Department of Environment, Great Lakes, and Energy

INTEROFFICE COMMUNICATION

TO: File for Cobalt-2-ethylhexanoate CAS #136-52-7

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: July 23, 2019

SUBJECT: Screening Levels for Cobalt-2-ethylhexanoate

The initial threshold screening level (ITSL) for cobalt-2-ethylhexanoate (CAS# 136-52-7) is the same as the ITSL for cobalt (Co) and cobalt compounds that release cobalt ions which is 0.2 µg/m^3 based on an 8-hour averaging time. This ITSL is consistent with the O'Brien (DNR, 1995) memo which established the cobalt ITSL of 0.2 µg/m^3 based on an 8-hour averaging time. The initial risk screening level (IRSL) for cobalt (Co) and cobalt compounds that release cobalt ions is 0.00013 µg Co/m^3 based on an annual averaging time and the secondary risk screening level (SRSL) is 0.0013 µg Co/m^3 based on an annual averaging time. This ITSL, IRSL, and SRSL apply to the following cobalt compounds listed in the table below:

Table 1: List of Cobalt Compounds Covered Under this Initial Threshold Screening Level and Initial Risk Screening Level*

CAS #	Chemical Name (+2 valence unless otherwise stated)	Formula	Molecular Weight (g/mol)	Bioaccessibility
71-48-7	Cobalt acetate	$Co(C_2H_2O_2)_2$	249.1	Soluble in water and lung physiologic fluids
136-52-7	Cobalt -2-ethyl-hexanoate	$Co(C_8H_{15}O_2)_2$	173.7	Soluble in water and lung physiologic fluids
513-79-1	Cobalt carbonate	$CoCO_3$	118.9	Insoluble in water; soluble in lysosomal fluid
814-89-1	Cobalt oxalate	CoC_2O_4	147.0	Insoluble in water; soluble in lysosomal fluid
1002-88-6	Cobalt stearate	$Co(C_{18}H_{35}O_2)_2$	625.9	Moderately soluble in biological fluids
1307-96-6	Cobalt oxide (II)	CoO	74.9	Insoluble in water; soluble in lysosomal fluid
1308-06-1	Cobalt oxide (II, III)	Co_3O_4	240.8	Insoluble in water; slightly soluble in lysosomal fluid
1317-42-6	Cobalt sulfide	CoS	91.0	Slightly soluble in water; slightly soluble in lysosomal fluid
1560-69-6	Cobalt propionate	$Co(C_3H_5O_2)_2$	205.1	Soluble in biological fluids
7440-48-4	Cobalt (metal, particles, nanoparticles, and dust)	Co	58.9	Insoluble in water; soluble in lysosomal fluid

CAS #	Chemical Name (+2 valence unless otherwise stated)	Formula	Molecular Weight (g/mol)	Bioaccessibility
7646-79-9	Cobalt chloride	$CoCl_2$	129.9	Soluble in water and lung physiologic fluids
10026-24-1	Cobalt sulfate heptahydrate	$CoSO_4 \cdot 7H_2O$	281.1	Soluble in water and lung physiologic fluids
10141-05-6	Cobalt nitrate	CoN_2O_6	182.9	Soluble in water and lung physiologic fluids
21041-93-0	Cobalt hydroxide	$Co(OH)_2$	93.0	Slightly soluble in water; soluble in lysosomal fluid
61789-51-3	Cobalt naphthenate	$Co(C_{11}H_7O_2)_2$	401.3	Highly soluble and lipophilic; soluble in lung physiologic fluids

* Based on information obtained from NTP [2016] and OEHHA [2019] (see text for more information).

Cobalt predominantly occurs in two oxidation states: Co(II) and Co(III). Co(II) is much more stable than Co(III) in aqueous solution. “The solubility of cobalt compounds in water is largely pH dependent, and cobalt is generally more mobile in acidic solutions than in alkaline solutions…. Sulfates, nitrates, and chlorides of cobalt tend to be soluble in water, whereas oxides (including the mixed oxide, Co_3O_4), hydroxides, and sulfides tend to be poorly soluble or insoluble in water…. Organic cobalt compounds can be either soluble, as with cobalt(II) carbonate and cobalt(II) oxalate…. In addition to low pH, solubilization of some poorly water-soluble compounds in biological fluids may be enhanced in the presence of binding proteins….” (NTP, 2016). In the Earth’s crust, cobalt is never found in pure form, but is found as a component of more than 70 naturally occurring minerals, including arsenides, sulfides, and oxides. Cobalt compounds are listed as a hazardous air pollutant under the U.S. Clean Air Act.

Cobalt is used in the manufacture of superalloys (e.g., high strength steel, orthopedic and dental prosthetics), magnets, rechargeable battery electrodes, jewelry, electroplating, pigments, oxidation, and medical applications. Bound cobalt is found in the body in coenzymes called cobalamins, also known as vitamin B_{12}. Cobalt salts may be added as a micronutrient in animal feeds for animals grazing in cobalt poor soils. Tobacco plants readily absorb cobalt along with other heavy metals, which are stored in the leaves and is inhaled during tobacco smoking (NTP, 2016; OEHHA, 2019).

People can be exposed to cobalt through burning of fossil fuels, occupational exposures (such as mining, extraction of ores, metal production and use, chemical operations, electronic waste disposal and recycling) and through failed medical implants. Medical implants can cause an increase in cobalt concentrations in the urine of patients (NTP, 2016).

The following references and databases were searched to derive the above screening levels: United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2017 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), SciFinder online (searched 1/17/19), National Library of Medicine (NLM)-online, EPA Chemview Database, EPA Superfund Provisional Peer-Reviewed Toxicity Values (PPRTVs), and European Chemicals Agency.

ITSL Derivation:

An acute ITSL for Cobalt and cobalt compounds that release cobalt ions is derived to protect for short-term exposure and will be used in conjunction with the IRSL to protect against lung cancer.

United States EPA has not set an acute exposure guideline level (AEGL) for cobalt. The DOE set a Protective Action Criteria (PAC-1) for cobalt at 0.18 mg/m^3.

The California Division of Occupational Safety and Health (Cal/OSHA) permissible exposure limits (PELs) establish minimum requirements for controlling worker exposure to airborne contaminants. Cal/OSHA PELs generally follow the ACGIH TLVs. ACGIH set a TLV-TWA of 0.02 mg/m^3 for cobalt and inorganic cobalt compounds to minimize the potential for developing asthma, pulmonary function alterations, and myocardial effects. “Threshold Limit Values (TLVs) refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime without adverse health effects” (ACGIH, 2017).

Table 2: Cobalt and cobalt compounds non-cancer health benchmarks and candidate ITSLs.

Available Inhalation Non-cancer Health Benchmarks	Value (µg/m^3)	Candidate ITSL (µg/m^3)	Candidate ITSL Averaging Time
Cobalt metal, dust and fume (as Co)			
OSHA PEL	100	PEL/100 = 1	8-hour
Cal/OSHA PEL	20	PEL/100 = 0.2	8-hour
ACGIH TLV-TWA	20	TLV/100 = 0.2	8-hour
NIOSH REL	50	REL/100 = 0.5	8-hour
EPA AEGL-1	No recommended value		
DOE PAC-1	180	PAC-1/100 = 1.8	8-hour
Cobalt carbonyl and cobalt hydrocarbonyl as Co			
Cal/OSHA PEL	100	PEL/100 = 1	8-hour
ACGIH TLV-TWA	100	TLV/100 = 1	8-hour
NIOSH REL	100	REL/100 = 1	8-hour
EPA AEGL-1	No recommended value		

ACGIH TLV-TWA of 0.02 mg/m^3 (20 µg/m^3) was recommended “to minimize the potential for developing asthma, pulmonary function alterations, and myocardial effects” in occupational settings. An occupational exposure is used to protect healthy workers exposed during an 8-hour workday over a typical work week. The ITSL is a conservative value which accounts for the differences in susceptibility of the general population which includes sensitive populations. The ITSL is consistent with the O’Brien (DNR, 1995) memo which established the cobalt ITSL of 0.2 µg/m^3 based on an 8-hour averaging time. Therefore, the cobalt ITSL is not changing, but is now the ITSL for cobalt (Co) and cobalt compounds that release cobalt ions is 0.2 µg/m^3 based on an 8-hour averaging time.

IRSL Derivation:

NTP (2016) lists cobalt and cobalt compounds that release cobalt ions *in vivo* as reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data from studies on mechanisms of carcinogenesis. Mechanistic data summarized by NTP (2016) indicate that the release of cobalt

ions *in vivo* is a key event for cobalt-induced carcinogenicity, and that cobalt metal and cobalt compounds that release cobalt ions *in vivo* (regardless of their solubility in water) act via similar modes of action and induce similar cytotoxic, genotoxic, and carcinogenic effects. NTP (2016) concludes that, "the cobalt ion is largely responsible for the toxicity and carcinogenicity."

Multiple carcinogenicity studies have been performed on different forms of cobalt, including cobalt metal, cobalt nanoparticles, cobalt salts, and poorly soluble cobalt compounds. The focus of this document is only on the studies relevant for developing a screening level for cobalt and cobalt compounds that release cobalt ions. NTP (2014) performed a two-year inhalation study on F344/N rats and B6C3F1/N mice (50 per sex/dose group) with cobalt metal particulate aerosol via whole body exposure to concentrations of 0, 1.25, 2.5, or 5 mg/m^3 (6 hours + 12 minutes/day, 5 days/week, for 105 weeks). Additional groups of 35 female rats and mice per dose group were exposed for the same concentrations for 105 weeks for a concurrent lung burden study.

Results of NTP (2014) study, abnormal breathing and low body weight were noted in exposed male and female rats and mice. Other major effects are listed in the following table.

Table 3. Carcinogenic Results from the NTP (2014) 2-year Inhalation Study on Rats and Mice

	Male F344/NTac Rats	**Female F344/NTac Rats**	**Male B6C3F1/N Mice**	**Female B6C3F1/N Mice**
Lung	Alveolar/bronchiolar adenoma (2/50, 10/50, 10/50, 14/50)	Alveolar/bronchiolar adenoma (2/50, 7/50, 9/50, 13/50)	Alveolar/bronchiolar adenoma (7/50, 11/49, 15/50, 3/50)	Alveolar/bronchiolar adenoma (3/49, 9/50, 8/50, 10/50)
Lung	Alveolar/bronchiolar carcinoma (0/50, 16/50, 34/50, 36/50)	Alveolar/bronchiolar carcinoma (0/50, 9/50, 17/50, 30/50)	Alveolar/bronchiolar carcinoma (11/50, 38/49, 42/50, 46/50)	Alveolar bronchiolar carcinoma (5/49, 25/50, 38/50, 43/50)
Lung	Alveolar/bronchiolar adenoma or carcinoma (combined) (2/50, 25/50, 39/50, 44/50)	Alveolar/bronchiolar adenoma or carcinoma (combined) (2/50, 15/50, 20/50, 38/50)	Alveolar/bronchiolar adenoma or carcinoma (16/50, 41/49, 43/50, 47/50)	Alveolar/bronchiolar adenoma or carcinoma (8/49, 30/50, 41/50, 45/50)
Adrenal medulla	Benign or malignant pheochromocytoma (17/50, 23/50, 38/50, 41/50)	Benign or malignant pheochromocytoma (6/50, 13/50, 23/50, 40/50)		
Pancreatic islets	Pancreatic islet adenoma or carcinoma (2/50, 2/50, 10/48, 9/49)			
		Mononuclear cell leukemia (16/50, 29/50, 28/50, 27/50)		

Using the data from the NTP (2014) study, OEHHA (2019) derived an inhalation unit risk factor of 7.8×10^{-3} $(\mu g/m^3)^{-1}$ for cobalt metal and water-insoluble cobalt compounds. OEHHA (2019) used EPA's (2017) Benchmark Dose Software (version 2.7) to model the dose-response data from NTP (2014). OEHHA (2019) found that the multistage model was the best model to fit the alveolar/bronchiolar lung tumors in male rats and alveolar/bronchiolar lung tumors in male mice.

OEHHA also evaluated an NTP (1998) to derive an inhalation unit risk for water-soluble cobalt compounds. The NTP (1998) performed a two-year inhalation study on F344 rats and B6C3F1 mice (50 per sex/dose group) with cobalt sulfate heptahydrate (as a dry particulate) via whole body exposure to concentrations of 0, 0.3, 1.0, or 3.0 mg/m^3 (6 hours/day, 5 days/week, for 105 weeks). The NTP (1998) study results revealed a statistically significant increase incidence of alveolar/bronchiolar neoplasms in female rats and male and female mice, and increased incidences of pheochromocytomas in female rats, which supports the findings of the NTP (2014) study.

"Carcinogenicity studies conducted by NTP established clear evidence of carcinogenicity for cobalt metal and cobalt sulfate heptahydrate. The lungs were the primary site of tumor formation in both rats and mice. Cobalt metal and cobalt sulfate heptahydrate also caused tumors at multiple sites in rats. Carcinogens that produce tumors in more than one species have the greatest potential to induce tumors in other species, including humans….The cobalt ion is considered the primary factor for cancer risk for both cobalt metal and cobalt compounds, and both cobalt metal and cobalt sulfate heptahydrate induced tumors of the same histogenic type in lungs" (OEHHA, 2019).

A thorough review of OEHHA's risk assessment and derivation of an inhalation unit risk (IUR) for cobalt revealed that OEHHA's IUR was calculated properly and forms the best bases for calculating an IRSL. OEHHA (2019) derived an inhalation unit risk factor for cobalt of 7.8 x 10^{-3} $(\mu g/m^3)^{-1}$. Rule 231(1) was used to calculate the IRSL, using the following equation:

$$IRSL = \frac{1\ x\ 10^{-6}}{Unit\ Risk} = \frac{1\ x\ 10^{-6}}{7.8\ x\ 10^{-3}(^{\mu g}/_{m^3})^{-1}} = 0.000128205\ ^{\mu g}/_{m^3} \approx 0.00013\ ^{\mu g}/_{m^3}$$

The IRSL of 0.00013 µg Co/m^3 is for cobalt and cobalt compounds that release cobalt ions and the SRSL is 0.0013 µg Co/m^3. Rule 231(3) states that the averaging time for IRSLs and SRSLs is an annual averaging time.

The following footnote #42 is included: "The combined ambient impact of cobalt and cobalt compounds that release cobalt ions cannot exceed the IRSL of 0.00013 µg Co/m^3 or SRSL of 0.0013 µg Co/m^3 (annual averaging time)."

References:

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