individual substance, data were generated for category and non-category cobalt salts with a range of solubilities (from 146 g Co/L for Co dichloride to 2.6 mg Co/L for Co resinate) in order to validate this read-across approach. For the assessment of cobalt-containing substances that do not undergo complete and rapid dissolution, transformation/dissolution testing (TDp; OECD Method 29) is used to quantify the amount of dissolved cobalt ion generated, which allows the prediction of the toxicity of those substances that are not included in this category.

Substances Previously Assessed in the OECD Programme:

Initial targeted assessment profile (Human Health and Environment), SIAM 31, 20-22 October 2010, based on the 2011 Canadian Screening Assessment (CSA):

Sponsored Substances: Cobalt [Elemental cobalt]: CAS RN 7440-48-4; Cobalt chloride: CAS RN 7646-79-9; Sulfuric acid, cobalt (2+) salt (1:1) [Cobalt sulfate]: CAS RN 10124-43-3, CAS RN 10393-49-4

Supporting Substances: Nitric acid, cobalt salt [Cobalt nitrate]: CAS RN 14216-74-1*;* Acetic acid, cobalt salt [Cobalt acetate]: CAS RN 5931-89-5

Endpoints Targeted: Toxicokinetics, repeated dose toxicity, genetic toxicity, carcinogenicity, fertility.

PHYSICAL-CHEMICAL PROPERTIES

Cobalt sulfate is typically marketed as the heptahydrate, which is a rose, odourless, crystalline, inorganic solid. The relative density of cobalt sulfate is 3.71. Upon heating of the hydrated form, water of crystallisation is lost and the anhydrous form is formed. The melting point for the anhydrous cobalt sulfate is reported to be > 700°C. The water solubility of cobalt sulfate monohydrate at 20°C and 37°C is 376.7 g/L and 391.5 g/L (measured), respectively. The particle size distribution of a typical commercial sample of cobalt sulfate heptahydrate is characterised by a median diameter of D_{50} = 917.6µm.

Cobalt dinitrate is typically marketed as the hexahydrate, which is a red purple, flaked, inorganic solid. The relative density of cobalt dinitrate is 2.49. Cobalt dinitrate decomposes at 100-105 °C before melting. The water solubility of cobalt dinitrate hexahydrate at 20 °C is > 669.6 g/L (measured). The particle size distribution of a typical commercial sample of cobalt dinitrate hexahydrate is characterised by a median diameter of D_{50} = 993.68 µm.

Cobalt dichloride is typically marketed as the hexahydrate, which is a purple, odourless, crystalline, inorganic solid. The relative density of cobalt dichloride is 3.36-3.37. Upon heating of the hydrated form, water of crystallisation is lost and the anhydrous form is formed. The melting point for the anhydrous cobalt dichloride is reported to be between 735°C - 737°C, the boiling point is 1049°C. The water solubility of cobalt dichloride hexahydrate at room temperature is 585.8 g/L (measured). The particle size distribution of a typical commercial sample of cobalt dichloride hexahydrate is characterised by a median diameter of D_{50} approx. 570 µm.

Cobalt diacetate is typically marketed as the tetrahydrate, which is a red, crystalline inorganic solid with a relative density of 1.76 (measured at 21.4 °C). A decomposition temperature of cobalt diacetate tetrahydrate was determined at 370°C. Distinct melting or boiling points are not available. The water solubility of cobalt diacetate tetrahydrate at 20 °C is 348.04 g/L - 360 g/L (measured). The particle size distribution of a typical commercial sample of cobalt diacetate tetrahydrate is characterised by a median diameter of D_{50} = 219.04 µm.

Remark: Vapour pressure and Kow are not considered relevant parameters for the fate and effects assessment of inorganic chemicals.

HUMAN HEALTH

Toxicokinetics

Human data

Reliable human toxicokinetic data for soluble cobalt substances are scarce. Two toxicokinetic studies in human volunteers exist, which allow some quantitative conclusions:

- in a study in which cobalt chloride was administered once i.v. or orally, it is eliminated from blood rapidly (30% of dose within 24h p.a.), the liver initially retaining an estimated 20% of the dose.

- in a study with ten consecutive daily oral doses of cobalt chloride, increased blood and urine concentrations were observed, in comparison to the reference (non-exposed control subjects). The increases were 14-20-fold and 16-59-fold in males and females respectively.

Animal data

Absorption, oral route: in a reasonably well-described study, the oral absorption in rats following a single dose of cobalt chloride (33.3 mg Co/kg bw) is described. The oral absorption as judged by the extent of excretion via urine was 23.9 %

Absorption, inhalation route: Experimentally determined inhalation absorption rates have not been reported for any cobalt substance, which is why model predictions were performed (see in vitro data below). However, detailed lung clearance investigations have been conducted, which provide a basis for the assessment of the fate of inhaled cobalt particles: the clearance of soluble cobalt (as radioisotopic cobalt chloride) deposited intratracheally in the lungs of various species is rapid, with the mean fraction of ^{57}Co retained in lungs for >100 days accounting for merely 0.13-0.58% of dose. In a similar study in Sprague-Dawley rats involving head-only exposure to cobalt dichloride, a clearance half-time of 1.8h was reported.

Absorption, dermal route: there are no reliable in-vivo dermal absorption data in animals.

Metabolism: cobalt is not subject to any metabolism; regardless of its original chemical speciation, cobalt transforms to divalent cobalt cations, depending on its solubility in water and physiological media.

Distribution: cobalt is an essential metal (vitamin B12 component), and as such will be present as a low level, natural "background" in most tissues, such as muscle, lung, lymph nodes, heart, skin, bone, hair, stomach, brain, pancreatic juice, kidneys, plasma, urinary bladder, and highest in liver (0.5-1 µg/g). Laboratory animal studies in various species indicate that cobalt absorbed via the gastrointestinal tract is primarily retained in the liver.

Elimination: Ingested soluble cobalt substances are excreted primarily via faeces to ca. 70-83%, with urinary excretion accounting for the remainder of the dose. The overall elimination after systemic uptake is very rapid, with whole body retention rates of only ca. 1.5% 36 hours after administration of cobalt dichloride. The biliary excretion of cobalt (chloride) in rats has been reported in one study to be 2.6-7.3% of the dose within 24h p.a. In another study with cobalt chloride also in rats, total (faecal + urinary) excretion was relatively rapid (87.7% of dose in 4d), whereas biliary excretion in the first 2h p.a. ranged from 2.3-4.7% of dose.

There are no data suggesting that cobalt has any bioaccumulation potential.

In vitro data

In vitro bioaccessibility testing: The bioaccessibility of the cobalt category substances was investigated by measuring their solubility in seven different simulated physiological fluids. Soluble cobalt substances are readily soluble in water as well as in all tested physiological media, rendering them similarly highly bioaccessible under all relevant physiological circumstances. The in vitro bioaccessibility results are shown in the table below.

in vitro bioaccessibility data for the category substances

simulated physiological fluids	**Cobalt sulfate**	**Cobalt dichloride**	**Cobalt di(acetate)**	**Cobalt dinitrate**
	cobalt release concentration [µg Co/mL]			
Gastric	441.4[1]	432.1[1]	452.7[2]	393.2[2]
Alveolar	211.0[1]	256.7[1]	49.0[2]	64.4[2]
Intestinal	278.0[2]	397.4[1]	81.1[2]	119.4[2]
Lysosomal	330.8[1]	446.0[1]	362.9[2]	407.9[2]
Interstitial	292.5[1]	240.1[1]	45.9[2]	84.4[2]
Serum	3434.0[4]	4254.0[4]	445.5[3]	367.0[3]
Sweat (at 37°C)	386.5[2]	446.6[2]	457.6[2]	381.9[2]

[1]: incubation of 100 mg in 50 mL medium, measured cobalt concentration after 2 hrs.
[2]: incubation of 100 mg in 50 mL medium, measured cobalt concentration after 5 hrs.
[3]: incubation of 20 mg in 10 mL medium, measured cobalt concentration after 5 hrs.
[4]: incubation of 200 mg in 10 mL medium, measured cobalt concentration after 2 hrs.

In vitro dermal absorption data: The percutaneous absorption potential of cobalt chloride following topical application to human skin in vitro was investigated at two different application rates: ca. 100 µg/cm² and ca. 1000 µg/cm², exposure duration was 8h. For the two exposure concentrations, the corresponding absorbable doses corresponded to 0.38% and 1.08%, respectively, rendering dermal absorption of soluble cobalt substances as very low.

In vitro inhalation deposition/absorption model predictions: the uptake of different cobalt particles was predicted based upon their particle-size dependant respiratory tract deposition, coupled with their measured gastric bioaccessibility, and assuming at the same time conservatively that pulmonary deposition would involve complete dissolution/uptake. The thus predicted inhalation absorption factors for cobalt substances range from approx. 2% to 25%.

Acute Toxicity

Acute inhalation toxicity studies are not available for any of the soluble cobalt salts in this category due to a lack of technical feasibility

No information on the acute dermal toxicity of the category substances are available. Due to the poor dermal absorption of soluble cobalt salts, it can be concluded that the dermal route is not relevant for the acute systemic toxicity of soluble cobalt salts in this category.

All substances within the category show a moderate acute oral toxicity, with LD_{50} values between 300 and 2000 mg/kg body-weight as experimentally determined. Hence, cobalt diacetate, cobalt dichloride, cobalt dinitrate and cobalt sulfate are considered to be harmful if swallowed.

Available key study data for acute oral toxicity in rats

Test substance	**Study type**	**Result**	**Source**
Cobalt sulfate $CoSO_4$	Acute Oral Toxicity (OECD 401)	LD_{50}: 768 mg/kg bw (male/female) (cobalt sulfate heptahydrate) LD_{50}: 424 mg/kg bw (male/female) (cobalt sulfate) LD_{50}: 161 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
		LD_{50}: 1330 mg/kg bw (male/female) (cobalt sulfate heptahydrate) LD_{50}: 279 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983
Cobalt dinitrate $Co(NO_3)_2$	Acute Oral Toxicity (OECD 401)	LD_{50}: 691 mg/kg bw (male/female) (cobalt dinitrate hexahydrate) LD_{50}: 434 mg/kg bw (male/female) (cobalt dinitrate) LD_{50}: 140 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
		LD_{50}: 978 mg/kg bw (male/female) (cobalt dinitrate hexahydrate) LD_{50}: 198 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983
Cobalt dichloride $CoCl_2$	Acute Oral Toxicity (OECD 401)	LD_{50}: 537 mg/kg bw (male/female) (cobalt dichloride hexahydrate) LD_{50}: 133 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983
		LD_{50}: 766 mg/kg bw (male/female) (cobalt dichloride hexahydrate) LD_{50}: 418 mg/kg bw (male/female) (cobalt dichloride) LD_{50}: 190 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
Cobalt diacetate $Co(CH_3COO)_2$	Acute Oral Toxicity (OECD 401)	LD_{50}: 708 mg/kg bw (male/female) (cobalt diacetate tetrahydrate) LD_{50}: 503 mg/kg bw (male/female) (cobalt diacetate) LD_{50}: 168 mg/kg bw (male/female) (cobalt)	Speijers, G.J.A. et al., 1982
		LD_{50}: 819 mg/kg bw (male/female) (cobalt diacetate) LD_{50}: 273 mg/kg bw (male/female) (cobalt)	Llobet, J.M. & Domingo, J.L., 1983

The following clinical signs were predominantly observed in all studies: highest dose caused sedation and diarrhoea. tremors and convulsions prior to death, decrease in body temperature, increased heart rate, pilo erection. The temperature reductions were time- and dose-related. No macroscopic alterations were observed at the most significant organs. Most effects disappeared after 72 hours.

Skin, Eye and Respiratory Irritation

Available key study data for skin and eye irritation

Test substance	Study type	Result
Cobalt sulfate $CoSO_4$	Skin irritation, in vitro (OECD 439)	Not irritating
	Eye irritation, in vivo (OECD 405)	Reversible effects on the eye
Cobalt dinitrate $Co(NO_3)_2$	Skin irritation, in vivo (OECD 404)	Not irritating
	Eye irritation, in vivo (OECD 405)	Irreversible effects on the eye
Cobalt dichloride $CoCl_2$	Skin irritation, in vivo (OECD 404)	Not irritating
	Eye irritation, in vivo (OECD 405)	Irreversible effects on the eye
Cobalt diacetate $Co(CH_3COO)_2$	Skin irritation, in vivo (OECD 404)	Not irritating
	Eye irritation, in vivo (OECD 405)	Reversible effects on the eye

All substances of this category show minimal to mild skin effects, predominantly present as erythema formation. In all three tests, the values of erythema and oedema were below the threshold irritation score of ≥ 2.3 and the effects were fully reversible within 48 hours, thus would be considered as not irritating to the skin.

All cobalt substances within the category were shown to be irritating to eyes; however, whereas these effects were reversible with cobalt diacetate and cobalt sulfate, cobalt dichloride and cobalt dinitrate produce irreversible effects.

Five well-characterised exposure studies in two cobalt facilities producing cobalt substances support observations that worker exposures to inorganic cobalt substances (in the absence of other metal exposures) is associated with occupational asthma, being defined by clinically-compliant lung function testing. However, none of the studies were able to discriminate between individual cobalt substances and their specific potential to impair lung function, and also none of them indicated a high frequency of occurrence of occupational asthma among the worker population. An industry-wide questionnaire survey of industrial experience with occupational asthma did not indicate that the frequency of occupational asthma in workers is particularly high.

Skin Sensitisation

Cobalt dichloride and cobalt sulfate were identified as skin sensitisers in animal studies (guinea pig maximisation test and adjuvant and patch test, respectively) and cobalt dichloride was identified as a skin sensitiser in human observations (largely studies with volunteers). Based on similar bioaccessibility in artificial sweat, cobalt diacetate and cobalt dinitrate are also considered as skin sensitisers.

Repeated-Dose Toxicity

Oral: Oral 90-day animal studies for any of the cobalt substances within this category are not available[1]. However, as supportive information, data from 28-day oral repeated dose toxicity studies in rats with other cobalt substances are available (see Annex to this SIAP). The NOAELs identified in those studies cover a range of 5-1000 mg/kg bw/day (equivalent to approx. 0.5-700 mg Co/kg bw/day). In those cases where macroscopic and microscopic adverse effects were observed in those studies, they were consistently related to the gastrointestinal tract, described as degeneration/necrosis of mucosal epithelium, atrophy of villi and crypts, regeneration of mucosal epithelium and mucosal inflammation. Several human case reports exist on adverse effects in specific organs in humans potentially associated with cobalt exposure. These include cases of non-inflammatory cardiomyopathy (potentially associated with heavy consumption of beer containing cobalt as an additive), interferences with thyroid metabolism (under circumstances of oral Co supplementation or occupational exposure), effects on the haematopoietic system (manifesting itself as anaemia resulting from oral treatment with cobalt chloride), and neurotoxic effects characterised by progressive bilateral deafness with tinnitus and visual failure. The majority of these reports are insufficient for human health hazard assessment, since the persons were either exposed to other substances as well, or only single cases of overexposure with no further information on other confounding factors were reported. Consequently, no reliable causal or dose-response relationship to cobalt exposure can be established.

[1] At the time of finalisation of this document, a repeated dose oral toxicity study with cobalt chloride in rats according to OECD guideline 408 was ongoing, scheduled for finalisation in 2015.

Inhalation: 13-week repeated dose inhalation toxicity studies in rats and mice with cobalt sulfate were conducted primarily as range finders for corresponding 2-year inhalation carcinogenicity bioassays. For this reason, the full-range of histopathological investigations was not conducted. Animals were exposed to concentrations of 0, 0.3, 1, 3, 10, 30 mg/m³ which resulted primarily in necrotising injury to the respiratory tract. The larynx appeared to be the most sensitive tissue. Rats developed chronic inflammation of the larynx at concentrations of 1 mg/m³ and more severe effects in the nose, larynx, and lung at higher concentrations. Mice exhibited acute inflammation of the nose at concentrations of 1 mg/m³ and more severe effects in the nose, larynx, and lung at higher exposures. A NOAEC for local effects in the respiratory was not reached in these studies, as lesions, particularly in the larynx, were observed at the lowest concentration of 0.3 mg/m³ cobalt sulfate which represents the LOAEC.

Several epidemiological studies have been conducted in the past for the assessment of adverse health effects in particular on respiratory function in workers exposed to different concentrations of cobalt metal, oxides and salts under various occupational conditions. The reported effects of occupational inhalation exposure to inorganic cobalt compounds included reduced pulmonary function, increased frequencies of phlegm, cough, wheezing, and dyspnoea. No other clinical findings could be related to an exposure to cobalt substances. Based on cases of occupational asthma in workers exposed to cobalt compounds alone, no adverse effects were observed at cobalt exposures of up to 0.12 mg/m³ (min to max 0.02 -0.3 mg/m³). Effects on respiratory function were only observed at lower concentrations when co-exposure to irritant gases occurred. Acute responses of the lung to chemical injury are associated with irritant and inflammatory reactions that may cause changes in airway reactivity and pulmonary oedema. Chronic inflammatory reactions are likely threshold-based responses associated with lung tissue fibrosis, emphysema, asthma, and finally tumour formation. Persistent inflammatory processes may lead to unrestricted cell growth (lung tumours) by a cascade of mechanisms.

Dermal: No information on the repeated dose toxicity via dermal route of the category substances is available. Due to the poor dermal absorption of soluble cobalt salts, it can be concluded that the dermal route is not relevant for the repeated dose toxicity of soluble cobalt salts in this category.

Conclusion: An oral repeated-dose toxicity study is not available for the category substances. The hazard for repeated dose toxicity can be estimated by cross reference to non-category substance information, identifying the digestive tract as primary target organ. The repeated dose toxicity studies via inhalation with cobalt sulfate in rats and mice are not suitable for use in the hazard assessment of systemic effects (via route to route extrapolation). The respiratory tract of test animals is more susceptible to adverse effects by inhaled cobalt, showing an inflammatory response at concentrations at which systemic effects cannot be observed.

Genetic Toxicity

Bacterial test systems: Two published reports showing weak evidence for mutagenic activity of cobalt chloride and cobalt sulfate are available. Therefore, a series of GLP studies were performed using the bacterial strains that had shown evidence of potential mutagenic effects: cobalt chloride was tested in strain TA97a and cobalt sulfate was tested in strain TA100. The studies were performed in two different laboratories using an identical study design. In both laboratories, there was no evidence of any increases in revertant numbers with any of the test chemicals under any of the treatment conditions, and all 2 were appropriately concluded as negative. Overall there is no convincing evidence that soluble cobalt salts (tested as chloride and sulfate) are mutagenic in the bacterial reverse mutations test systems.

In-vitro mammalian mutagenicity: The only published reference from a mouse lymphoma tk assay with cobalt dichloride does not meet current recommendations. There are weak positive findings of induction of hprt mutations in 2 published studies with cobalt dichloride. However, a GLP study with cobalt sulfate has not confirmed hprt gene mutation activity tested to limits of toxicity, and over both 3 and 24 h incubation periods. The overall conclusion is that cobalt salts/compounds do not induce biologically relevant gene mutation responses in mammalian cells.

In-vitro clastogenicity: The in vitro clastogenicity of the cobalt salts within the category was investigated in numerous chromosomal aberration, micronucleus and tk mutation (small colony mutants) assays, indicating in vitro clastogenic effects.

In-vivo clastogenicity: There are two studies in the public domain which appear to suggest clastogenic and/or aneugenic effects in vivo, which however are either biologically implausible with respect to their time and or dose-dependency of effects, employ non-physiological routes of exposure or suffer from other deficiencies. These are however balanced by several reliable, negative in vivo bone marrow micronucleus and chromosomal aberration results with cobalt dichloride and cobalt sulfate. Further, a survey in workers occupationally exposed to cobalt,

inorganic cobalt substances did not detect significant increases of genotoxic effects (micronuclei and DNA damage in peripheral blood) in workers exposed to cobalt-containing dust at a mean level of 20 µg Co/m³.

In summary, soluble cobalt salts do not elicit any mutagenic activity either in bacterial or mammalian test systems. However they induce some genotoxic effects in vitro, mainly manifest as DNA strand or chromosome breaks, which are consistent with a reactive oxygen mechanism, as has been proposed by various authors. A weight-of-evidence approach was applied, considering positive as well as negative in vivo clastogenicity studies and the absence of such chromosome damage in humans that are occupationally exposed to inorganic cobalt substances. It was concluded that effective protective processes exist in vivo to prevent genetic toxicity with relevance for humans from the soluble cobalt salts category.

Carcinogenicity

Two 2-year inhalation carcinogenicity studies with cobalt sulfate heptahydrate in rats and mice are available, which are considered adequate to assess the carcinogenic potential. Following chronic inhalation exposure of cobalt sulfate in rats and mice at concentrations of 0, 0.3, 1 and 3 mg/m³. Respiratory tract tumours developed in rats and mice of both sexes at concentrations ≥ 0.3 mg/m³ cobalt sulfate hexahydrate (equivalent to ≥ 0.067 mg Co/m³), thus this concentration represents a LOAEC for inhalation carcinogenicity.

Taking into account the lack of a NOAEC in the concentration-response assessment of cobalt sulphate a benchmark dose (BMD) was calculated using the US EPA BMD software (Version 2.0) with the Gamma Model (Version 2.13). The numbers of alveolar/bronchiolar adenoma or carcinoma in the lung of rats and mice were selected as benchmark response. The 95% lower confidence limit of the BMD for a treatment-related increase in response of 10% was calculated (BMDL10). The lowest BMDL10 value was that for female rat tumours with 0.414 mg/m³ cobalt sulphate hexahydrate. There was also an increase in adrenal pheochromocytoma in female rats. It was uncertain whether a marginal increase in pheochromocytoma in mid-dose male rats was caused by cobalt sulfate. Limited epidemiological studies in workers of a cobalt producing plant in France did not find an increase in lung cancer risk among cobalt production workers. However, the significance of these studies was limited by the very small number of cases.

Based on the above information, all substances of the soluble cobalt salts category are considered as inhalation carcinogens.Reproductive Toxicity

A set of investigations of limited reliability exist in the public domain which nevertheless indicate an adverse impact on male reproductive function. These studies suffer from several shortcomings including a lack of a clear dose-response relationship, rendering them unreliable for the purposes of human health risk assessment. The above-mentioned studies also focus primarily on effects in males, so that there is a complete absence of adequate data allowing an assessment of effects on female fertility. Based on the above information, the soluble cobalt salt category substances are considered to impair male fertility.

No reliable data on developmental toxicity are currently available[2].

Conclusions

The soluble cobalt salts in this category present a hazard for human health, based on the significant bioaccessibility of cobalt ions (acute oral toxicity, respiratory and eye irritation, skin sensitisation, repeated dose toxicity, carcinogenicity and reproduction). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme, except for developmental toxicity for which testing was ongoing at the time of finalisation of this document.

ENVIRONMENT

Essentiality and Cobalt Background Level

Cobalt is required to form vitamin B_{12}, which is essential for the growth of many aquatic organisms. Any detectable toxicity of cobalt in aquatic systems is most likely attributable to Co(II). Reported background concentrations of dissolved cobalt in European freshwaters are 0.333 ± 1.01 µg Co/L (median 0.16 µg Co/L) (Salminen, R. (ed.) 2005.

[2] At the time of finalisation of this document, repeated dose oral toxicity, reproduction and pre-natal developmental studies with cobalt chloride in rats were mandatory according to a Decision under the EU REACH Regulation. The repeated dose oral toxicity and pre-natal developmental studies were ongoing, scheduled for finalisation in 2015. The SIAP will be updated once these studies are finalised.

Geochemical Atlas of Europe. FOREGS database: http://www.gtk.fi/publ/foregsatlas/).

Environmental Fate Properties

In waters, cobalt has two common oxidation states, +2 and +3. Under most environmental conditions including natural waters, Co exists as the divalent cation Co(II) and is able to form strong complexes with organic ligands. The divalent cobalt species is highly soluble (with increased solubility at lower pH) and is readily available for uptake by organisms, while the trivalent cobalt species is relatively insoluble and usually found as insoluble oxides or hydroxides. Available data for Co(III) species are limited but do not suggest toxicity greater than that shown for Co(II) species; therefore, the limiting toxicity of cobalt in aquatic systems is most likely to be that of Co(II). In the absence of speciation data, ecotoxicity data derived for cobalt using soluble Co(II) compounds should provide a conservative estimate of the toxicity of other sparingly soluble cobalt compounds. With any cobalt salt, the transport and bioavailability of the cobalt cation and associated anion are determined by their solubility in environmental media (i.e., water, soils, sediments) and biological fluids (e.g., gastric fluid, blood), which is dictated by environmental parameters such as pH. Under most environmentally relevant conditions, cobalt salts will be present as the free metal and free anion. This is sufficient justification for the implementation of a "read-across strategy" using results obtained in tests conducted with soluble cobalt salts (e.g., cobalt dichloride), and this is applicable for all relevant environmental fate endpoints (e.g., adsorption/desorption coefficients and bioconcentration/ bioaccumulation factors).

Environmental Partitioning

Similar median values were obtained for the suspended particulate matter (SPM) distribution functions in freshwater (Log Kd of 4.59) and marine water (Log Kd of 4.94). The median Kd for sediment-seawater is one order of magnitude higher (Log Kd of 5.15), whereas the median Kd of sediment-freshwater and median Kd soil are more than one order of magnitude lower (Log Kd of 2.94 – 3.47) compared to the median Kd for suspended matter. An overview of derived 10^{th}, 50^{th} and 90^{th} percentiles of cobalt distribution coefficients in different environmental compartments, is presented below.

Summary of 10^{th}, 50^{th} and 90^{th} percentile of cobalt K_D values in different environmental compartments

	Suspended Particulate Matter		**Sediment**		
	Freshwater	**Seawater**	**Freshwater**	**Seawater**	**Soil**
10^{th} percentile	2.97	3.78	2.63 (Min)	3.28	1.10
50^{th} percentile	4.59	4.94	2.94	5.15	3.47
90^{th} percentile	6.25	6.05	3.60 (Max)	6.28	4.18

Bioconcentration

The state-of-the-science on metals bioconcentration/bioaccumulation factors (BCF, BAF) do not support the use of BAF or BCF values as a measure of environmental hazard for inorganic forms of cobalt since uptake is not an intrinsic property for cobalt. Cobalt is an essential element and therefore tissue levels are typically homeostatically controlled, thus elevated bioconcentration (BCF) values are commonly observed in waters containing suboptimal Co concentrations. Available data suggest that, as is the case with most metals, cobalt does not biomagnify (i.e., increase in cobalt concentration with increasing trophic level), but rather exhibits biodilution, particularly in upper levels of both aquatic and terrestrial food chains. For example, in marine water, the highest bioconcentration factor (BCF) was reported for phytoplankton (15,600) and plants (including moss and algae; 181-1485). A lower BCF was reported in marine invertebrates (11-156), while the lowest BCF was reported in marine fish (0.143-161).

Biodegradation

For the inorganic cobalt metal and cobalt salts in this dossier, biotic degradation is irrelevant, regardless of the environmental compartment: biotic processes may alter the speciation form of an element (e.g., binding dissolved organic carbon), but it will not eliminate the element from the aquatic compartment by degradation or transformation. Risk and hazard assessment of these compounds is based on the total elemental concentration in the environment, assuming that all cobalt is present as a dissolved cobalt species. This approach can be considered a worst-case approach for chemical assessment of cobalt.

Aquatic Toxicity According to Standard Protocols

Freshwater

A total of 13 acute toxicity tests were conducted using eleven species exposed to the test substance, cobalt dichloride hexahydrate. Although toxicity tests were not conducted using the other soluble cobalt salts in this category, these results are considered to be representative of the divalent cation released by other soluble cobalt salts. Further discussion of this read-across approach is detailed under the section titled Category Assessments. There was a significant concentration effect on juvenile and larval organism survival in all tests. Among the species assessed, acute toxicity values (LC_{50}, dissolved Co) differed from a low of 90.1 µg Co/L for duckweed, *Lemna minor*, to a high of 157,000 µg Co/L for the midge, *C. tentans*. The acute toxicity species sensitivity ranking, in order from most to least sensitive, was as follows: *L. minor* > *P. subcapitata* > *O. mykiss* > *C. dubia* > *D. magna* > *P. promelas* > *H. azteca* > *D. rerio* > *Aeolosoma* sp. > *L. stagnalis* > *C. tentans.* For the acute studies that included both larval and juvenile life stages of *P. promelas* and *D. rerio*, the larvae were more sensitive by factors of 18 and 5, respectively, with larval and juvenile LC_{50} of 3,090 and 54,100 µg Co/L, respectively, for *P. promelas* and 15,980 and 85,290 µg Co/L, respectively, for *D. rerio*. The $L(E)C_{50}$ for each species following acute cobalt exposure are summarised below.

Acute toxicity test results for organisms exposed to cobalt dichloride (µg dissolved Co/L)

Test species	**Common name**	**Life stage**	**$L(E)C_{50}$ (95% CI)**
Lemna minor	Duckweed		90.1 (69.9-116.1)
Pseudokirchneriella subcapitata	Algae		144 (118-176)
Oncorhynchus mykiss	Rainbow trout	Juvenile	1,512 (1,343 – 1,704)
Ceriodaphnia dubia	Water flea	Neonates	2,154 (1,566 - 2964)
Daphnia magna	Water flea	Juveniles	5,890 (5,680 – 6,100)
Pimephales promelas	Fathead minnow	Larval	3,090 (2,720 – 3,520)
		Juvenile	54,100 (45,500 – 64,300)
Hyalella azteca	Amphipod	Juveniles	3,290 (2,920 – 3,710)
Danio rerio	Zebrafish	Larval	15,980 (13,630 – 18,730)
		Juvenile	85,290 (72,300 – 100,700)
Aeolosoma sp.	Oligochaete	Neonates	42,700 (39,680 – 45,960)
Lymnaea stagnalis	Snail	1 month old	61,600 (44,100 – 86,100)
Chironomus tentans	Midge	2nd instar larvae	157,000 (116,000 – 211,000)

* NR - not reported

The chronic toxicity tests provided EC_{10}-NOEC values (dissolved Co) for 11 different freshwater organisms (*Lemna minor, Hyalella azteca, Ceriodaphnia dubia, Lymnaea stagnalis, Pseudokirchneriella subcapitata, Daphnia magna, Aeolosoma headleyi, Chironomus tentans, Pimephales promelas, Danio rerio, Oncorhynchus mykiss*) ranging from 4.9 µg Co/L (*Lemna minor*) to 2,171 µg Co/L (*Oncorhynchus mykiss*). The EC_{10} for each species following chronic cobalt exposure are summarised below.

Chronic species EC_{10} values (µg dissolved Co/L) for the most sensitive endpoint for all freshwater water-column dwelling organisms

Organism	**Common name**	**EC_{10} (95% CI)**
Lemna minor	Duckweed	4.9 (2.7-8.7)
Hyalella azteca	Amphipod	7.55 (4.00-14.27)
Ceriodaphnia dubia	Water flea	7.89 (0.72-86.37)
Lymnaea stagnalis	Snail	9.61 (3.65-25.24)
Pseudokirchneriella subcapitata	Algae	23.0 (14.1-37.5)
Daphnia magna	Water flea	32.36 (21.83-47.99)
Aeolosoma headleyi	Oligochaete	154.6 (124.9-191.5)
Chironomus tentans	Midge	167.1 (104.8-266.6)
Pimephales promelas	Fathead minnow	351.4 (210.6-586.5)
Danio rerio	Zebrafish	1,085 (569-2068)
Oncorhynchus mykiss	Rainbow trout	2,171 (1,658-2,842)

Marine

Marine organisms were exposed to the test substance, cobalt dichloride hexahydrate. Although toxicity tests were not conducted using the other soluble cobalt salts in this category, these results are considered to be representative of the divalent cation released by other soluble cobalt salts. Further discussion of this read-across approach is detailed under the section titled Category Assessments. The EC_{10}/NOEC values (dissolved Co) available for 10 different marine organisms (*Champia parvula, Neanthes arenaceodentata, Mysidopsis bahia, Skeletonema costatum, Dendraster, Mytilus* sp., *Strongylocentrotus purpuratus, Crassostrea* sp., *Dunaliella tertiolecta, Cyprinodon variegates*) ranged from 1.23 µg Co/L (*Champia parvula*) to 31,802 µg Co/L (*Cyprinodon variegates*). The EC_{10} for each species following chronic cobalt exposure are summarised below.

Species EC_{10}/NOEC values (µg dissolved Co/L) for the most sensitive endpoint for all marine organisms

Task	Endpoint	EC_{10} (95% CI)
Seaweed, *Champia parvula*	Cystocarp production	1.23 (0.5 – 2.9)
Marine annelid, *Neanthes arenaceodentata*	Reproduction	206.4 (98.4 – 432.9)
Mysid, *Mysidopsis bahia*	Reproduction	219 (24.6 – 1945)
Marine diatom, *Skeletonema costatum*	Growth rate	590.3 (377.5 – 922.8)
Sand dollar, *Dendraster excentricus*	Proportion normal	967.7 (820.5 – 1141)
Mussel, *Mytilus sp.*	Proportion normal	1656 (1580 – 1735)
Sea urchin, *Strongylocentrotus purpuratus*	Proportion normal	1786 (1733 – 1841)
Oyster, *Crassostrea sp.*	Proportion normal	2763 (2743 – 2783)
Marine flagellate, *Dunaliella tertiolecta*	Growth rate	11961 (10065 – 14214)
Sheepshead minnow, *Cyprinodon variegates*	Biomass	31802 (29938 – 33783)

Sediment

Sediment-dwelling organisms were exposed to the test substance, cobalt dichloride hexahydrate. Although toxicity tests were not conducted using the other soluble cobalt salts in this category, these results are considered to be representative of the divalent cation released by other soluble cobalt salts. Further discussion of this read-across approach is detailed under the section titled Category Assessments. The EC_{10}/NOEC values (total Co) available for cobalt for six different sediment-dwelling organisms (*Hyalella azteca, Ephoron virgo, Chironomus riparius, Gammarus pulex, Tubifex, Lumbriculus variegatu*) ranged from 86 mg Co/kg dry wt (*H. azteca*) to 2,170 mg Co/kg dry wt (*L. variegatus*). The EC_{10} for each species following chronic cobalt exposure are summarised below.

Species EC_{10}/NOEC values (total Co) for the most sensitive endpoint for all sediment dwelling organisms

Organism	Most sensitive endpoint	EC_{10}/NOEC (mg Co/kg dry wt)	Remark
Hyalella azteca	Growth	86 (50-144)	EC_{10}
Ephoron virgo	Growth	136 (96-192)	EC_{10}
Chironomus riparius	Emergence	148 (65-334)	EC_{10}
Gammarus pulex	Survival	273 (186-399)	EC_{10}
Tubifex	Reproduction	1176 (699-1978)	EC_{10}
Lumbriculus variegatus	Survival	2170	NOEC

Soil

A robust data set is available for evaluating the toxicity of cobalt to terrestrial organisms (plants, invertebrates, and microorganisms) and processes. A total of 141 individual toxicity studies were identified representing a total of 14 species; data are provided in the table below) In addition, toxicity data were identified from studies run in 15 separate

soils displaying a range of soil properties typical of those found throughout Europe.

Generic species/process mean values of EC_{10}/NOEC values for most sensitive endpoint for the 14 species and microbial processes (based on added cobalt concentrations).

Generic		Generic, aged	
Species/microbial process	**Species mean (mg Co/kg)**	**Species/microbial process**	**Species mean (mg Co/kg)**
Medicago sativa, shoot yield	3.2	*Medicago sativa*, shoot yield	4.2
Raphanus sativus, total yield	17.8	*Raphanus sativus*, total yield	23.7
Brassica napus, shoot yield	25.3	*Brassica napus*, shoot yield	40.0
Hordeum vulgare, root yield	33.8	*Hordeum vulgare*, root yield	45.0
Elymus lanceolatus, root yield	41.4	*Elymus lanceolatus*, root yield	79.4
Lycopersicon esculentum, root yield	46.7	*Lycopersicon esculentum*, shoot yield	85.1
Eisenia andrei, reproduction	54.8	*Eisenia andrei*, reproduction	105.1
Nitrification	77.2	Glucose induced respiration	124.9
Glucose induced respiration	78.1	Nitrification	127.6
Trifolium pratense, root length	90.1	*Trifolium pratense*, root length	172.9
Eisenia fetida, reproduction	144.4	*Eisenia fetida*, reproduction	238.6
Enchytraeus albidus, reproduction	176.0	*Enchytraeus albidus*, reproduction	319.4
Maize residue mineralisation	208.0	Maize residue mineralisation	343.7
Folsomia candida, reproduction	285.3	*Folsomia candida*, reproduction	466.3

Safe Threshold Values for Aquatic, Sediment, and Soil Compartments

The available chronic toxicity data were used for the construction of a site-specific Species Sensitivity Distribution (SSD) from which the median 5th percentile (HC_5) was derived. This value represents the $HC_{5,50\%}$ with 5%-95% confidence interval. The effects data set for cobalt with EC_{10} values is based on a range of algal, invertebrate and fish species, depending on the compartment, and ensures that the cobalt data set reflects organisms exposed to cobalt by a range of exposure pathways.

Employing a log-normal distribution function resulted in a calculated generic HC_5 value of 1.63 µg Co/L (95% CI 0.15-6.61) for the freshwater compartment, HC_5 value of 33.6 mg Co/kg dry wt (26.4-104.7 95%CI) for freshwater sediment, and HC_5 value of 7.09 µg Co/L (0.025 – 47.26; 95% CI) for the marine water compartment. No reliable acute or chronic toxicity data for the marine sediment compartment were identified in the open literature or in the grey literature; however, based on similar toxicity levels for freshwater versus marine water, it was assumed that the freshwater sediment values would be in the same range for the marine system. Comparison of the cobalt sensitivity of freshwater and marine water column dwelling organisms suggests that freshwater organisms are generally more sensitive to the effects of cobalt than marine organisms; therefore, the application of the freshwater sediment HC_5 to the marine environment should be both protective and conservative. An $HC_{5,50\%}$ of 7.7 mg/kg (5.3-10.7 mg/kg) was derived for the soil compartment by taking into account the effect of ageing, without consideration of the normalisation. The extant data for microorganisms are insufficient to perform a statistical extrapolation analysis (i.e., Species Sensitivity Distribution). A single study using an Activated Sludge Respiration Inhibition Test following OECD Method 209 that was conducted with cobalt dichloride resulted in estimated 30-minute EC_{10} and EC_{50} values for cobalt of 3.73 and 120 mg Co/L, respectively.

Site-specific Approach using the Biotic Ligand Model (BLM)

Cobalt chronic toxicity to aquatic organisms changes as a function of water quality parameters (e.g., Ca and Mg content, pH, dissolved organic carbon (DOC)); Co toxicity is principally affected by Ca and Mg concentration, with toxicity decreasing as a function of increasing Ca/Mg concentration. A biotic ligand model (BLM) was developed based upon extensive empirical data to predict cobalt chronic toxicity for several species including the algae (*P. subcapitata*), invertebrates (*Ceriodaphnia dubia* and *Daphnia magna*) and fathead minnows (*Pimephales promelas*) over a range of physicochemical conditions (i.e., pH, DOC, and hardness). Additionally, site-specific SSDs were developed for a series of European waters representing a range of water types. HC_5 values for each of the modelled locations ranged from 2.22 to 5.08 µg Co/L; a "reasonable worst case" scenario resulted in an HC_5 value of 1.88 µg Co/L.

Conclusion

Cobalt water soluble salts possess properties indicating a hazard for the environment (acute aquatic toxicity less than 1mg/L for two plant/algae species). The chemical has a low bioaccumulation potential. Adequate screening-level data are available to characterize the hazard to the environment for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Exposure

Production: The EU tonnage bands for all of the category substances is 1,000 – 5,000 tonnes per year. Main uses for the category substances range from corrosion inhibition, water treatment and oxygen scavenger, to passivation and plating agent in surface treatment, to nutrient in fertilisers and feed additives, in fermentation processes and biogas production, as catalyst in chemical processes, as intermediate in the production of batteries, as intermediate in the production of other cobalt substances as well as inorganic pigments, frits, glass, ceramic ware, and dyes.

Human exposure: Trace levels of cobalt are found in a wide variety of foods, and human exposure to cobalt may occur via the diet, drinking water, air and occupational as well as consumer exposure. Cobalt is present in nearly all foods in trace amounts. Furthermore, it should be noted that cobalt constitutes 4% by weight of vitamin B12 (cobalamin), an essential human nutrient.

Occupational exposure: Workers can be exposed to dusts of cobalt substances during their manufacture and use. Primary routes of exposure at the workplace are via inhalation and dermal contact.

A comprehensive assessment of occupational exposure during manufacture and each individual downstream use in Europe was recently conducted in the context of regulation EC 1907/2006 (REACH). Within this context monitoring data from manufacturers and downstream users have been collated and used to assess inhalation exposure during manufacture and downstream uses.

Dermal exposure has been assessed on a qualitative basis due to the sensitising effects of the cobalt substances. Workers are required to wear personal protective equipment as a precautionary measure to protect from any residual exposures unless exposure to the substance can be excluded.

Consumer exposure: Opportunities are low for consumer exposure to category substances. Out of the category consumer uses have been identified for cobalt diacetate, only. Cobalt diacetate is used as rubber adhesion agent in steel radial tires, were exposure can be neglected. Exposure associated with the use of recycled rubber in consumer applications, have been assessed to be negligible. Cobalt diacetate is used in the anodic oxidation of consumer goods, however, it will be transformed to cobalt dihydroxide during this process. Furthermore, cobalt diacetate is used as colouring agent in PET bottles allowed for use as food contact materials within the scope of Regulation (EC) 1935/2004, were specific migration limit (SML) for cobalt apply.

Environmental monitoring: Background levels of cobalt in water, sediment and soil are reported in the EU FOREGS Geochemical Atlas (Forum of European Geological Surveys). Typical (i.e. median) background concentration levels in Europe are 0.16 µg Co/L for surface water, 8.0 mg Co/kg dw for freshwater sediment, and 7.78 mg Co/kg dw for topsoil. An analysis of ambient total and dissolved Co-levels in water has been conducted for a limited number of countries. Country-specific reasonable worst-case (RWC) ambient levels were situated between 0.68 and 1.81 µg total Co/L (countries: Belgium, Spain, Sweden, United Kingdom). Dissolved RWC values were 0.07 and 1.32 µg Co/L for France and United Kingdom, respectively. The RWC ambient level represents the 90^{th} percentiles of ambient waters that are not directly affected by point source contamination (diffuse sources only). Cobalt monitoring data for the sediment compartment were identified for 5 countries (Belgium, Finland, France, Spain, Sweden), with the RWC ambient measured concentrations ranging from 16.4 to 29.4 mg Co/kg dry weight (FOREGS Geochemical Atlas).

ANNEX

Table: available key study data for repeated dose toxicity via oral route in rats related to non-category substances

Test substance	Study type	Key results
Cobalt sulfide Co content: 62.95%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 100, 300, 1000 mg/kg bw/day (actual ingested) Dose: 0, 63, 189, 630 mg Co/kg bw/day rat (Crl:CD (SD)) male/female	NOAEL: 1000 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (The only treatment-related finding, not regarded as adverse, was piloerection noted in few male or female rats from a dose level of 100 mg cobalt sulphide/kg bw/day onwards.)
Tricobalt tetraoxide Co content: 73.4%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 100, 300, 1000 mg/kg bw/day (actual ingested) Dose: 0, 73, 220, 734 mg Co/kg bw/day rat (Crl:CD (SD)) male/female	NOAEL: 1000 mg/kg bw/day (actual dose received) (male/female) based on: test mat.
Cobalt (powder) Co content: 99.9%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 30, 100, 300, 1000 mg/kg bw/day (actual ingested) Dose: 0, 30, 100, 300, 1000 mg Co/kg bw/day rat (Crl:CD (SD)) male/female	NOAEL: 30 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (Based on mortality, clinical signs of toxicity, effects on food consumption and macroscopic pathological changes observed at and above 100 mg cobalt powder/kg bw/day and reduced body weight at and above 300 mg cobalt powder/kg bw/day.)
cobalt(II) 4-oxopent-2-en-2-olate Co content: 20.32%	EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral)) Dose: 0, 15, 50, 150 mg/kg/day (actual ingested) Dose: 0, 3, 10, 30 mg Co/kg bw/day rat (Sprague-Dawley) male/female	NOEL: 15 mg/kg bw/day (actual dose received) (male/female) based on: test mat. based on reduced body weight gain, mean body weights and mean food consumption in male rats at 50 mg/kg bw/d.
Resin acids and Rosin acids, cobalt salts Co content: 7.77%	EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral)) Dose: 0, 15, 50, 150 mg/kg/day (actual ingested) Dose: 0, 1.2, 3.9, 11.7 mg Co/kg bw/day rat (Sprague-Dawley) male/female	NOAEL: 15 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (Based on based on reduced body weight gain, mean body weights, in vivo and histopathology findings noted at 150 and 50 mg/kg/day, the No Observed Adverse Effect Level (NOAEL) was identified as 15 mg/kg/day.)
Cobalt, borate neodecanoate complexes Co content: 22.15%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0.5, 1.5, 5 mg/kg bw/day (actual ingested) Dose: 0.1,0.3, 1 mg Co/kg bw/day rat (Crj: CD(SD)) male/female	NOAEL: 5 mg/kg bw/day (nominal) (male/female) based on: test mat. (no endpoints e.g., body weights, feed consumption, clinical signs, behavioural tests, clinical chemistry, organ weights, histopathology, etc. which indicate any toxicity to the adults or offspring)
Stearic acid, cobalt salt Co content: 9.5%	OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) Dose: 0, 5, 15 and 100 mg/kg/day (females) (actual ingested) 0, 5, 15 and 40 mg/kg/day (males) (actual ingested) Dose: 0, 0.5, 1.5, 9.5 mg Co/kg/day (females) 0, 0.5, 1.5, 3.8 mg Co/kg/day (males) rat (Crj: CD(SD)) male/female	NOAEL: 5 mg/kg bw/day (actual dose received) (female) based on: test mat. (The NOAEL for systemic toxicity in P1 females was considered 5.0 mg/kg/day based on decreased body weight and food consumption, clinical signs of toxicity, mortality, and microscopic pathology effects.) NOAEL: 40 mg/kg bw/day (actual dose received) (male) based on: test mat.