Cobalt and Cobalt Compounds

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definition
ADAF	age-dependent adjustment factor
AIC	Akaike's information criterion
ATSDR	Agency for Toxic Substances and Disease Registry
AMCV	Air Monitoring Comparison Values
BMD	benchmark dose
$BMDL_{10}$	BMD 95% lower confidence limit at the 10% response level
C	concentration
°C	degrees Celsius
CDI	Chromium Development Institute
CI	confidence interval
cm^3	cubic centimeter
Co	cobalt
d	day(s)
DNA	deoxyribonucleic acid
DSD	development support document
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold (e.g., linear) dose-response cancer effect
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose-response noncancer effect
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
g	gram

Acronyms and Abbreviations	Definition
h	hour(s)
HEC	human equivalent concentration
Hg	mercury
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IOAEL	inhalation observed adverse effect level
^{acute}IOAEL	acute inhalation observed adverse effect level
^{subacute}IOAEL	subacute inhalation observed adverse effect level
^{chronic}IOAEL$_{(nc)}$	chronic inhalation observed adverse effect level (noncancer effects)
^{chronic}IOAEL$_{(c)}$	chronic inhalation observed adverse effect level (cancer effects)
IRIS	Integrated Risk Information System
L	liter
LCL	95% lower confidence limit
LEC_{10}	effective concentration 95% lower confidence limit at 10% response level
LOAEL	lowest-observed-adverse-effect-level
m^3	cubic meter of air
µg	microgram
mm	millimeter
µm	micrometer
mg	milligram
MW	molecular weight
MMAD	mass median aerodynamic diameter
MEF	maximum expiratory flow (e.g., between 25 and 75% of the FVC)
MOE	margin of exposure
MOA	mode of action
MRL	Minimal Risk Level
MW	molecular weight
n	number

Acronyms and Abbreviations	Definition
NOAEL	no-observed-adverse-effect-level
NTP	National Toxicology Program
OR	odds ratio
PEF	peak expiratory flow
PM	particulate matter
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
POD_{OC}	point of departure (occupational)
PPM	parts per million
PPRTV	provisional peer-reviewed toxicity value
R	correlation coefficient
RDDR	regional deposited dose ratio
ReV	Reference Value
Acute ReV	acute (e.g., 1-hour) health-based reference value for chemicals meeting minimum database requirements
Acute ReV-24hr	acute 24-hour health-based reference value for chemicals meeting minimum database requirements
Chronic $ReV_{threshold(nc)}$	chronic health-based reference value for threshold dose response noncancer effects
RfC	Reference Concentration
RPF	relative potency factor
σ_g	geometric standard deviation
T	time or exposure duration
TAMIS	Texas Air Monitoring Information System
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UCL	95% upper confidence limit
UF	uncertainty factor

Acronyms and Abbreviations	Definition
UF_D	incomplete database uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_{Sub}	subchronic-to-chronic uncertainty factor
URF	unit risk factor
USEPA	United States Environmental Protection Agency
VE_{ho}	default occupational ventilation rate for an 8-h day
VE_h	default non-occupational ventilation rate for a 24-h day
wk	week(s)
WOE	weight of evidence
yr	year(s)

Chapter 1 Summary Tables

Table 1 and Table 2 provide a summary of health- and welfare-based values from an acute and chronic evaluation of cobalt (Co), respectively, for use in air permitting and air monitoring. Please refer to Section 1.6.2 of the TCEQ Guidelines to Develop Toxicity Factors (TCEQ 2015) for an explanation of air monitoring comparison values (AMCVs), reference values (ReVs), and effects screening levels (ESLs) used for review of ambient air monitoring data and air permitting. Table 3 presents chemical and physical properties of cobalt and cobalt compounds.

Table 1. Acute Health and Welfare-Based Screening Values for Co

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated / RPF	Critical Effect(s)	Notes
Acute ReV	1 h	0.69	--	M	A	--	Respiratory irritation in humans.	Calculated as µg Co/m^3.
Acute ReV-24hr	24 h	0.095	--	M	A	--	Same as above.	Used for the evaluation of 24-h air monitoring data.
^{acute}ESL [a]	**1 h**	**0.21**	**--**	**P**	**S,D**	**--**	**Same as above.**	**Respiratory sensitizer, exceedances during air permit reviews should be discouraged.**
^{acute}IOAEL	6 h	38	--	N	none	--	Same as above.	--
^{subacute}IOAEL	--	--	--	--	--	--	--	--
^{acute}ESL$_{odor}$	--	--	--	--	--	--	--	No odor potential.
^{acute}ESL$_{veg}$	--	--	--	--	--	--	--	No data found.

Bold values used for air permit reviews.

[a] Based on the acute 1-h ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 2. Chronic Health and Welfare-Based Screening Values for Co

Screening Level Type	Duration	Value 1 (µg/m^3)	Value 2 (ppb)	Usage	Flags	Surrogated/ RPF	Critical Effect(s)	Notes
Chronic $ReV_{threshold(nc)}$	70 yr	0.063	--	N	none	--	Respiratory irritation (i.e., eye, nose, and throat irritation, cough) and reduced lung function in humans.	Calculated as µg Co/m^3, study duration unknown.
$^{chronic}ESL_{threshold(nc)}$ [a]	70 yr	0.019	--	N	none	--	Same as above.	--
$^{chronic}IOAEL_{(nc)}$	70 yr	15.1	--	N	none	--	Same as above.	Duration not known.
$^{chronic}ESL_{threshold(c)}$	--	--	--	--	--	--	--	No data found.
$^{chronic}ESL_{nonthreshold(c)}$ [b]	**70 yr**	**0.0017**	**--**	**M,P**	**A,S,D**	**--**	**Lung neoplasms in laboratory animals (i.e., rodents).**	**Respiratory sensitizer, exceedances during air permit reviews should be discouraged.**
$^{chronic}IOAEL_{(c)}$	70 yr	179	--	N	none	--	Same as above.	--
$^{chronic}ESL_{veg}$	--	--	--	--	--	--	--	No data found.
$^{chronic}ESL_{animal}$	--	--	--	--	--	--	--	No data found.

Bold values used for air permit reviews.

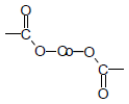
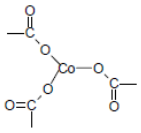
[a] Based on the chronic ReV multiplied by 0.3 (i.e., HQ = 0.3) to account for cumulative and aggregate risk during the air permit review.

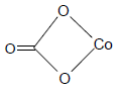
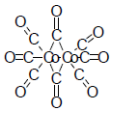
[b] Based on the URF of 6.0E-03 (µg Co/m^3)$^{-1}$ and a no significant risk level of 1 in 100,000 excess cancer risk, and applicable to all forms of cobalt compounds.

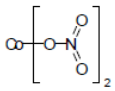
Usage:
P = Used in Air Permitting
M = Used to Evaluate Air Monitoring Data
R = Used to Calculate Remediation Cleanup Levels
N = Usage Not Defined

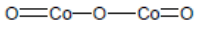
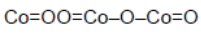
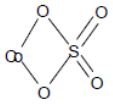
Flags:
A = AMCV report
S = ESL Summary Report
D = ESL Detail Report

Table 3. Chemical and Physical Properties of Cobalt (Co) and Select Compounds [a]

Parameter	Value	Value	Value
Name of Chemical	Cobalt	Cobalt(II) acetate	Cobalt(III) acetate
Molecular Formula	Co	$Co(C_2H_4O_2)_2$	$Co(C_2H_4O_2)_3$
Chemical Structure	Co		
CAS Registry Number	7440-48-4	71-48-7	917-69-1
Molecular Weight	58.93	177.03	236.07
Physical State	Solid	Solid	Solid
Color	Silvery gray	Light pink	Dark green
Odor	No data	No data	No data
Synonyms	Cobalt-59; cobalt metal	Cobaltous acetate; cobalt diacetate	Cobaltic acetate; cobalt triacetate
Solubility in water (mg/L)	Insoluble	Soluble	Soluble
Log K_{ow}	No data	No data	No data
Vapor Pressure (mm Hg)	1 at 1,910°C	No data	No data
Density (g/cm^3)	8.9 at 20°C	No data	No data
Melting Point	1,495°C	No data	Decomposes at 100°C
Boiling Point	2,870°C	No data	Not relevant

Parameter	Value	Value	Value
Name of Chemical	Cobalt(II) carbonate	Cobalt carbonyl	Cobalt(II) chloride
Molecular Formula	$CoCO_3$	$Co_2(CO)_8$	$CoCl_2$
Chemical Structure			
CAS Registry Number	513-79-1	10210-68-1	7646-79-9
Molecular Weight	118.94	341.9	129.84
Physical State at 25°C	Solid	Solid	Solid
Color	Red	Orange (white when pure)	Blue
Odor	No data	No data	No data
Synonyms	Cobaltous carbonate; carbonic acid, cobalt (+2) salt	Dicobalt octacarbonyl; cobalt tetracarbonyl	Cobalt dichloride; cobaltous chloride
Solubility in water (mg/L)	1,800 at 15°C	Insoluble	450,000 at 7°C
Log K_{ow}	No data	No data	No data
Vapor Pressure (mm Hg)	No data	199.5 at 25°C	No data
Density (g/cm^3)	4.13 at unspecified °C	1.73 at 18°C	3.356 at 36°C
Melting Point	Decomposes	51°C	724°C
Boiling Point	Not relevant	Decomposes	1,049°C

Parameter	Value	Value	Value
Name of Chemical	Cobalt(II) hydroxide	Cobalt(II) nitrate	Cobalt(II) oxide
Molecular Formula	$Co(OH)_2$	$Co(NO_3)_2{\cdot}6H_2O$	CoO
Chemical Structure			
CAS Registry Number	21041-93-0	10141-05-6 (anhydrous) 10026-22-9 (hexahydrate)	1307-96-6
Molecular Weight	92.95	182.94	74.93
Physical State at 25°C	Solid	Solid	Solid
Color	Rose red or blue-green	Red	Pink
Odor	No data	No data	No data
Synonyms	Cobaltous hydroxide; cobalt dihydroxide	Cobaltous nitrate	Black 13; cobalt monoxide; cobaltous oxide; C.I. pigment
Solubility in water (mg/L)	3.2 at unspecified °C	133.8 at 0°C	Insoluble
Log K_{ow}	No data	No data	No data
Vapor Pressure (mm Hg)	No data	No data	No data
Density (g/cm^3)	3.597 at 15°C	2.49 at unspecified °C	6.45 at unspecified °C
Melting Point	No data	Decomposes at 100-105°C	1,795°C
Boiling Point	No data	Not relevant	No data

Parameter	Value	Value	Value
Name of Chemical	Cobalt(III) oxide	Cobalt(II, III) oxide	Cobalt(II) sulfate
Molecular Formula	Co_2O_3	Co_3O_4	$CoSO_4$
Chemical Structure			
CAS Registry Number	21158-51-0	1308-06-1	10124-43-3
Molecular Weight	165.86	250.80	154.99
Physical State at 25°C	Solid	Solid	Solid
Color	Black-gray	Black	Dark blue
Odor	No data	No data	No data
Synonyms	Cobalt black; cobaltic oxide; cobalt trioxide; cobalt sesquioxide	Cobaltic-cobaltous oxide; cobalt tetraoxide; tricobalt tetraoxide; cobaltosic oxide; cobalt black; C.I. pigment black 13	Cobalt sulfate; cobaltous sulfate
Solubility in water (mg/L)	Insoluble	Insoluble	38,300 at 25°C
Log K_{ow}	No data	No data	No data
Vapor Pressure (mm Hg)	No data	No data	No data
Density (g/cm^3)	5.18 at unspecified °C	6.07 at unspecified °C	3.71 at unspecified °C
Melting Point	Decomposes at 895°C	900-950°C ($-O_2$)	Decomposes at 735°C
Boiling Point	Not relevant	Not relevant	Not relevant

[a] Based on Tables 4-1 and 4-2 of ATSDR (2004).

Chapter 2 Background Information

2.1 Chemical/Physical Properties

Cobalt is the 33rd most abundant element and comprises approximately 0.0025% of the weight of the earth's crust. It is often found in association with nickel, silver, lead, copper, and iron ores and occurs in mineral form as arsenides, sulfides, and oxides. Cobalt commonly occurs in the 0, +2, and +3 valence states. Compounds containing cobalt in the -1, +1, +4, and +5 oxidation state are few and uncommon. Co(II) is much more stable than Co(III), and Co^{3+} is a sufficiently powerful oxidizing agent to oxidize water, liberating oxygen. Table 3 summarizes important physical and chemical properties of elemental cobalt and some common cobalt compounds. These properties are similar to those of its neighbors in Group 9 of the periodic table, iron and nickel. Metallic cobalt, Co(0), occurs as two allotropic forms, hexagonal and cubic; the hexagonal form is stable at room temperature. There is only one stable isotope of cobalt, ^{59}Co. There are about 26 known radioactive isotopes of cobalt, of which only two are of commercial importance, ^{60}Co and ^{57}Co. ^{60}Co, a commonly-used source of gamma radiation, is the most important radionuclide. A biochemically important cobalt compound is vitamin B_{12}, or cyanocobalamin, in which cobalt is complexed with four pyrrole nuclei joined in a ring called the corrinoid ligand system (similar to porphyrin). (ATSDR 2004)

2.2 Uses

The following information on the uses of cobalt and cobalt compounds was taken directly from ATSDR (2004). Information on the radioactive isotopes of cobalt is not presented, as this development support document (DSD) does not address the radioactive cobalt isotopes. See ATSDR (2004) for information on the uses of the radioactive isotopes of cobalt.

> The United States is the world's largest consumer of cobalt. Cobalt is used in a number of essential military and industrial applications. The largest use of metallic cobalt is in superalloys that are used in gas turbines aircraft engines. Superalloys are alloys developed for applications where elevated temperatures and high mechanical stress are encountered. It is also used in magnetic alloys and alloys that are required for purposes requiring hardness, wear resistance, and corrosion resistance. Cobalt is used as a binder for tungsten carbide (cemented carbides) cutting tools to increase impact strength. Cobalt compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers; and as trace element additives in agriculture and medicine.
>
> Over 40% of nonmetallic cobalt is used in catalysis, and most cobalt catalysts are used in hydrotreating/desulfurization in the oil and gas industry, the production of terephthalic acid and dimethylterephthalate, and the production of aldehydes using the high pressure oxo process (hydroformylation). Cobalt chemicals primarily used as catalysts include cobalt(III) acetate, cobalt(II) bromide, carbonate, manganate, oxalate, and

sulfide, cobalt carbonyl, and cobalt naphthenate. Cobalt carbonate and chromate are mainly used as pigments and cobalt(II) acetate, 2-ethylhexanoate, linoleate, naphthenate, nitrate, oleate, and stearate are mainly used as driers. Cobalt has been used for hundreds of years as a blue colorant in glass, ceramics, and paints (Richardson 1993). A growing use for cobalt is as an addition to the Ni/Cd, Ni-metal hydride battery or as the main component of the lithium ion cell ($LiCoO_2$). The reported U.S. cobalt consumption in 2002 was 7,930 metric tons with a use pattern of (end use, metric tons cobalt content, percent): superalloys, 3,700, 46.7%; steel alloys, 555, 7.0%; other alloys, including magnetic alloys, 1,050, 13.2%; cemented carbides, 617, 7.8%; chemical and ceramic use, 1,950, 24.6%; and miscellany, 63, 0.8%. Cobalt is also used a target material in electrical x-ray generators (Cobalt Development Institute (CDI) 2004; Donaldson 1986; Hodge 1993; IARC 1991; Richardson 1993; USGS 2002).

2.3 Ambient Air Levels

Although the largest source of cobalt exposure for the general population is food (e.g., intake in the U.S. has been estimated to be 5-40 µg Co/day with relatively high concentrations in vegetables and fish; WHO 2006), cobalt is also released into the atmosphere from both anthropogenic and natural sources. However, emissions from natural sources are estimated to slightly exceed those from manufactured sources. Natural sources include windblown soil, seawater spray, volcanic eruptions, and forest fires. Primary anthropogenic sources include fossil fuel and waste combustion, vehicular and aircraft exhausts, processing of cobalt and cobalt-containing alloys, copper and nickel smelting and refining, and the manufacture and use of cobalt chemicals and fertilizers derived from phosphate rocks (Barceloux 1999; Lantzy and Mackenzie 1979; Nriagu 1989; Smith and Carson 1981). Cobalt compounds are nonvolatile and cobalt will be emitted to the atmosphere only in particulate form. It is generally assumed that anthropogenic cobalt originating from combustion sources exists primarily as the oxide; arsenides or sulfides may be released during mining and ore processing (Schroeder et al. 1987). However, except for a negligible amount of byproduct cobalt produced from some mining operations, no cobalt is presently mined or refined in the United States (ATSDR 2004).

From 2006-2014, annual averages at ambient air monitoring sites in Texas ranged from not detected to 0.0010 µg Co/m^3 ($PM_{2.5}$ or PM_{10}), with nondetects being the most frequent contributor to the annual mean at all sites. Maximum 24-hour concentrations ranged from not detected to 0.0069 µg Co/m^3, with a 95th percentile of approximately 0.0043 µg Co/m^3 and a median of 0.00064 µg Co/m^3 (Texas Air Monitoring Information System (TAMIS) data for 2006-2014).

Chapter 3 Acute Evaluation

In addition to deriving a 1-hour (h) acute ReV, a 24-h acute ReV was also developed. The cobalt monitoring data that the TCEQ collects are based on a 24-h sampling duration. Thus, development of a 24-h acute ReV for cobalt will allow the TCEQ to more fully evaluate available

monitoring data. Additionally, intermediate exposure duration (i.e., subacute, subchronic) studies are available in the toxicological database to support the conservativeness of the 24-h ReV point of departure (POD), which is based on a more limited acute database. The Kusaka et al. (1986b) human study was identified as the key study for derivation of the acute 1- and 24-h ReVs for cobalt, supported by acute/subacute animal studies (i.e., the subacute portion of NTP 1991; Palmes et al. 1959; Kyono et al. 1992). Additionally, the results from multiple subchronic animal studies (e.g., the subchronic portion of NTP 1991; Johansson et al. 1987, 1992; Kerfoot 1975) are used to support the conservativeness of the acute assessment. These studies are described in the relevant sections below (Sections 3.1 and 3.2).

The TCEQ will develop both acute and chronic values based on the cobalt content of the compound(s) in the key studies (i.e., on a cobalt equivalent basis (µg Co/m^3)). The cobalt equivalent for a given dose of a cobalt compound is based on the percent of the compound's molecular weight (MW) that cobalt comprises (i.e., the compound's concentration in µg/m^3 × (MW of cobalt in compound / MW of compound)). From a protection of public health perspective, use of cobalt equivalents assumes that other forms are equally as toxic as the compound(s) in the key study on a µg Co/m^3 basis. This science policy decision is necessary given the lack of available studies to derive separate values for every cobalt compound and is consistent with the approach of other agencies (e.g., ATSDR). However, the derived ReV and ESL values are expected to be sufficiently health-protective regardless of the environmental chemical form (e.g., cobalt oxide, sulfate, metal) because they will be based on the cobalt compound(s) that have produced adverse effects at the lowest concentrations (i.e., the most toxic form(s) in the most sensitive species), which is the most conservative (i.e., health-protective) choice. *The toxicity factors derived in this DSD, however, do not apply to radioactive cobalt.*

3.1 Health-Based Acute 1-h ReV and ESL

3.1.1 Key and Supporting Studies for 1-h ReV

3.1.1.1 Key Human Study

Studies of hard metal workers have reported respiratory effects (ATSDR 2004; e.g., Kusaka et al. 1986a, 1986b). Kusaka et al. (1986a) report that 42 workers (three with occupational asthma related to hard metal) exposed to hard metal (i.e., a cobalt-tungsten carbide alloy) showed no pre-/post-shift decrease in ventilatory function following 7-h exposure to a mean concentration of 85 µg Co/m^3, but statistically significant changes in FEV_1 (forced expiratory volume in 1 second) compared to matched controls at a multiple-year (1981-1984) mean of 126 µg Co/m^3. By contrast, Kusaka et al. (1986a) also describe an acute exposure of 15 healthy young men to hard metal dust containing 38 µg Co/m^3 for 6 h, resulting in complaints of airway irritation in all subjects (e.g., coughing, expectoration, or sore throat) and statistically significantly reduced forced vital capacity (FVC percent decrease not provided). Similar symptoms of respiratory

irritation were observed among the hard metal workers (over the period 1981-1984). Thus, a lowest-observed-adverse-effect-level (LOAEL) of 38 µg Co/m^3 for 6-h exposure to hard metal dust may be identified based on effects reported in this study. Nevertheless, ATSDR (2004) did not utilize the Kusaka et al. (1986a) study of hard metal exposure in humans (or any study) to derive an acute inhalation minimal risk level (MRL) for cobalt because the toxicity of hard metal is thought to involve an interaction between cobalt metal and tungsten carbide (i.e., inert tungsten dust potentiating the effects of cobalt on the respiratory tract). However, studies suggest that cobalt (not tungsten carbide) is the causative agent for the respiratory effects induced by hard metal exposure (ATSDR 2004), and there is potential for cobalt emissions from the hard metal industry (e.g., tool production, grinding). Therefore, the LOAEL from Kusaka et al. (1986a) of 38 µg Co/m^3 for respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC) due to 6-h exposure to hard metal dust will conservatively serve as the POD for derivation of the cobalt 1-h ReV (data were not amenable to benchmark dose (BMD) modeling).

3.1.1.2 Supporting Animal Studies

Although human data are preferred for derivation of toxicity factors (TCEQ 2015), as with exposures in humans, inhalation exposures of animals to cobalt have resulted in pronounced respiratory effects (ATSDR 2004). Acute/subacute animal studies such as the subacute portion of NTP (1991; also published as Bucher et al. 1990) and other studies (i.e., Palmes et al. 1959; Kyono et al. 1992) support the key human study (Kusaka et al. 1986a) for derivation of the acute 1-h ReV. Furthermore, even results from multiple subchronic animal studies (e.g., the subchronic portion of NTP 1991; Johansson et al. 1987, 1992; Kerfoot 1975) support the conservativeness of the acute assessment. Supporting animal study results, primarily as summarized by ATSDR (2004), are provided below.

3.1.1.2.1 NTP (1991)

Necrosis and inflammation of the respiratory tract epithelium (nasal turbinates, larynx, trachea, bronchioles) were reported in rats subacutely exposed to 19 mg Co/m^3 and mice subacutely exposed to 1.9 mg Co/m^3 or greater as cobalt sulfate over 16 days (Bucher et al. 1990; NTP 1991). Subchronic exposure of rats and mice to cobalt as cobalt sulfate for 13 weeks resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive part (Bucher et al. 1990; NTP 1991). At concentrations of ≥ 0.11 mg Co/m^3, rats and mice developed squamous metaplasia of the larynx. Histiocytic infiltrates in the lung were also reported at similar levels in both the rats and mice. In rats, chronic inflammation of the larynx was found at ≥ 0.38 mg Co/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures. In mice, acute inflammation of the nose was found at ≥ 1.14 mg Co/m^3, and more severe effects on the nose, larynx, and lung were reported at higher exposures (ATSDR 2004).

Thus, the lowest LOAEL from the subacute portion of NTP (1991) was 1,900 µg Co/m^3 for respiratory tract inflammation in mice exposed for 16 d. This LOAEL is 50-fold higher than the LOAEL (38 µg Co/m^3) from the key study (Kusaka et al. 1986a) for respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC) due to 6-h exposure to hard metal dust that conservatively serves as the POD for derivation of the 1-h ReV. Even the lowest LOAEL from the subchronic portion of the NTP study (110 µg Co/m^3 for effects on the larynx) is higher, providing great confidence in the conservativeness of the POD for derivation of the 1-h ReV.

3.1.1.2.2 Other Studies

Animals exposed to aerosols of cobalt oxides and cobalt sulfate developed respiratory effects that varied in severity with exposure level and duration (ATSDR 2004). A single 30-minute exposure of rats to relatively high levels (26-236 mg Co/m^3 as cobalt hydrocarbonyl) resulted in congestion, edema, and hemorrhage of the lung (Palmes et al. 1959). Subacute (4-day) exposure of rats to 2.12 mg Co/m^3 as cobalt metal resulted in slight damage to respiratory tissues as assessed by electron microscopy, although 2.72 mg Co/m^3 was the NOAEL for acute (5-h) exposure (Kyono et al. 1992). Subchronic/chronic (3-4 month) exposure of rats and rabbits to various cobalt compounds (0.4-9 mg Co/m^3) resulted in lung inflammation and lesions in the alveolar region of the respiratory tract characterized histologically by nodular accumulation of Type II epithelial cells, accumulations of enlarged highly vacuolated macrophages, interstitial inflammation, and fibrosis (Johansson et al. 1984, 1987, 1991, 1992; Palmes et al. 1959). In at least one instance, the lesions appeared to regress when exposure was terminated (Palmes et al. 1959). Guinea pigs sensitized to cobalt by repeated dermal application and then exposed subchronically (for 66 days) to 2.4 mg Co/m^3 as cobalt chloride showed pulmonary inflammatory changes (altered BAL fluid recovery, increased neutrophils and eosinophils in the recovered BAL fluid) that were different than those in exposed animals not sensitized to cobalt (Camner et al. 1993). Decreased lung compliance was found in pigs subchronically exposed to 0.1 mg Co/m^3 as cobalt metal dust for 3 months (Kerfoot 1975). Lastly, as reported in CDI (2016), in order to identify a NOAEL and examine the early time course of cobalt-induced inflammation, rats were exposed for 4 hours to cobalt sulfate and lung inflammation was assessed by lung lavage at various time points after cessation of exposure. The NOAEL for inflammation was 0.381 mg Co/m^3, with a LOAEL of 3.81 mg Co/m^3. The inflammation response, as evidenced by the appearance of neutrophils in bronchoalveolar lavage fluid, was maximal at 20 hours after the cessation of exposure.

Thus, similar to the discussion in Section 3.1.1.2.1, the lowest potential acute/subacute LOAEL values from these studies are orders of magnitude higher than the LOAEL (38 µg Co/m^3) from the key study (Kusaka et al. 1986a). Moreover, even the lowest LOAEL from the subchronic studies (100 µg Co/m^3 for decreased lung compliance in Kerfoot 1975) is higher. In conjunction with NTP (1991), these supporting study results provide great confidence in the conservativeness of the POD for derivation of the 1-h ReV.

3.1.1.3 Consideration of Developmental/Reproductive Effects

In laboratory animals, longer-term (i.e., subacute to chronic) exposure to cobalt has resulted in effects on reproductive endpoints. Testicular atrophy was reported in rats, but not in mice, exposed to 19 mg Co/m^3 (as cobalt sulfate) over 16 days (Bucher et al. 1990; NTP 1991), and the absolute testis weight of rats exposed to 10 mg Co/m^3 (as cobalt metal) for 16 days was significantly less than that of controls (NTP 2014a). Following exposure of mice to cobalt (as cobalt sulfate) for 13 weeks, a decrease in sperm motility was found at 1.14 mg Co/m^3 with testicular atrophy at 11.4 mg Co/m^3 (Bucher et al. 1990; NTP 1991). Following exposure of mice to cobalt (as cobalt metal) for 14 weeks, the testes weights of males exposed to 5 or 10 mg Co/m^3 were significantly less than those of the chamber controls (NTP 2014a). A significant increase in the length of the estrous cycle was reported in female mice exposed to 11.4 mg Co/m^3 (as cobalt sulfate) for 13 weeks (Bucher et al. 1990; NTP 1991). No effects on the male or female reproductive systems were observed in rats similarly exposed to cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991), or in mice or rats exposed to up to 1.14 mg Co/m^3 for 104 weeks (Bucher et al. 1999; NTP 1998). Male rats and mice exposed to 5 mg Co/m^3 (as cobalt metal) for 105 weeks had significant increases of infarct in the testis and germinal epithelial degeneration in the testes, respectively (NTP 2014a).

No studies were located regarding developmental effects in humans or animals after inhalation exposure to cobalt, so information from oral studies is presented. No developmental effects on human fetuses were observed following treatment of pregnant women with cobalt chloride to raise hematocrit and hemoglobin levels that are often depressed during pregnancy. Dosages up to 0.6 mg Co/kg-day for 90 days were given (Holly 1955). Examination of the fetuses was for overt birth defects and exposure only occurred in the final trimester. Oral exposure of female rats to cobalt chloride at 5.4 or 21.8 mg Co/kg-day from gestation day 14 through lactation day 21 has been shown to result in stunted growth and decreased survival, respectively, of newborn pups (Domingo et al. 1985). The effects on the offspring occurred at levels that also caused maternal toxicity (reduced body weight and food consumption, and altered hematological measurements) and might therefore have been an indirect effect of maternal toxicity rather than a direct effect of cobalt on the fetus (Domingo et al. 1985). Teratogenic effects were not observed. Szakmary et al. (2001) reported that exposure of pregnant rats to 0-38 mg Co/kg-day as cobalt sulfate did not result in changes in fetal death rates, maternal body weight gain, average litter size, or average fetal or placental weights; however, a dose-related trend was seen for the percent of rat fetuses with retarded body weights that was significant beginning at 19 mg Co/kg-day, although average fetal body weight was not significantly reduced at any dose (e.g., ≈ 2% at 38 mg Co/kg-day). In contrast, no effects on fetal growth or survival were found following exposure of rats to 24.8 mg Co/kg-day as cobalt chloride during gestation days 6-15 (Paternian et al. 1988). In mice, exposure to 81.7 mg Co/kg-day as cobalt chloride during gestation days 8-12 was reported to have no effect on fetal growth or mortality in mice (Seidenberg et al. 1986). In a later mouse study that exposed pregnant mice to 19 mg Co/kg-day as cobalt sulfate, no changes in litter size, post-implantation loss, or average fetal or

placental weights were seen; the only difference seen was an increase in the percent of fetuses with retarded body weights (Szakmary et al. 2001). The same study reported that rabbits exposed to ≥ 38 mg Co/kg-day, as cobalt sulfate, showed nearly complete maternal lethality, and complete fetal loss. Rabbits exposed to 7.6 mg Co/kg-day, as cobalt sulfate, showed significant increases in mortality and fetal resorption, as well as an increase in fetuses with retarded body weight (Szakmary et al. 2001). Lastly, mouse exposure to approximately 13-21 mg Co/kg-day as cobalt ethylenediamine tetraacetic acid in drinking water during late gestation and followed through day 90 showed both statistically significant increases and decreases in spleen index (spleen to body weight ratio) at various time points, although there was no consistent dose-response relationship (Gluhcheva et al. 2012). These studies show that only high doses of cobalt have the potential to induce developmental effects in laboratory animals (i.e., exceedingly high air concentrations would be required to produce the high internal doses required to produce such effects).

Even considering longer-term (i.e., subacute to chronic) exposure, the lowest potential LOAEL values referenced above based on developmental/reproductive endpoint data range from approximately 1,140 to 15,400 µg Co/m^3. These values are significantly (i.e., 30-405 times) higher than the human study LOAEL (38 µg Co/m^3) used to derive the 1-h ReV. Thus, the 1-h ReV and ESL are expected to be protective of developmental and reproductive effects.

3.1.2 Mode-of-Action (MOA)

This section contains MOA information relevant to cobalt-induced adverse effects. Additional MOA information relevant to carcinogenesis is discussed in Section 4.2.2. The toxicity of cobalt compounds is generally driven by the extent of release of the divalent Co^{2+} ion (upon dissolution of cobalt-containing substances), the common toxic moiety and environmentally stable form (CDI 2016, OECD 2014). The following summary information was taken from ATSDR (2004).

The primary effects of cobalt on respiratory tissues are seen following inhalation exposure, and include diminished pulmonary function, increased frequency of cough, respiratory inflammation, and fibrosis. Animal studies have further identified respiratory tract hyperplasia, pulmonary fibrosis, and emphysema as sensitive effects of cobalt on respiratory tissues. A number of these effects are believed to be the result of the generation of oxidants and free radicals by the cobalt ion (e.g., *in vitro* exposure to soluble cobalt increases indices of oxidative stress). Cobalt exposure also results in sensitization of the immune system. Additional information on potential MOAs is provided below.

As studies suggest that cobalt (not tungsten carbide) is the causative agent for the respiratory effects observed in hard metal (i.e., alloy with a tungsten carbide and cobalt matrix) workers and the key short-term study (Kusaka et al. 1986b) was in hard metal workers, MOA information specific to hard metal is relevant for this DSD (in addition to that for cobalt alone).

Exposure to hard metal has been shown in a number of studies to cause respiratory effects, including respiratory irritation, diminished pulmonary function, asthma, and fibrosis, at exposure levels lower than those that would produce similar effects following exposure to cobalt metal alone, making the key hard metal study a conservative choice for deriving short-term (e.g., 1-h, 24-h) ReVs. In the proposed mechanism by which hard metal may exert its effects, tungsten carbide, which is a very good conductor of electrons, facilitates the oxidation of cobalt metal to ionic cobalt (presumably Co^{2+}) by transferring electrons from the cobalt atom to molecular oxygen adjacent to the tungsten carbide molecule (the cobalt ions formed may be absorbed into the blood and transported throughout the body). The result is an increased solubility of cobalt, relative to cobalt metal alone, and the generation of active oxygen species (Lasfargues et al. 1995; Lison et al. 1995, 1996). *In vitro* evidence for this mechanism includes the ability of hard metal particles, but neither cobalt nor tungsten carbide alone at the same concentrations, to generate substantial levels of oxidant species and cause significant lipid peroxidation (Lison et al. 1995; Zanetti and Fubini 1997). Hard metal particles have also been shown to increase the levels of inducible nitric oxide synthase (iNOS), a gene responsive to oxidant stress (Rengasamy et al. 1999).

In regard to the potential for cobalt toxicity mediated through oxidant-based and free radical-based processes, exposure to soluble cobalt increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, activation of the hexose monophosphate shunt, and free-radical-induced DNA damage (Hoet et al. 2002; Kasprzak et al. 1994; Lewis et al. 1991; Zhang et al. 1998); hydrogen peroxide appears to be a necessary cofactor for cobalt-induced oxidative DNA damage (Ivancsits et al. 2002). Cobalt has been shown to generate oxygen radicals, including superoxide, both *in vitro* and *in vivo* (Kadiiska et al. 1989; Kawanishi et al. 1994; Moorhouse et al. 1985), through what may be a Fenton-type mechanism (Lloyd et al. 1997). *In vivo* exposure to cobalt in rats and guinea pigs resulted in increased lipid peroxidation in the liver (Christova et al. 2001, 2002; Sunderman and Zaharia 1988), as well as changes in reduced glutathione and hepatic levels of superoxide dismutase, catalase, heme oxygenase, and glutathione peroxidase (Christova et al. 2001, 2002). Exposure to cobalt also elicits effects on a number of genes known to be sensitive to oxidant status, including hypoxia-inducible factor 1, erythropoietin, vascular endothelial growth factor, catalase, and monooxygenase enzymes (Bunn et al. 1998; Daghman et al. 1999; Dalvi and Robbins 1978; Di Giulio et al. 1991; Goldberg et al. 1988, 1994; Ho and Bunn 1996; Hoet et al. 2002; Ladoux and Frelin 1994; Legrum et al. 1979; Semenza et al. 1994; Yasukochi et al. 1974), and may also lead, through these genes or other pathways, to the induction of apoptosis (Zou et al. 2001). A number of investigators have reported that cobalt ions can result in increased damage to DNA when co-exposed with oxidants *in vitro*, such as UV radiation or H_2O_2 (De Boeck et al. 1998; Hartwig et al. 1991; Nackerdien et al. 1991). It is believed that cobalt acts by inhibition of DNA repair, particularly the incision and polymerization steps (Asmuss et al. 2000; Kasten et al. 1997), accomplishing this through interaction with zinc finger DNA repair proteins (Asmuss et al. 2000; Sarkar 1995).

Another potential mechanism by which cobalt may exert effects is through interactions with the immune system. Exposure of humans to cobalt by the inhalation and dermal routes have resulted in sensitization to cobalt (Alomar et al. 1985; Bencko et al. 1983; Dooms-Goossens et al. 1980; Fischer and Rystedt 1983; Goh et al. 1986; Kanerva et al. 1988; Marcussen 1963; Shirakawa et al. 1988, 1989; Valer et al. 1967). Exposure to inhaled cobalt chloride aerosols can precipitate an asthmatic attack in sensitized individuals (Shirakawa et al. 1989), suggesting cobalt sensitization as one mechanism by which cobalt-induced asthma may be produced. IgE and IgA antibodies specific to cobalt have been reported in humans (Bencko et al. 1983; Shirakawa et al. 1988, 1989). There is evidence that cobalt sensitivity in humans may to be regulated by T-lymphocytes (Katsarou et al. 1997). A human helper T-lymphocyte cell line specific for cobalt ($CoCl_2$) has been established (Löfström and Wigzell 1986). Cobalt may also interact directly with immunologic proteins, such as antibodies or Fc receptors, to result in immunosensitization (Cirla 1994).

See other sources (e.g., Paustenbach et al. 2013, WHO 2006) for additional information on potential modes/mechanisms of action for cobalt and cobalt compounds.

3.1.3 Dose Metric, POD, and Critical Effects

The air concentration of cobalt (µg Co/m^3) is available for use as the dose metric and was used for derivation of the 1-h ReV. The POD is the human LOAEL of 38 µg Co/m^3 for the critical effects of respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC) due to 6-h exposure (Kusaka et al. 1986a).

3.1.4 Dosimetric Adjustments

The 6-h duration LOAEL/POD (C_1) from Kusaka et al. (1986a) was adjusted to a POD_{ADJ} of 1-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 3, where both concentration and duration play a role in toxicity (TCEQ 2015):

$$C_2 = [(C_1)^3 \times (T_1 / T_2)]^{1/3}$$
$$= [(38\ \mu g\ Co/m^3)^3 \times (6\ h/1\ h)]^{1/3}$$
$$= 69.05\ \mu g\ Co/m^3 = POD_{ADJ}$$

Thus, the duration-adjusted POD_{HEC} for derivation of the 1-h ReV for cobalt is 69.05 µg Co/m^3.

3.1.5 Adjustments of the POD

The POD_{HEC} of 69.05 µg Co/m^3 for the critical effects of respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC) was used to derive the 1-h ReV. The default approach for noncarcinogenic effects is to determine a POD and apply appropriate uncertainty factors (UFs) to derive the acute 1-h ReV (i.e., assume a threshold MOA) (TCEQ 2015).

A total UF of 100 was applied to the POD_{HEC} of 69.05 µg Co/m^3 to derive the 1-h ReV: a UF_H of 10, a UF_L of 10, and a UF_D of 1. The following is more specific concerning the rational for the applicable UFs:

- A full UF_H of 10 was used for intrahuman variability to account for potentially sensitive subpopulations (e.g., children, the elderly, those with pre-existing medical conditions);
- A full UF_L of 10 was used to extrapolate from a LOAEL-to-NOAEL; and
- A reduced UF_D of 1 was used because while the acute database for cobalt is limited, toxicological data from multiple longer-term (i.e., subacute, subchronic) animal studies strongly support the POD from the key human study as conservative. For example, the 6-h human LOAEL is ≈ 3-300 times lower than even subchronic LOAELs for less serious effects in multiple animal studies (e.g., see the intermediate exposure section of Table 3-1 in ATSDR 2004). Additionally, information regarding the potential for cobalt-induced developmental/reproductive effects is available (e.g., reproductive and developmental studies in multiple species; see Section 3.1.1.3) and indicates that the acute 1-h ReV and ESL are expected to be protective of potential developmental/reproductive effects. Thus, confidence in the database is considered high for exposure durations relevant to the evaluation and derivation of a health-protective 1-h ReV.

$$\text{acute 1-h ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$

$$= 69.05\ \mu g\ Co/m^3 / (10 \times 10 \times 1)$$
$$= 69.05\ \mu g\ Co/m^3 / 100$$
$$= 0.69\ \mu g\ Co/m^3$$

3.1.6 Health-Based Acute 1-h ReV and ^{acute}ESL

The acute 1-h ReV for cobalt is 0.69 µg Co/m^3 (rounded to two significant figures). The rounded 1-h ReV was then used to calculate the 1-h ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the acute 1-h ^{acute}ESL is 0.21 µg Co/m^3 (Table 4).

Table 4. Derivation of the Acute 1-h ReV and ^{acute}ESL

Parameter	Summary
Key Study	Kusaka et al. (1986a)
Study Population	Humans
Study Quality Confidence Level	Medium
Exposure Method	Inhalation
Critical Effects	Respiratory irritation (and reduced FVC)
Exposure Duration	6 h
POD (LOAEL)	38 µg Co/m^3
Extrapolation to 1-h	Haber's Rule, as modified by ten Berge (1986) with n=3
POD_{HEC}	69.05 µg Co/m^3
Total uncertainty factors (UFs)	100
Intraspecies UF	10
LOAEL-to-NOAEL UF	10
Database UF *Database Quality*	1 High
1-h acute ReV (HQ = 1)	**0.69 µg Co/m^3**
1-h ^{acute}ESL (HQ = 0.3)	**0.21 µg Co/m^3**

3.2 Health-Based Acute 24-h ReV

3.2.1 Key and Supporting Studies for 24-h ReV

3.2.1.1 Key Human Study

As with the 1-h ReV, the LOAEL from Kusaka et al. (1986a) of 38 µg Co/m^3 for respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC) due to 6-h exposure to hard metal dust will serve as the POD for derivation of the 24-h ReV.

3.2.1.2 Supporting Animal Studies

As with the 1-h ReV, acute/subacute animal studies such as the subacute portion of NTP (1991) and other studies (i.e., Palmes et al. 1959; Kyono et al. 1992) strongly support the key human study (Kusaka et al. 1986a) for derivation of the acute 24-h ReV. Moreover, even results from multiple subchronic animal studies (e.g., the subchronic portion of NTP 1991; Johansson et al. 1987, 1992; Kerfoot 1975) support the conservativeness of the acute assessment. More

specifically, the lowest potential acute/subacute LOAEL values from supporting studies are orders of magnitude higher than the LOAEL (38 µg Co/m^3) from the key study, and even the lowest LOAEL from the subchronic studies is higher (see Section 3.1.1.2 for more detailed information). These supporting study results provide great confidence in the conservativeness of the POD for derivation of the 24-h ReV.

3.2.1.3 Consideration of Developmental/Reproductive Effects

The potential for cobalt-induced developmental/reproductive effects is discussed in Section 3.1.1.3, which indicates that even considering longer-term (i.e., subacute to chronic) exposure, the lowest potential LOAEL values based on developmental/reproductive endpoint data range from approximately 1,140 to 15,400 µg Co/m^3. These values are significantly (i.e., 30-405 times) higher than the human study LOAEL (38 µg Co/m^3) used to derive the 24-h ReV. Consequently, the 24-h ReV and ESL are expected to be protective of developmental and reproductive effects.

3.2.2 MOA, Dose Metric, POD, and Critical Effects

See Section 3.1.2 for a discussion of the MOA information available for cobalt. The air concentration of cobalt (µg Co/m^3) is available for use as the dose metric and was used for derivation of the 24-h ReV. The POD is the human LOAEL of 38 µg Co/m^3 for the critical effects of respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC) due to 6-h exposure (Kusaka et al. 1986a).

3.2.3 Dosimetric Adjustments

The 6-h duration LOAEL/POD (C_1) from Kusaka et al. (1986a) was adjusted to a POD_{ADJ} of 24-h exposure duration (C_2) using Haber's Rule as modified by ten Berge et al. (1986) ($C_1^n \times T_1 = C_2^n \times T_2$) with n = 1, where both concentration and duration play a role in toxicity (TCEQ 2015):

$$C_2 = C_1 \times (T_1 / T_2)$$
$$= 38 \text{ µg Co/m}^3 \times (6 \text{ h}/24 \text{ h})$$
$$= 9.5 \text{ µg Co/m}^3 = POD_{ADJ}$$

Thus, the duration-adjusted POD_{HEC} for derivation of the 24-h ReV for cobalt is 9.5 µg Co/m^3.

3.2.4 Adjustments of the POD

The POD_{HEC} of 9.5 µg Co/m^3 for the critical effects of respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC) was used to derive the 24-h ReV. The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive the acute 24-h ReV (i.e., assume a threshold MOA) (TCEQ 2015).

Like the 1-h ReV, a total UF of 100 was applied to the POD_{HEC} of 9.5 µg Co/m^3 to derive the 24-h ReV: a UF_H of 10, a UF_L of 10, and a UF_D of 1. The following is more specific concerning the rational for the applicable UFs:

- A full UF_H of 10 was used for intrahuman variability to account for potentially sensitive subpopulations (e.g., children, the elderly, those with pre-existing medical conditions);
- A full UF_L of 10 was used to extrapolate from a LOAEL-to-NOAEL; and
- A reduced UF_D of 1 was used because while the acute database for cobalt is limited, toxicological data from multiple longer-term (i.e., subacute, subchronic) animal studies strongly support the POD from the key human study as conservative. For example, the 6-h human LOAEL is ≈ 3-300 times lower than even subchronic LOAELs for less serious effects in multiple animal studies (e.g., see the intermediate exposure section of Table 3-1 in ATSDR 2004). Additionally, information regarding the potential for cobalt-induced developmental/reproductive effects is available (e.g., reproductive and developmental studies in multiple species; see Section 3.1.1.3) and indicates that the acute 24-h ReV and ESL are expected to be protective of potential developmental/reproductive effects. Thus, confidence in the database is considered high for exposure durations relevant to the evaluation and derivation of a health-protective 24-h ReV.

$$\text{acute 24-h ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$

$$= 9.5\ \mu g\ Co/m^3 / (10 \times 10 \times 1)$$
$$= 9.5\ \mu g\ Co/m^3 / 100$$
$$= 0.095\ \mu g\ Co/m^3$$

3.2.5 Health-Based Acute 24-h ReV

The acute 24-h ReV for cobalt is 0.095 µg Co/m^3 (Table 5).

Table 5. Derivation of the Acute 24-h ReV

Parameter	Summary
Key Study	Kusaka et al. (1986a)
Study Population	Humans
Study Quality Confidence Level	Medium
Exposure Method	Inhalation
Critical Effects	Respiratory irritation (and reduced FVC)
Exposure Duration	6 h
POD (LOAEL)	38 µg Co/m^3
Extrapolation to 24-h	Haber's Rule, as modified by ten Berge (1986) with n=1
POD_{HEC}	9.5 µg Co/m^3
Total uncertainty factors (UFs)	100
Intraspecies UF	10
LOAEL-to-NOAEL UF	10
Database UF *Database Quality*	1 High
24-h acute ReV (HQ = 1)	**0.095 µg Co/m^3**

3.3 Welfare-Based Acute ESLs

3.3.1 Odor Perception

An $^{acute}ESL_{odor}$ value is not applicable to cobalt and cobalt compounds due to a lack of odor potential (Table 3).

3.3.2 Vegetation Effects

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne cobalt and cobalt compounds.

3.4 Acute Values for Air Permitting and Air Monitoring Evaluations

This acute evaluation resulted in the derivation of the following acute values for cobalt and cobalt compounds:

- 1-h acute ReV = 0.69 µg Co/m^3
- 1-h $^{acute}ESL$ = 0.21 µg Co/m^3

- 24-h acute ReV = 0.095 µg Co/m^3

The 1-h ^{acute}ESL for air permit evaluations is 0.21 µg Co/m^3 (Table 4). The acute 24-h ReV of 0.095 µg Co/m^3 will be used for the evaluation of 24-h air monitoring data (Table 5), although the 1-h ReV may be used as appropriate in the event air sampling is conducted over a comparable duration (Table 4). The ^{acute}ESL (HQ = 0.3) is not used to evaluate ambient air monitoring data.

3.5 Acute Inhalation Observed Adverse Effect Level

Risk assessors and the general public are interested in information on air concentrations where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific observed adverse effects levels in DSDs (TCEQ 2015). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies may identify a lower POD for this purpose.

Regarding critical effects due to acute cobalt exposure, the human study of Kusaka et al. (1986a) provides a 6-h LOAEL of 38 µg Co/m^3 for respiratory irritation complaints such as coughing, expectoration, or sore throat (and reduced FVC). Consistent with guidelines, no duration adjustment was made for the acute (i.e., 6-h) inhalation observed adverse effect level (TCEQ 2015). Thus, the $LOAEL_{HEC}$ of 38 µg Co/m^3 will serve as the acute (i.e., 6-h) inhalation observed adverse effect level (IOAEL). This 6-h IOAEL represents a concentration at which similar effects could occur in some individuals exposed to this level over the same duration as used in the study (6 h) or longer. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity. The acute (i.e., 6-h) IOAEL of 38 µg Co/m^3 is provided for informational purposes only (TCEQ 2015).

The margin of exposure (MOE) between the 6-h IOAEL and the 24-h acute ReV of 0.095 µg Co/m^3 is a factor of 400. The MOE between the 6-h IOAEL and the 1-h acute ReV of 0.69 µg Co/m^3 is a factor of approximately 55, which would be a factor of 100 if a 6-h acute ReV had been developed instead (i.e., if a duration adjustment from 6 h to 1 h had not been conducted, providing a more appropriate MOE comparison).

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

When chronic toxicity factors are identified in the scientific literature or elsewhere (e.g., databases, ATSDR toxicological profiles), they are reviewed to determine whether the approach used is similar to the procedures used by TCEQ (2015) to develop chronic ReVs. If so, the TCEQ considers adoption of the published toxicity factor, with preference given to values that have undergone an external peer review and public involvement process. This is the case for cobalt, for which ATSDR derived a chronic inhalation MRL in 2004 (ATSDR 2004). A scientific literature

search through April 2016 did not identify more appropriate key and supporting studies than those used by ATSDR to develop the chronic inhalation MRL. Additionally, ATSDR toxicological profiles and MRLs undergo internal agency review, a public comment period, and are externally reviewed by a peer review panel. Much of the text in the sections below (e.g., Section 4.1.1) was taken directly from ATSDR (2004).

The inhalation toxicity database indicates that respiratory effects are the most sensitive endpoints for derivation of a chronic toxicity factors (i.e., the respiratory system is the primary target following chronic inhalation exposure). Furthermore, the effects of chronic occupational exposure to cobalt and cobalt compounds on the respiratory system in humans are well-documented. These effects include respiratory irritation, diminished pulmonary function, wheezing, asthma, pneumonia, and fibrosis and occurred at exposure levels ranging from 0.007 to 0.893 mg Co/m^3 (exposure from 2 to 17 years) (Anttila et al. 1986; Davison et al. 1983; Demedts et al. 1984a, 1984b; Deng et al. 1991; Gennart and Lauwerys 1990; Gheysens et al. 1985; Hartung et al. 1982; Kusaka et al. 1986a, 1986b, 1996a, 1996b; Nemery et al. 1992; Raffn et al. 1988; Rastogi et al. 1991; Ruokonen et al. 1996; Shirakawa et al. 1988, 1989; Sprince et al. 1988; Sundaram et al. 2001; Swennen et al. 1993; Tabatowski et al. 1988; Van Cutsem et al. 1987; Zanelli et al. 1994). These effects have been observed in workers employed in cobalt refineries, as well as hard metal workers, diamond polishers, and ceramic dish painters (painting with cobalt blue dye).

As mentioned in Chapter 3, the TCEQ will develop chronic values (in addition to acute values) based on the cobalt content of the compound (i.e., on a Co equivalent basis). The cobalt equivalent for a given dose of a cobalt compound is based on its cobalt content, that is, the percent of the compound's MW that cobalt comprises (i.e., the compound's concentration in µg/m^3 × (MW of Co in compound / MW of compound)). From a protection of public health perspective, use of cobalt equivalents assumes that other forms are equally as toxic as the compound(s) in the key study on a µg Co/m^3 basis. This science policy decision is necessary given the lack of available studies to derive individual values for every cobalt compound and is consistent with the approach of other agencies (e.g., ATSDR). However, the derived chronic ReV and ESL values are expected to be sufficiently health-protective regardless of the environmental chemical form (e.g., cobalt oxide, sulfate, metal) because they will be based on the cobalt compound(s) that have produced adverse effects at the lowest concentrations (i.e., the most toxic form(s) in the most sensitive species based on a robust database), which is the most conservative (i.e., health-protective) choice. *The toxicity factors derived in this DSD, however, do not apply to radioactive cobalt.*

4.1.1 Key and Supporting Studies

4.1.1.1 Key Human Study

Nemery et al. (1992) conducted a cross-sectional study of cobalt exposure and respiratory effects in diamond polishers. Exposure occurred mainly from the generation of airborne cobalt resulting from the use of cobalt-containing polishing discs. Because exposure duration was not given for this occupational study, subchronic exposure was conservatively assumed for these diamond polishers. The study group was composed of 194 polishers working in 10 different workshops. In two of these workshops (#1, 2), the workers used cast iron polishing disks almost exclusively, and in the others, they used cobalt-containing disks primarily. An additional three workshops with workers engaged in sawing diamonds, cleaving diamonds, or drawing jewelry were studied as a control group (n=59). Subjects were asked to fill out a questionnaire regarding employment history, working conditions, medical history, respiratory symptoms, and smoking habits, to give a urine sample for cobalt determination, and to undergo a clinical examination and lung function tests. Both area air samples and personal air samples were collected. Sampling for area air determinations started 2 h after work began and continued until 1 h before the end of the work day. Personal air samples were collected from the breathing zone of several workers per workshop for four successive 1-h periods. In addition, personal air samplers were used to sample the air 1 cm above the polishing disks.

The polishing workshops were divided into two groups: those with low exposure to cobalt (#1-5, n=102) and those with high exposure to cobalt (#6-10, n=91). Mean cobalt exposure concentrations were 0.4, 1.6, and 10.2 µg Co/m^3 by area air sampling and 0.4, 5.3, and 15.1 µg Co/m^3 by personal air sampling in the control, low-exposure, and high-exposure groups, respectively. The mean air concentration for the controls was consistent with ambient air concentrations outside the buildings (0.7 ± 0.4 µg Co/m^3). Analysis of samples taken near the disks showed the presence of cobalt, with occasional traces of copper, zinc, titanium, manganese, chromium, silicates, and silicon dioxide. No tungsten was detected. The researchers considered cobalt to be the only relevant exposure. Smoking habits were similar in workers from the high-exposure, low-exposure, and control groups.

Workers in the high-exposure group were more likely than those in the other groups to complain about respiratory symptoms. The prevalences of eye, nose, and throat irritation and cough, and the fraction of these symptoms related to work, were significantly increased ($p<0.05$) in the high-exposure group (15.1 µg Co/m^3). Workers in the high-exposure group also had significantly reduced lung function compared to both controls and low-exposure group workers ($p<0.05$) as assessed by FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 second), MEF (maximum expiratory flow between 25 and 75% of the FVC), and mean PEF (peak expiratory flow rate). For example, FEV_1 and MEF were reduced 9-14% in men and women in the high-exposure group relative to controls, and a statistically significant FEV_1 decrease of less than 20% is considered a mild adverse effect (TCEQ 2015, OEHHA 2008). Results in the low-

exposure group did not differ from controls. This subchronic LOAEL (15.1 µg Co/m^3) is essentially identical to that for decreased pulmonary function (15.2 µg Co/m^3) in exposed workers (mean exposure of 6 years) of a diamond-cobalt circular saw plant (Gennart and Lauwerys 1990 as cited by CDI 2016). Two-way analysis of variance demonstrated that the effect on spirometric parameters in the high exposure group was present in both men and women. Women seemed to be affected more than men, but the interaction between exposure and sex was not significant. Smoking was found to exert an effect on lung function, but both the covariance analysis and multiple regression analysis found that lung function level remained negatively correlated with exposure to cobalt, independently of smoking.

ATSDR (2004) derived a chronic inhalation MRL (0.1 µg Co/m^3) based on the NOAEL of 5.3 µg Co/m^3 for significantly reduced lung function in exposed workers at the study LOAEL of 15.1 µg Co/m^3. The TCEQ will use this same POD (human NOAEL of 5.3 µg Co/m^3) based on statistically increased complaints of respiratory irritation (i.e., eye, nose, and throat irritation, cough) and reduced lung function for derivation of the chronic ReV.

4.1.1.2 Supporting Human and Animal Studies

4.1.1.2.1 Finish Cobalt Plant Studies (Roto 1980, Linna et al. 2003, Sauni et al. 2010)

CDI (2016) provides information on several studies examining lung effects in workers of a Finnish cobalt metallurgical plant in Kokkola that started operations in 1966. As summarized, the Roto (1980) study was carried out between February 1 and November 1, 1977. In the case-control study with 21 cases (male workers with bronchial asthma) and 55 controls (sex and age matched), the risk of asthma was increased for subjects exposed to cobalt (age-adjusted odds ratio (OR)=4.8, 95% confidence interval (CI)=2.0-11.7) as cobalt sulfate or cobalt metal dust for at least six months, compared to non-exposed workers. Smoking was not associated with asthma. The exposure levels ranged from less than 10 to 100 µg Co/m^3 in the cobalt plant (stationary sampling) and from 10 to 50 µg Co/m^3 in the roasting area (personal sampling). Among workers exposed to cobalt metal and/or cobalt salts, 15 cases of asthma were diagnosed. Five of them had a positive reaction to $CoCl_2$ in a provocation test and one had a positive reaction to dust from the cobalt roasting building. In 12 of the asthmatic cobalt workers, asthma disappeared after removal from workplace exposure. In a cross-sectional part of the study, the occurrence of symptoms of chronic bronchitis and an eventual decrease of ventilatory capacity in workers exposed to cobalt-containing aerosols was determined. Asthmatic subjects were excluded from the cross-sectional study. The population of 224 cobalt workers exposed to cobalt metal, oxides, and salts at concentrations ranging from 10 to about 50 µg Co/m^3 showed significantly more wheezing than the reference population of 161 non-exposed subjects, as assessed by questionnaire. These findings were predominantly observed in the presence of irritant gases. The chronic production of phlegm and wheezing were clearly associated with smoking among the cobalt workers. The prevalence of chronic bronchitis was 2% in the cobalt-exposed workers and 0% among the reference group. Multiple regression

analyses indicated that exposure to the air of the cobalt plant did not significantly decrease the FEV_1 or FVC of workers when the exposure level was below 100 µg Co/m³. The authors concluded that workers exposed to air containing cobalt sulfate at concentrations below 100 µg Co/m³ for 6-8 years did not show an increased risk of developing chronic bronchitis in this study. However, smoking highly significantly decreased the FEV_1 of cobalt workers.

In the later Linna et al. (2003) study on respiratory symptoms/diseases in the same Finnish plant, the study population included 110 current and former male cobalt workers who had worked more than 10 years in the cobalt plant. The reference group consisted of 76 plant employees (68 white-collar workers) and 64 male blue-collar maintenance workers who had worked at least 10 years, but not in the cobalt factory, and who had not been exposed to harmful dusts or fumes. Among the exposed workers (mean cumulative exposure of 1,000 µg Co-year), there was a significantly increased prevalence of suspected work-related asthma (15 subjects), phlegm, cough with wheezing, shortness of breath with wheezing and breathlessness on exertion compared to controls. No chronic respiratory diseases, except asthma, were found among non- smoking cobalt production workers. FEV_1 and MEF were significantly lower among cobalt-exposed smokers compared to smoking controls. One new case of occupational asthma (cobalt) with a positive reaction in a provocation test and one case of allergic asthma were diagnosed. At concentrations lower than 100 µg Co/m³, cobalt metal or cobalt sulfate exposure increased the risk of asthma by about five times in exposed workers. However, one limitation is that all cases of "cobalt asthma" relate to workplace exposure conditions where additional irritant gases (e.g., sulfur dioxide, hydrogen sulfide, or ammonia) were present in the ambient air.

In a more recent study (Sauni et al. 2010) of the Kokkola cobalt plant, all cases of occupational asthma encountered in the plant and diagnosed in the Finnish Institute of Occupational Health were re-evaluated. The analysis was based on the clinical data at the time of diagnosis and during a follow-up visit six month later. In addition, the incidence of cobalt asthma in different departments was evaluated on the basis of occupational exposure data. The significance of exposure to cobalt and irritant gases in workplace air in relation to the risk of cobalt asthma was also evaluated based on lung function testing. Between 1967 and 2003, a total of 22 cases of cobalt asthma (out of about 700 cobalt-exposed workers) were diagnosed in the cobalt plant. All patients except one were male. None of them had positive reactions against cobalt in skin prick tests, indicating a non-immunologic mechanism. The mean duration of symptoms was 7.4 years on average before diagnosis of occupational asthma. Mostly late or dual asthmatic reactions were observed in specific bronchial challenge tests with cobalt which may also suggest a non-immunologic mechanism of asthma. The incidence of cobalt asthma correlated with the exposure levels of cobalt in the corresponding departments of the plant during 1967-1987. The incidence density of cobalt asthma (number of new cases per person-year) was highest in the reduction and powder production department (0.02), where the cobalt exposure levels were highest (median of 150 µg Co/m³ with a range of 100-400 µg Co/m³). The incidence

density in the sulfatizing roasting department and leaching and solution purification department was 0.006 and 0.005, respectively, with median exposure levels of 100 µg Co/m³ (range of 6 -1,000 µg Co/m³) and 30 µg Co/m³ (range of 10-100 µg Co/m³), respectively. There was significant inter-individual variation in the working time before the onset of symptoms (0.1-17 years). The shortest latencies were in the sulfatizing roasting department, where the total dust concentration and the sulfur dioxide level were high (mean exposure to dust of 8,500 µg/m³ and to sulfur dioxide of 1.4 ppm). All cases of cobalt asthma were encountered in those departments where irritant gases were also present in the ambient air, in addition to cobalt. *No cases of cobalt asthma were reported in the chemical department with a cobalt exposure level of 120 µg Co/m³ (median, range of 20-300 µg Co/m³) without co-exposure to additional irritant gases.* At the time of the follow-up examination six months later, non-specific bronchial hyperreactivity had mostly remained at the same level or increased.

Based on review of these studies, CDI (2016) concludes that: (1) the risk of cobalt-induced occupational asthma increases as mean cobalt exposure levels increase; (2) irritant gases contribute to the risk; and (3) in the absence of irritant gases in workplace air, exposure to cobalt alone at 120 µg Co/m^3 (median, range of 20-300 µg/m^3) did not induce asthma. These conclusions form the basis of the occupational NOAEL proposed by CDI (2016). This proposed NOAEL for cobalt-induced occupational asthma (120 µg Co/m³) is considered by TCEQ as supporting use of the lower NOAEL of 5.3 µg Co/m^3 from Nemery et al. (1992) based on respiratory irritation (i.e., eye, nose, and throat irritation, cough) and reduced lung function for derivation of TCEQ's chronic ReV (as well as ATSDR's chronic inhalation MRL).

4.1.1.2.2 NTP (1991, 1998)

As with exposures in humans, exposures of animals to cobalt-containing aerosols have resulted in pronounced respiratory effects. Animals exposed to aerosols of cobalt oxides and cobalt sulfate develop respiratory effects that vary in severity with exposure level and duration. Similar to the ATSDR (2004) chronic inhalation MRL, two National Toxicology Program studies (NTP 1991, 1998) will be used to support the chronic ReV derivation.

In NTP (1991), necrosis and inflammation of the respiratory tract epithelium (larynx, trachea, bronchioles, nasal turbinates) were reported in rats exposed to 19 mg Co/m^3 and mice exposed to ≥ 1.9 mg Co/m^3 as cobalt sulfate over 16 days. Exposure of rats and mice to cobalt as cobalt sulfate for 13 weeks resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive. At concentrations of ≥ 0.11 mg Co/m^3, rats and mice had squamous metaplasia of the larynx. Histiocytic infiltrates in the lung were also reported at similar levels in both the rats and mice. In rats, chronic inflammation of the larynx was found at ≥ 0.38 mg Co/m^3, and more severe effects on the larynx, nose, and lung were reported at higher exposures. In mice, acute inflammation of the nose was found at ≥ 1.14 mg Co/m^3, and more severe effects on the larynx, nose, and lung were reported at higher exposures.

In NTP (1998), exposure of rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations from 0.11 to 1.14 mg Co/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice. Squamous metaplasia of the larynx occurred in rats and mice at exposure concentrations of ≥ 0.11 mg Co/m^3, with severity of the lesion increasing with increased exposure concentration. Hyperplastic lesions of the nasal epithelium occurred in rats at concentrations of ≥ 0.11 mg Co/m^3, and in mice at concentrations of ≥ 0.38 mg Co/m^3. Both sexes of rats had greatly increased incidences (> 90% incidence) of alveolar lesions at all exposure levels, including inflammatory changes, fibrosis, and metaplasia. Similar changes were seen in mice at all exposure levels, though the changes in mice were less severe.

Unlike the key human study (Nemery et al. 1992), both NTP animal studies (NTP 1991, 1998) failed to establish a NOAEL, with the lowest concentration utilized (0.11 mg Co/m^3) being the LOAEL for a variety of respiratory effects (e.g., squamous metaplasia of the larynx in rats and mice, alveolar lesions). This animal study LOAEL (110 µg Co/m^3) was not used to derive the chronic ReV since it is significantly higher than the human key study LOAEL (15.1 µg Co/m^3), which has an associated human NOAEL (5.3 µg Co/m^3), would result in a higher $LOAEL_{HEC}$ (e.g., 110 µg Co/m^3 × ATSDR RDDR of 0.16 = 17.6 µg Co/m^3), and is free-standing. Thus, use of this animal LOAEL would result in greater uncertainty (e.g., interspecies extrapolation, lack of a NOAEL). The selection of the human data over these animal data is consistent with TCEQ (2015) and ATSDR (2004), which indicates that the Nemery et al. (1992) human study was selected as the basis for derivation of the chronic inhalation MRL as it is a well-performed study in humans that defined a NOAEL and LOAEL and associated with less uncertainty. The $LOAEL_{HEC}$ based on these animal studies (NTP 1991, 1998), however, is considered supportive of that based on the human study (Nemery et al. 1992).

4.1.1.3 Consideration of Developmental/Reproductive Effects

In laboratory animals, longer-term (i.e., subacute to chronic) exposure to cobalt has resulted in effects on reproductive endpoints. Testicular atrophy was reported in rats, but not in mice, exposed to 19 mg Co/m^3 (as cobalt sulfate) over 16 days (Bucher et al. 1990; NTP 1991), and the absolute testis weight of rats exposed to 10 mg Co/m^3 (as cobalt metal) for 16 days was significantly less than that of controls (NTP 2014a). Following exposure of mice to cobalt (as cobalt sulfate) for 13 weeks, a decrease in sperm motility was found at 1.14 mg Co/m^3 with testicular atrophy at 11.4 mg Co/m^3 (Bucher et al. 1990; NTP 1991). Following exposure of mice to cobalt (as cobalt metal) for 14 weeks, the testes weights of males exposed to 5 or 10 mg Co/m^3 were significantly less than those of the chamber controls (NTP 2014a). A significant increase in the length of the estrous cycle was reported in female mice exposed to 11.4 mg Co/m^3 (as cobalt sulfate) for 13 weeks (Bucher et al. 1990; NTP 1991). No effects on the male or female reproductive systems were observed in rats similarly exposed to cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991), or in mice or rats exposed to up to 1.14 mg Co/m^3 for 104 weeks (Bucher et al. 1999; NTP 1998). Male rats and mice exposed to 5 mg Co/m^3 (as

cobalt metal) for 105 weeks had significant increases of infarct in the testis and germinal epithelial degeneration in the testes, respectively (NTP 2014a).

No studies were located regarding developmental effects in humans or animals after inhalation exposure to cobalt, so information from oral studies is presented. No developmental effects on human fetuses were observed following treatment of pregnant women with cobalt chloride to raise hematocrit and hemoglobin levels that are often depressed during pregnancy. Dosages up to 0.6 mg Co/kg-day for 90 days were given (Holly 1955). Examination of the fetuses was for overt birth defects and exposure only occurred in the final trimester. Oral exposure of female rats to cobalt chloride at 5.4 or 21.8 mg Co/kg-day from gestation day 14 through lactation day 21 has been shown to result in stunted growth and decreased survival, respectively, of newborn pups (Domingo et al. 1985). The effects on the offspring occurred at levels that also caused maternal toxicity (reduced body weight and food consumption, and altered hematological measurements) and might therefore have been an indirect effect of maternal toxicity rather than a direct effect of cobalt on the fetus (Domingo et al. 1985). Teratogenic effects were not observed. Szakmary et al. (2001) reported that exposure of pregnant rats to 0-38 mg Co/kg-day as cobalt sulfate did not result in changes in fetal death rates, maternal body weight gain, average litter size, or average fetal or placental weights; however, a dose-related trend was seen for the percent of rat fetuses with retarded body weights that was significant beginning at 19 mg Co/kg-day, although average fetal body weight was not significantly reduced at any dose (e.g., ≈ 2% at 38 mg Co/kg-day). In contrast, no effects on fetal growth or survival were found following exposure of rats to 24.8 mg Co/kg-day as cobalt chloride during gestation days 6-15 (Paternian et al. 1988). In mice, exposure to 81.7 mg Co/kg-day as cobalt chloride during gestation days 8-12 was reported to have no effect on fetal growth or mortality in mice (Seidenberg et al. 1986). In a later mouse study that exposed pregnant mice to 19 mg Co/kg-day as cobalt sulfate, no changes in litter size, post-implantation loss, or average fetal or placental weights were seen; the only difference seen was an increase in the percent of fetuses with retarded body weights (Szakmary et al. 2001). The same study reported that rabbits exposed to ≥ 38 mg Co/kg-day, as cobalt sulfate, showed nearly complete maternal lethality, and complete fetal loss. Rabbits exposed to 7.6 mg Co/kg-day, as cobalt sulfate, showed significant increases in mortality and fetal resorption, as well as an increase in fetuses with retarded body weight (Szakmary et al. 2001).). Lastly, mouse exposure to approximately 13-21 mg Co/kg-day as cobalt ethylenediamine tetraacetic acid in drinking water during late gestation and followed through day 90 showed both statistically significant increases and decreases in spleen index (spleen to body weight ratio) at various time points, although there was no consistent dose-response relationship (Gluhcheva et al. 2012). These studies show that only high doses of cobalt have the potential to induce developmental effects in laboratory animals (i.e., exceedingly high air concentrations would be required to produce the high internal doses required to produce such effects).

The lowest potential LOAEL values referenced above based on developmental/reproductive endpoint data range from approximately 1,140 to 15,400 µg Co/m^3. These values are significantly (i.e., 75-1,020 times) higher than the human study LOAEL (15.1 µg Co/m^3) ultimately used to derive the chronic ReV. Thus, the chronic ReV and ESL are expected to be protective of developmental and reproductive effects.

4.1.2 MOA, Dose Metric, POD, and Critical Effects

Please refer to Section 3.1.2 for a discussion on MOA. The air concentration of cobalt (µg Co/m^3) is available for use as the dose metric and was used for derivation of the chronic ReV. The POD is the human NOAEL of 5.3 µg Co/m^3 for the critical effects of respiratory irritation (i.e., eye, nose, and throat irritation, cough) and reduced lung function in exposed workers (Nemery et al. 1992).

4.1.3 Dosimetric Adjustments

The duration-adjusted POD was calculated as follows, consistent with TCEQ (2015):

$POD_{HEC} = POD_{OC} \times (VE_{ho}/VE_h) \times (\text{days per week}_{oc}/\text{days per week}_{res})$

where: VE_{ho} = occupational ventilation rate for an 8-h day (10 m^3/day)

VE_h = non-occupational ventilation rate for a 24-h day (20 m^3/day)

$\text{days per week}_{oc}$ = occupational weekly exposure frequency (study specific)

$\text{days per week}_{res}$ = residential weekly exposure frequency (7 days per week)

$POD_{HEC} = 5.3\ \mu g\ Co/m^3 \times 10\ m^3/20\ m^3 \times 5\ days/7\ days = 1.89\ \mu g\ Co/m^3$

Thus, the duration-adjusted POD_{HEC} for cobalt is 1.89 µg Co/m^3. This value is 15-fold lower than that proposed by CDI (2016) when adjusted for 5 day per week exposure based on the absence of cobalt-induced asthma in an occupational study by Roto (1980) with follow-up analyses by Sauni et al. (2010) (i.e., proposed environmental POD_{HEC} of 40 µg Co/m^3 × 5 days/7 days = 28.6 µg Co/m^3).

4.1.4 Adjustments of the POD

The POD_{HEC} of 1.89 µg Co/m^3 for the critical effects of respiratory irritation (i.e., eye, nose, and throat irritation, cough) and reduced lung function was used to derive the chronic ReV. The default approach for noncarcinogenic effects is to determine a POD and apply appropriate UFs to derive the chronic ReV (i.e., assume a threshold MOA) (TCEQ 2015).

A total UF of 30 was applied to the POD_{HEC} of 1.89 µg Co/m^3 to derive the chronic ReV: a UF_H of 10, a UF_{Sub} of 3, as well as a UF_D of 1. The following is more specific concerning the rational for the applicable UFs:

- A full UF_H of 10 was used to account for potential intrahuman variability (e.g., those with pre-existing respiratory illnesses, possible sensitization, individuals with a polymorphism in the HLA-DP gene that may be more susceptible to hard metal lung disease);
- A UF_{Sub} of 3 was used to extrapolate from subchronic to chronic exposure; and
- A UF_D of 1 was used because the database for cobalt is robust, with multiple chronic studies examining a variety of endpoints in humans and laboratory animals (i.e., rats, mice, hamsters). Additionally, information regarding the potential for cobalt-induced developmental/reproductive effects is available (e.g., reproductive and developmental studies in multiple species; see Section 4.1.1.3) and indicates that the chronic ReV and ESL are expected to be protective of potential developmental/reproductive effects. Thus, confidence in the database is considered medium-to-high (TCEQ 2015).

$$\text{chronic ReV} = POD_{HEC} / (UF_H \times UF_{Sub} \times UF_D)$$
$$= 1.89\ \mu g\ Co/m^3 / (10 \times 3 \times 1)$$
$$= 1.89\ \mu g\ Co/m^3 / 30$$
$$= 0.063\ \mu g\ Co/m^3$$

4.1.5 Health-Based Chronic ReV and ^{chronic}ESL

The chronic ReV for cobalt is 0.063 µg Co/m^3 (rounded to two significant figures). The rounded chronic ReV was then used to calculate the $^{chronic}ESL_{threshold(nc)}$. At the target HQ of 0.3, the $^{chronic}ESL_{threshold(nc)}$ for cobalt is 0.019 µg Co/m^3 (Table 7).

Table 6. Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	Summary
Key Study	Nemery et al. (1992)
Study Population	Humans
Study Quality Confidence Level	Medium-High
Exposure	Occupational
Critical Effect	Respiratory irritation (i.e., eye, nose, and throat irritation, cough) and reduced lung function
Exposure Duration	Subchronic
POD	5.3 µg Co/m^3 (NOAEL)
POD_{HEC}	1.89 µg Co/m^3 (POD adjusted for duration)
Total uncertainty factors (UFs)	30
Intraspecies UF	10
Subchronic UF	3
Database UF *Database Quality*	1 Medium-High
chronic ReV (HQ = 1)	**0.063 µg Co/m^3**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	**0.019 µg Co/m^3**

4.1.6 Comparison of Results

The TCEQ chronic ReV of 0.063 µg Co/m^3 is somewhat lower than the ATSDR (2004) chronic inhalation MRL (0.1 µg Co/m^3) and the WHO (2006) tolerable inhalation concentration (0.1 µg Co/m^3) set to protect the public (including sensitive subpopulations) based on the same study (Nemery et al. 1992). These chronic inhalation values would be identical if the agencies rounded values to one significant figure, although the TCEQ rounds its toxicity factors to two significant figures (TCEQ 2015).

4.2 Carcinogenic Potential

The US Environmental Protection Agency (USEPA) does not have a unit risk factor (URF) for cobalt on their Integrated Risk Information System (IRIS). However, in 2008 the USEPA Superfund Health Risk Technical Support Center, part of the National Center for Environmental Assessment, derived a provisional peer-reviewed toxicity value (PPRTV) URF of 9 per mg Co/m^3 (or 9E-03 per µg Co/m^3) for environmental exposure to cobalt (as soluble cobalt sulfate heptahydrate) based on rat lung adenomas/carcinomas combined in a chronic cancer bioassay

in rats and mice (NTP 1998; also published as Bucher et al. 1999). While human data are preferable for derivation of toxicity factors (TCEQ 2015) and available human studies have suggested a possible association between exposure to cobalt and respiratory tumors in cobalt workers (Tuchsen et al. 1996; Mur et al. 1987; Morgan et al. 1983), the limitations of these studies (e.g., small numbers of subjects, inadequate exposure assessment, potential exposure to other chemicals) make them inadequate for assessing the carcinogenic potential of cobalt (USEPA 2008).

When chronic toxicity factors are identified in the scientific literature or elsewhere, they are reviewed to determine whether the approach used is similar to the procedures used by TCEQ (2015) to derive toxicity factors (e.g., URFs). If so, the TCEQ considers adoption of the toxicity factor, with preference given to values that have undergone an external peer review and/or public involvement process. This is the case for cobalt, for which a URF (as cobalt sulfate in NTP 1998) was derived as a PPRTV in 2008 (USEPA 2008) and a URF (as cobalt metal in NTP 2014a) was published in 2016 (Suh et al. 2016). PPRTVs are developed after a review of the relevant scientific literature using the same methods, sources of data, and guidance for toxicity value derivation generally used by the USEPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. The Suh et al. (2016) study also underwent external expert peer review prior to publication in the scientific literature and well as critical review by the TCEQ for purposes of this DSD.

4.2.1 Weight of Evidence (WOE) and Classifications

IARC (2006) classified cobalt metal with tungsten carbide as *Probably Carcinogenic to Humans* (Group 2A), and both cobalt metal without tungsten carbide and cobalt sulfate and other cobalt(II) salts as *Possibly Carcinogenic to Humans* (Group 2B). More recently, USEPA (2008) indicated that under the 2005 Guidelines for Carcinogen Risk Assessment (USEPA 2005a), cobalt sulfate (soluble) is classified as *Likely to be Carcinogenic to Humans* by the inhalation route, based on both the limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals as shown by a statistically significant increased incidence of alveolar/bronchiolar tumors in both sexes of rats and mice, pheochromocytomas in female rats, and hemangiosarcomas in male mice (Bucher et al. 1999). In regard to more recent relevant information on cobalt metal, NTP (2014a) provides clear evidence of carcinogenic activity of cobalt metal in male/female rats based on increased incidences of alveolar/bronchiolar adenoma and carcinoma in the lung (including multiples) and on increased incidences of benign and malignant pheochromocytoma of the adrenal medulla (including bilateral neoplasms), and in male/female mice based on increased incidences of alveolar/bronchiolar neoplasms of the lung (predominantly carcinoma), including multiple carcinoma. The National Toxicology Program (NTP) 13th Report on Carcinogens classified cobalt sulfate as *Reasonably Anticipated to be a Human Carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals, and classified cobalt-tungsten carbide powders and hard metals as

Reasonably Anticipated to be Human Carcinogens based on limited evidence of carcinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis (NTP 2014b). Lastly, NTP (2016) indicates that cobalt and cobalt compounds that release cobalt ions *in vivo* (this class of compounds does not include cobalt-containing alloys) are *Reasonably Anticipated to be Human Carcinogens* based on experimental animal data and supporting mechanistic data (Suh et al. 2016).

Consistent with recent WOE evaluations and relevant data for several cobalt compounds (e.g., USEPA 2008; NTP 2014a, 2014b, 2016), the TCEQ conservatively considers cobalt and cobalt compounds as a group as *Likely to Be Carcinogenic to Humans* via inhalation. The TCEQ's WOE classification and inhalation URF will be applied to all forms of cobalt. Carcinogenic dose-response assessments are performed for chemicals considered by the TCEQ as *Likely to Be Carcinogenic to Humans* (or *Carcinogenic to Humans*) (TCEQ 2015).

4.2.2 Carcinogenic MOA

In the context of the MOA analysis, USEPA (2008) summarizes information on the ability of cobalt to induce genotoxicity or mutagenicity as follows [*emphasis added*]:

> While the mode of action of cobalt-induced carcinogenicity has not been determined, data suggests a number of potential biological events that might be involved including non-mutagenic genotoxicity (e.g., clastogenicity). A recent review by Lison et al. (2001) of *in vitro* and *in vivo* experiments in animal models indicates that two different mechanisms of genotoxicity may contribute to the carcinogenic potential of cobalt compounds: DNA strand breakage and inhibition of DNA repair. DNA strand breaks have been reported at non-cytotoxic concentrations in human peripheral blood monocytes (De Boeck et al. 1998, 2003a). Furthermore, oral exposure of mice to cobalt chloride resulted in significantly increased percentages of both chromosomal breaks and chromosomal aberrations in bone marrow cells (Palit et al. 1991a,b,c,d). Mechanistic studies suggest cobalt-induced oxidative stress may be involved. Exposure to cobalt compounds increases indices of oxidative stress, including diminished levels of reduced glutathione, increased levels of oxidized glutathione, increased levels of oxygen radicals and increased free-radical-induced DNA damage (Kawanishi et al. 1994; Lewis et al. 1991; Kadiiska et al. 1989; Zhang et al. 1998; Moorehouse et al. 1985). To compound the potential DNA strand breaking effects of cobalt, it appears that cobalt may also inhibit the repair of such genetic damage. A review by Hartwig and Schwerdtle (2002) concluded that cobalt may specifically target zinc finger structures in DNA repair proteins, interfering with base and nucleotide excision repair. *Collectively, while data indicate that cobalt induces DNA damage and repair inhibition, there is weak evidence to suggest direct or indirect mutagenicity in bacterial or mammalian systems.*

Thus, per USEPA, evidence suggesting cobalt-induced direct or indirect mutagenicity is weak. Although it has been hypothesized that the bronchoalveolar tumors are the result of genotoxicity (De Boeck et al. 2003b; Hartwig and Schwerdtle 2002; Lison et al. 2001), no direct evidence is available linking cobalt-induced mutagenesis to the development of cancer. For example, direct evidence demonstrating cobalt-induced mutagenic changes in cells of the respiratory tract is lacking, so temporal and dose-response concordance cannot be evaluated (much less established) between respiratory tumors and any cobalt-induced mutagenesis following inhalation exposure. Carcinogenicity through an indirect mutagenic MOA could be mediated through activated oxygen species released by inflammatory cells (e.g., macrophages, polymorpohnuclear neutrophils) rather than directly by cobalt (Lison et al. 2001), or another MOA could be responsible for cobalt-induced carcinogenicity of the respiratory tract (USEPA 2008).

Results of subchronic and chronic inhalation studies in rats and mice (Bucher et al. 1990, 1999; NTP 1991, 1998) are consistent with the hypothesis that cobalt acts through a MOA involving cytotoxicity and cellular regeneration (USEPA 2008). For example, following 3-month inhalation exposure to 0.067-6.7 mg Co/m^3 (NTP 1991; Bucher et al. 1990), rats and mice developed several lesions indicative of cell damage and proliferation throughout the entire respiratory tract (e.g., nasal epithelial degeneration and metaplasia, laryngeal inflammation and metaplasia, bronchiolar epithelial regeneration and ectasia, alveolar hyperplasia and lung fibrosis, with squamous hyperplasia of the larynx being most sensitive). The results of the 2-year carcinogenesis study (Bucher et al. 1999; NTP 1998) in rats and mice revealed a statistically significant increase in combined alveolar/bronchiolar adenomas and carcinomas in the 0.67 mg Co/m^3 group, and in female rats and mice in the 0.22 and 0.67 mg Co/m^3 groups. In this same study, granulomatous inflammation of the lung was observed at all exposure levels in rats (0.067, 0.22 and 0.67 mg Co/m^3), with other markers of cell damage and proliferation (e.g., hyperplasia, metaplasia and fibrosis) being observed in the 0.22 and 0.67 mg Co/m^3 exposure groups. Mice appeared less sensitive to cobalt-induced cytotoxicity. These results show that bronchoalveolar tumors develop at exposure levels that also produce inflammation, cell damage, and reparative proliferation, which begin at lower exposure levels and may precede the development of cancers. Taken together, the results of studies (in rodents, humans) suggest that inhaled cobalt may produce a cytotoxic response in the respiratory tract that may contribute to decreases in pulmonary function and the development of bronchoalveolar tumors. Sustained cell proliferation, in response to cytotoxicity, can be a significant risk factor for cancer (Correa 1996). Sustained cytotoxicity and regenerative cell proliferation may increase the probability that damaged DNA will not be repaired or result in the perpetuation of mutations (spontaneous or directly or indirectly induced by the chemical), resulting in uncontrolled growth (USEPA 2008).

Consistent with much of the information discussed above, CDI (2016) posits a non-genotoxic/threshold MOA for cobalt-induced carcinogenesis citing: (1) the absence of genotoxic

effects from cobalt compounds or metal in robust GLP studies *in vivo*; and (2) cobalt's ability to increase reactive oxygen species and induce tissue hypoxia and a number of inflammatory pathways leading to inflammation that may be considered as the predominant precursor to carcinogenic effects. In regard to (1) the cobalt ion being proposed as a non-DNA reactive *in vivo* carcinogen, based on review of the complete genotoxicity database (i.e., publically available data supplemented by CDI-funded, guideline compliant GLP tests to fill identified data gaps), Kirkland et al. (2015) is cited as concluding that: (a) while some cobalt compounds and cobalt metal powder exert some genotoxicity *in vitro* (mainly manifesting as DNA strand or chromosome breaks), these effects are linked with a reactive oxygen mechanism wherein cobalt is not directly mutagenic but interacts with chromosomes by producing reactive oxygen species; and (b) the absence of genotoxic effects from cobalt compounds or metal in robust GLP studies *in vivo* suggests that effective protective processes exist in whole mammals and that these *in vivo* mechanisms are sufficient to prevent DNA damage resulting from reactive oxygen (even at high doses). Regarding (2), data is cited (e.g., Bucher 1998, Behl and Hooth 2013) as demonstrating that cobalt-induced respiratory inflammation begins to occur early (e.g., within 2-12 weeks) during inhalation exposure with chronic exposure producing lung inflammation at relatively low exposure levels and earlier than neoplasms, suggesting that inflammation may be a key event in cobalt-induced carcinogenesis as chronic and sustained inflammation is a known risk factor for cancer (i.e., inflammation can lead to epithelial necrosis and degeneration, and if sustained, reparative hyperplasia can lead to tissue metaplasia and ultimately cancer) (CDI 2016). As discussed previously, in the 2-year rat study (Bucher et al. 1999; NTP 1998), granulomatous inflammation of the lung was observed at all exposure concentrations (0.067, 0.22 and 0.67 mg Co/m^3) with other markers of cell damage and proliferation (e.g., hyperplasia, metaplasia and fibrosis) being observed at 0.22 and 0.67 mg Co/m^3, indicating that bronchoalveolar tumors develop at exposure levels (0.22 and 0.67 mg Co/m^3) that also produce inflammation, cell damage, and reparative proliferation that begin at lower exposure levels and may precede the development of cancers. See other sources (e.g., ECHA 2015, Kirkland et al. 2015, Paustenbach et al. 2013, Beyersmann and Hartwig 2008, IARC 2006) for additional information relevant to the MOA.

In conclusion, although existing data provide support for several potential MOA mechanisms (e.g., cytotoxicity-induced regenerative cell proliferation, carcinogenicity mediated through activated oxygen species released by inflammatory cells, inhibition of DNA repair), the MOA for cobalt-induced carcinogenicity is not sufficiently clear as it is yet to be more fully elucidated and currently available data appear insufficient to firmly conclude that cobalt can be considered a threshold carcinogen (e.g., ECHA 2015).

4.2.3 Carcinogenic Dose-Response Assessment

The TCEQ (2015) guidelines for carcinogenic assessments employ the four-step risk assessment process formalized by the National Research Council (NRC 1983, 1994) and the procedures recommended in the most recent USEPA cancer guidelines (USEPA 2005a, 2005b) and scientific

literature. Under TCEQ guidelines, the TCEQ evaluates and adopts low-dose extrapolation approaches (e.g., nonthreshold/linear, threshold) on a chemical-by-chemical basis in the context of the relevant data available. When data on the carcinogenic MOA support a nonthreshold, linear dose-response extrapolation or sufficiently informative data on the carcinogenic MOA are lacking (i.e., the MOA is unknown), a linear extrapolation is performed to estimate excess lifetime risk at lower, environmentally-relevant doses. More specifically, the calculation of a health-protective air concentration based on carcinogenic effects due to inhalation is accomplished through the use of linear low-dose extrapolation to derive a URF. Although existing data suggest several potential MOAs, the MOA for cobalt-induced carcinogenicity is unknown (see Section 4.2.2). *Therefore, the default linear low-dose extrapolation (i.e., URF) approach will be utilized in the following sections.*

Additionally, while human data are preferable (TCEQ 2015), the limitations of available human studies (e.g., small numbers of subjects, inadequate exposure assessment, potential exposure to other chemicals) make them inadequate for assessing the carcinogenic potential of cobalt (USEPA 2008). *Therefore, animal data from two studies (NTP 1998, 2014a) will be used for the carcinogenic dose-response assessment.* NTP (1998) exposed laboratory animals to cobalt via inhalation as cobalt sulfate, while NTP (2014a) exposed animals to cobalt via inhalation as cobalt metal.

4.2.3.1 Default Linear Low-Dose Extrapolation Approach

The following sections discuss key steps in deriving a URF for cobalt using default linear low-dose extrapolation and an air concentration associated with a 1 in 100,000 excess risk, the TCEQ policy-based target risk used to calculate the cancer-based chronic ESL (i.e., $^{chronic}ESL_{nonthreshold(c)}$) (TCEQ 2015). Application of the URF to all cobalt compounds inherently treats all cobalt compounds as toxicologically equivalent based on cobalt content, consistent with the TCEQ considering cobalt compounds as a group to be *Likely to Be Carcinogenic to Humans* via inhalation.

4.2.3.1.1 Key Study 1: NTP (1998)

As indicated in Section 4.2, when chronic toxicity factors are identified in the scientific literature or elsewhere, they are reviewed to determine whether the approach used is similar to the procedures used by TCEQ (2015) to derive toxicity factors (e.g., URFs). If so, the TCEQ considers adoption of the toxicity factor. This is the case for cobalt, for which a URF (as cobalt sulfate heptahydrate) was derived as a PPRTV (USEPA 2008) based on NTP (1998) and is considered acceptable under TCEQ guidelines (TCEQ 2015). As such, this section presents the dose-response assessment documentation as found in USEPA (2008) almost verbatim.

4.2.3.1.1.1 Dosimetric Adjustments and Dose-Response Data

In USEPA (2008), the NTP (1998; also published as Bucher et al. 1999) 2-year carcinogenicity study in rats and mice exposed to cobalt sulfate heptahydrate was chosen as the principal study

for the derivation of an inhalation URF, based on the dose-response relationship for statistically significant increased incidences of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma). Groups of 50 male and 50 female rats and mice were exposed to aerosols containing 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate heptahydrate 6 h per day, 5 days per week, for 105 weeks. Although statistically significant increases in the incidences of pheochromocytomas and hemangiosarcomas were observed in female rats and male mice, respectively, these tumors were not considered for the derivation of the URF because a higher and more consistent response across species was observed for alveolar/bronchiolar tumors.

In 3.0 mg/m^3 male rats, the combined incidence of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma) was significantly greater than in the chamber controls. In female rats exposed to 1.0 or 3.0 mg/m^3, the incidences of alveolar/bronchiolar neoplasms (including combined adenoma and/or carcinoma) were significantly greater than those in the chamber control group and exceeded the NTP historical control ranges. In mice, the incidences of alveolar/bronchiolar neoplasms (including combined adenoma and/or carcinoma) in 3.0 mg/m^3 males and females were significantly greater than those in the chamber control groups, and per Table 11 of NTP (1998) the combined incidence of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma) in female mice was also significantly greater than in the chamber controls at 1.0 mg/m^3. Additionally, the combined incidences of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma) and the incidences of alveolar/bronchiolar carcinoma in 3.0 mg/m^3 males and females, and the incidence of alveolar/bronchiolar adenoma in 3.0 mg/m^3 females, exceeded the NTP historical control ranges for inhalation studies (NTP 1998).

The exposure concentrations were adjusted to continuous exposure as follows:

$$Conc_{[ADJ]} = Conc \times \frac{5\ days/\ week}{7\ days/\ week} \times \frac{6\ hours/\ day}{24\ hours/\ day}$$

This adjustment resulted in duration-adjusted concentrations of 0, 0.012, 0.040, and 0.120 mg Co/m^3, respectively, for exposure to cobalt sulfate hexahydrate at 0, 0.3, 1.0, and 3.0 mg/m^3 exposure levels. As specified in the RfC guidelines (USEPA 1994), human equivalent concentrations (HECs) were calculated in mg Co/m^3 at each exposure level for each species and sex assuming exposure to particulates (MMAD = 1.5 µm, σg = 2.2) (USEPA 2008). Table 7 shows the resulting HECs.

Table 7. Human Equivalent Concentrations (HECs) for the NTP (1998) Study [a]

Duration-Adjusted Exposure Group Concentrations	HECs based on Male Rat Exposures (mg Co/m^3)	HECs based on Female Rat Exposures (mg Co/m^3)	HECs based on Male Mouse Exposures (mg Co/m^3)	HECs based on Female Mouse Exposures (mg Co/m^3)
Controls	0	0	0	0
Low (0.012 mg Co/m^3)	0.010	0.0095	0.018	0.017
Medium (0.040 mg Co/m^3)	0.033	0.032	0.059	0.058
High (0.120 mg Co/m^3)	0.10	0.095	0.18	0.17

[a] Based on RDDRs of 0.83, 0.79, 1.48, and 1.44 for the thoracic region of the respiratory tract in male rats, female rats, male mice, and female mice, respectively.

Table 8 provides the rat and mouse alveolar/bronchiolar tumor incidence data, along with the calculated HECs.

Table 8. Alveolar/Bronchiolar Tumor Dose-Response Data for the NTP (1998) Study [a]

Species/Gender	Human Equivalent Concentration (mg Co/m^3)			
F-344 Rats/Male	0	0.010	0.033	0.10
Incidence of Lung Adenomas/Carcinomas	1/50	4/50	4/48	7/50 [b]
	Human Equivalent Concentration (mg Co/m^3)			
F-344 Rats/Female	0	0.0095	0.032	0.095
Incidence of Lung Adenomas/Carcinomas	0/50	3/49	15/50 [b]	15/50 [b]
	Human Equivalent Concentration (mg Co/m^3)			
F-344 Mice/Male	0	0.018	0.059	0.18
Incidence of Lung Adenomas/Carcinomas	11/50	14/50	19/50 [c]	28/50 [b]
	Human Equivalent Concentration (mg Co/m^3)			
F-344 Mice/Female	0	0.017	0.058	0.17
Incidence of Lung Adenomas/Carcinomas	4/50	7/50	13/50 [b]	18/50 [b]

[a] From Table 6 of USEPA (2008).
[b] Statistically significantly elevated per Tables 5 and 11 of NTP (1998).
[c] p=0.071 per Table 11 of NTP (1998).

These dose-response data (i.e., HECs, lung adenoma/carcinoma incidences) were used by USEPA (2008) for the BMD modeling of alveolar/bronchiolar tumors in rats and mice.

4.2.3.1.1.2 BMD Modeling

All models for quantal data in the USEPA BMD software were fit to incidence for tumors (adenomas and carcinomas combined) in rats and mice. Males and females were modeled separately for both rats and mice. All datasets modeled showed a statistical trend for increased tumor incidence with increasing exposure concentration. In accordance with the USEPA BMD methodology (USEPA 2000, 2012), the default benchmark response (BMR) of 10% increase in extra risk was used as the basis for the BMD (i.e., $BMD_{10\text{-}HEC}$), with the $BMDL_{10\text{-}HEC}$ represented by the 95% lower confidence limit on the BMD_{10}. Table 9 summarizes the BMD modeling results.

Table 9. Summary of BMD Modeling Results based on the NTP (1998) Study [a]

Tumor Type	Species	Gender	Best-Fitting Model [b]	Dataset	$BMD_{10\text{-}HEC}$ (mg Co/m^3)	$BMDL_{10\text{-}HEC}$ (mg Co/m^3)
Lung Adenomas/ Carcinomas	rat	male	log logistic	full	0.085	0.035
		female	log probit	high dose dropped	0.014	**0.011**
	mouse	male	log logistic	full	0.026	0.015
		female	log logistic	full	0.038	0.023

[a] From Table 6 of USEPA (2008).
[a] Lowest AIC with goodness-of-fit p value > 0.1.

$BMDL_{10\text{-}HEC}$ values shown in Table 9 were derived from acceptable model fits (i.e., all goodness-of-fit p values ≥ 0.51). As is shown in Table 9, $BMDL_{10\text{-}HEC}$ values were similar (i.e., within a factor of 3.2) across study groups, with a range of 0.011-0.035 mg Co/m^3. Lung tumors in female rats were chosen as the endpoint for use as a POD ($BMDL_{10\text{-}HEC}$ of 0.011 mg Co/m^3 or 11 µg Co/m^3) for derivation of the URF. The $BMDL_{10\text{-}HEC}$ for this endpoint was the lowest for all study groups (i.e., male and female rats and mice) and was based on a model (log probit model) that showed a good fit to the data (p = 0.843, lowest AIC), as reflected in the similarity of the $BMDL_{10\text{-}HEC}$ and $BMD_{10\text{-}HEC}$ values (i.e., within a factor of 1.3 apart) after dropping the high exposure group (see Figure 1). Dropping the high exposure group is recommended according to USEPA procedure (USEPA 2000, 2012) when no models achieve adequate fit using all exposure levels, which was the case for the full female rat dataset. Although this left only two exposure levels (in addition to the control), these exposure levels are in the low-dose portion of the curve within the region of the dose-response relationship in which response is increasing with exposure level (i.e., the region of interest for deriving the POD) and bracket the derived $BMD_{10\text{-}HEC}$/$BMDL_{10\text{-}HEC}$ (USEPA 2008).

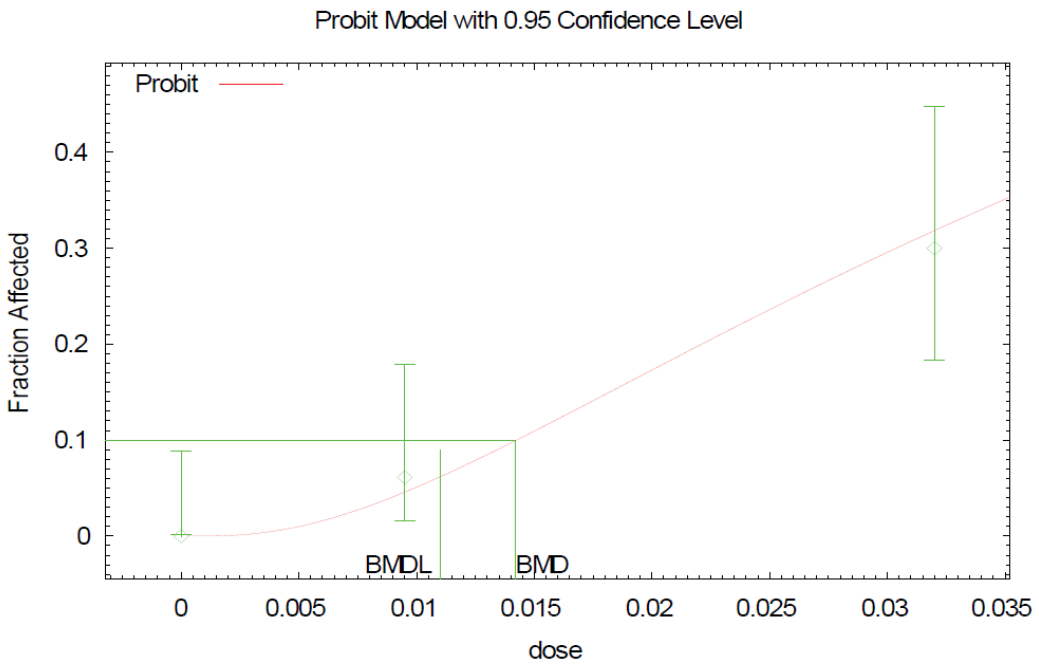


Figure 1. Log Probit Model Fit to Female Rat Lung Adenoma/Carcinoma Data from NTP (1998) [high dose dropped]

Additionally, the TCEQ notes that the selected POD ($BMDL_{10\text{-}HEC}$ of 11 µg Co/m^3) is: (1) identical to the $BMDL_{10\text{-}HEC}$ from the log logistic model that almost achieved adequate model fit based on the goodness-of-fit p value (p = 0.09, lowest AIC) for female rats using the full dataset (i.e., all dose groups); (2) similar to the HEC (0.0095 mg Co/m^3) where a 6.1% increase in incidence (not statistically significant) was observed; and (3) also similar to the $BMDL_{10\text{-}HEC}$ value for lung tumors in male rats (0.015 mg Co/m^3) based on the full dataset.

4.2.3.1.1.3 URF based on NTP (1998)

URFs express cancer potency in units of excess risk per air concentration (e.g., excess risk per µg/m^3) assuming continuous lifetime exposure. They are calculated using linear low-dose extrapolation when the carcinogenic MOA is mutagenic, unknown, or sufficient information to justify an alternative extrapolation approach is not available (TCEQ 2015). As mentioned previously, since the MOA for cobalt-induced lung carcinogenesis is yet to be fully elucidated, default linear low-dose extrapolation is utilized to derive the URF estimates herein.

When a dose-response curve is modeled for tumor data (see Figure 2 below), the URF is the slope of a straight line from the POD to the origin, with the POD being the lowest tumor response level supported by the study data.

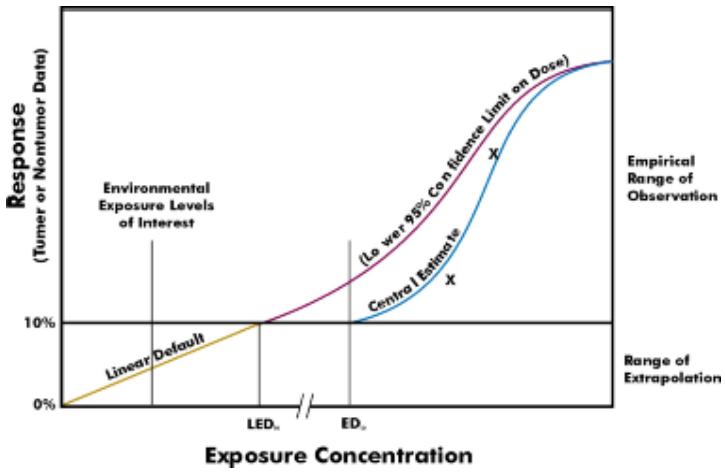


Figure 2. Example of Linear Approach for Low-Dose Extrapolation

Frequently in animal-based risk estimates, the lower statistical bounds on the concentration producing a 10% excess tumor response (LEC_{10}) is used as the POD for linear low-dose extrapolation and calculation of the URF since the limit of detection of tumor studies is often around 10%, and the resulting equation is:

$$URF = \text{risk per } \mu g/m^3 = 0.10 / LEC_{10} \text{ (where } LEC_{10} \text{ is expressed in } \mu g/m^3)$$

Such is the case for this cancer assessment. Thus, the URF based on the NTP (1998) study is calculated as follows:

$$URF = 0.10 / LEC_{10} = 0.10 / BMDL_{10\text{-}HEC} \text{ of 11 } \mu g\ Co/m^3 = 9.09E\text{-}03 \text{ per } \mu g\ Co/m^3$$

This URF (9.1E-03 per µg Co/m^3 rounded to two significant figures) would be identical to the USEPA (2008) URF (9E-03 per µg Co/m^3) if rounded to one significant figure, although the TCEQ rounds toxicity factors to two significant figures (TCEQ 2015). *Thus, based on the preferred BMD analysis (see Section 4.2.3.1.1.2), the TCEQ URF for cobalt based on NTP (1998) is 9.1E-03 per µg Co/m^3.*

Because NTP (1998) exposed laboratory animals to cobalt via inhalation as cobalt sulfate while NTP (2014a) exposed animals to cobalt via inhalation as cobalt metal, the TCEQ will also utilize a URF for cobalt based on the results of NTP (2014a) as evaluated by Suh et al. (2016) prior to determining the final URF.

4.2.3.1.2 Key Study 2: NTP (2014a)

As indicated in Section 4.2.3.1.1, when chronic toxicity factors are identified in the scientific literature or elsewhere, they are reviewed to determine whether the approach used is similar

to the procedures used by TCEQ (2015) to derive toxicity factors (e.g., URFs). If so, the TCEQ considers adoption of the toxicity factor. This is the case for cobalt, for which a URF (as cobalt metal) was proposed in Suh et al. (2016) based on NTP (2014a) and is considered acceptable under TCEQ guidelines (TCEQ 2015). As such, this section presents relevant dose-response assessment documentation as provided in Suh et al. (2016).

4.2.3.1.2.1 Dosimetric Adjustments and Dose-Response Data

In Suh et al. (2016), the NTP (2014a) 2-year carcinogenicity study in rats and mice exposed to cobalt metal was the principal study for the derivation of a proposed URF for cobalt (as cobalt metal), based on the dose-response relationship for statistically significant increased incidences of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma). Groups of 50 male and 50 female rats and mice were exposed to aerosols containing 0, 1.25, 2.5, or 5.0 mg/m^3 cobalt metal 6 h per day, 5 days per week, for 105 weeks. Although statistically significant increases in the incidences of pheochromocytomas and pancreatic neoplasms (adenoma and/or carcinoma) were observed in rats (male and/or female), use of these tumor endpoints for derivation of the URF would be less conservative than using alveolar/bronchiolar tumors as the basis for the URF proposed in this study (see Table 3 of Suh et al. 2016).

In rats, the incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) occurred with positive trends in male and female rats, and the incidences were significantly greater than those in the chamber controls with the exception of the incidence of alveolar/bronchiolar adenoma in 1.25 mg/m^3 females. The incidences of multiple alveolar/bronchiolar adenoma and carcinoma generally increased with increasing exposure concentration, and the incidences of multiple carcinoma were significantly increased in all exposed groups of males and in 5 mg/m^3 females. In mice, carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) occurred with positive trends in male and female mice, and the incidences were all significantly greater than those in the chamber controls. The incidences of alveolar/bronchiolar adenoma were significantly increased in 2.5 mg/m^3 males and in 5 mg/m^3 females. The incidences of multiple alveolar/bronchiolar carcinoma were significantly increased in all exposed groups of males and females.

The exposure concentrations were adjusted to continuous exposure as follows:

$$Conc_{[ADJ]} = Conc \times \frac{5\ days/\ week}{7\ days/\ week} \times \frac{6\ hours/\ day}{24\ hours/\ day}$$

This adjustment resulted in duration-adjusted concentrations of 0, 0.223, 0.446, and 0.893 mg Co/m^3, respectively, for exposure to cobalt metal at 0, 1.25, 2.5, and 5.0 mg Co/m^3 exposure levels. HECs were calculated at each exposure level for each species and sex with the MMAD and σg values shown in Table 10, which also provides the resulting HECs.

Table 10. HECs for the NTP (2014a) Study [a]

Duration-Adjusted Exposure Group Concentrations (mg Co/m³)	MMAD (µm)	GSD	RDDR	HEC [b] (mg Co/m³)	Incidence of Lung Adenomas/Carcinomas [c]
Male Mice					
0				0	33.0%
0.223	1.65	1.8	0.984	0.220	85.0% [d]
0.446	1.85	1.7	0.95	0.424	89.7% [d]
0.893	1.85	1.7	0.95	0.848	95.9% [d]
Female Mice					
0				0	18.0%
0.223	1.65	1.8	0.957	0.214	63.7% [d]
0.446	1.85	1.7	0.926	0.413	84.6% [d]
0.893	1.85	1.7	0.926	0.827	91.6% [d]
Male Rats					
0				0	4.0%
0.223	1.55	1.8	0.55	0.123	50.0% [d]
0.446	1.8	1.7	0.564	0.252	78.0% [d]
0.893	1.8	1.75	0.552	0.493	88.0% [d]
Female Rats					
0				0	4.5%
0.223	1.55	1.8	0.592	0.132	34.7% [d]
0.446	1.8	1.7	0.635	0.283	48.5% [d]
0.893	1.8	1.75	0.619	0.553	86.2% [d]

[a] Based on Table S1 of Suh et al. (2016).

[b] Calculated as the duration-adjusted concentration × RDDR for the pulmonary region.

[c] Conservatively, rates adjusted for intercurrent mortality (i.e., non-tumor related deaths during the study) were used for all exposure groups of a species/sex when survival was significantly reduced ($p<0.05$) or practically statistically reduced (e.g., $p=0.061$ for female mice in the highest exposure group) for at least one exposure group per Tables 9 and 26 of NTP (2014a).

[d] Statistically significantly elevated per Tables A2, B2, C2, and D2 of NTP (2014a).

These dose-response data (i.e., HECs, lung adenoma/carcinoma incidences) were used by Suh et al. (2016) for the BMD modeling of alveolar/bronchiolar tumors.

4.2.3.1.2.2 BMD Modeling

USEPA BMD software (v2.4) was used to model the incidences of lung tumors (adenomas and carcinomas combined) based on results in rats and mice and corresponding continuous exposure HECs. Males and females were modeled separately for both rats and mice, using the multistage cancer model. In accordance with the USEPA BMD methodology (USEPA 2000, 2012), the default BMR of 10% increase in extra risk was initially used as the basis for the BMD (i.e., $BMD_{10\text{-}HEC}$), with the $BMDL_{10\text{-}HEC}$ represented by the 95% lower confidence limit on the $BMD_{10\text{-}HEC}$. Table 11 summarizes the BMD modeling results from Suh et al. (2016).

Table 11. Summary of BMD Modeling Results based on the NTP (2014a) Study [a]

Tumor Type	Species	Gender	$BMD_{10\text{-}HEC}$ (mg/m^3)	$BMDL_{10\text{-}HEC}$ (mg/m^3)	BMR_{Alt}	$BMDL_{Alt\text{-}HEC}$ (mg/m^3)
Lung Adenomas/ Carcinomas	rat	male	0.0209	0.0174	48%	0.108
		female	0.0365	0.0295	**32%**	**0.108**
	mouse	male	0.0226	0.0174	78%	0.250
		female	0.0304	0.0244	56%	0.190

[a] From Tables 3 and 4 of Suh et al. (2016); air concentrations are continuous HECs.

However, the level of the BMR chosen for BMD modeling should be the lowest dose level adequately supported by the data (TCEQ 2015) and the $BMDL_{10\text{-}HEC}$ values estimated are approximately 4.5- to13-fold lower than even the lowest non-zero, duration-adjusted HEC doses (see Tables 10 and 11), resulting in a greater than desired level of extrapolation below the empirical study data and appreciable uncertainty in the estimation of a potential POD. Consequently, alternative BMRs were utilized by Suh et al. (2016) consistent with a recent USEPA assessment (USEPA 2011). More specifically, USEPA derived dataset-specific alternative BMR values as follows:

$$BMR_{Alt} = [P(\text{lowest dose group}) - P(\text{control}) \div [1 - P(\text{control})]]$$

Using female rats as an example…

$$BMR_{Alt} = [0.347 - 0.045 \div [1 - 0.045]] = 0.302 \div 0.955 = 0.32 \text{ or } 32\%$$

Thus, consistent with USEPA methodology, dataset-specific BMR_{Alt} values were calculated and used to calculate corresponding $BMDL_{Alt\text{-}HEC}$ values which account for the high incidences of lung adenomas/carcinomas in the NTP (2014a) study. The multistate cancer model adequately fit the male rat, female rat, and female mouse data based on the goodness of fit p-value

criterion generally recommended (p-value > 0.1), visual inspection of the dose-response curves relative to data points, and scaled residuals less than an absolute value of 2 (Thompson 2016). Additionally, the multistage cancer model had an acceptable goodness of fit p value (0.0665) for the male mouse data considering scaled residuals less than an absolute value of 2 and that USEPA guidance indicates that an exception to the general recommendation for the goodness of fit criterion (p-value > 0.1) is when there is an a priori reason to prefer a specific model (e.g., using the multistage cancer model to model cancer/neoplasm incidence), in which case a more conventional value such as 0.05 may be considered (see p.33 of USEPA 2012). Furthermore, this is consistent with USEPA (2013), which indicates that the "cancer model" does not fit adequately if the p-value is not greater than 0.05 (see p. C-9 of USEPA 2013). Notably, the female rat data showed the lowest scaled residual (0.013) at the low dose with excellent fit confirmed by visual inspection (Figure 3), which complements the lowest dataset-specific BMR_{Alt} (32%) that is most similar to the default BMR of 10%.

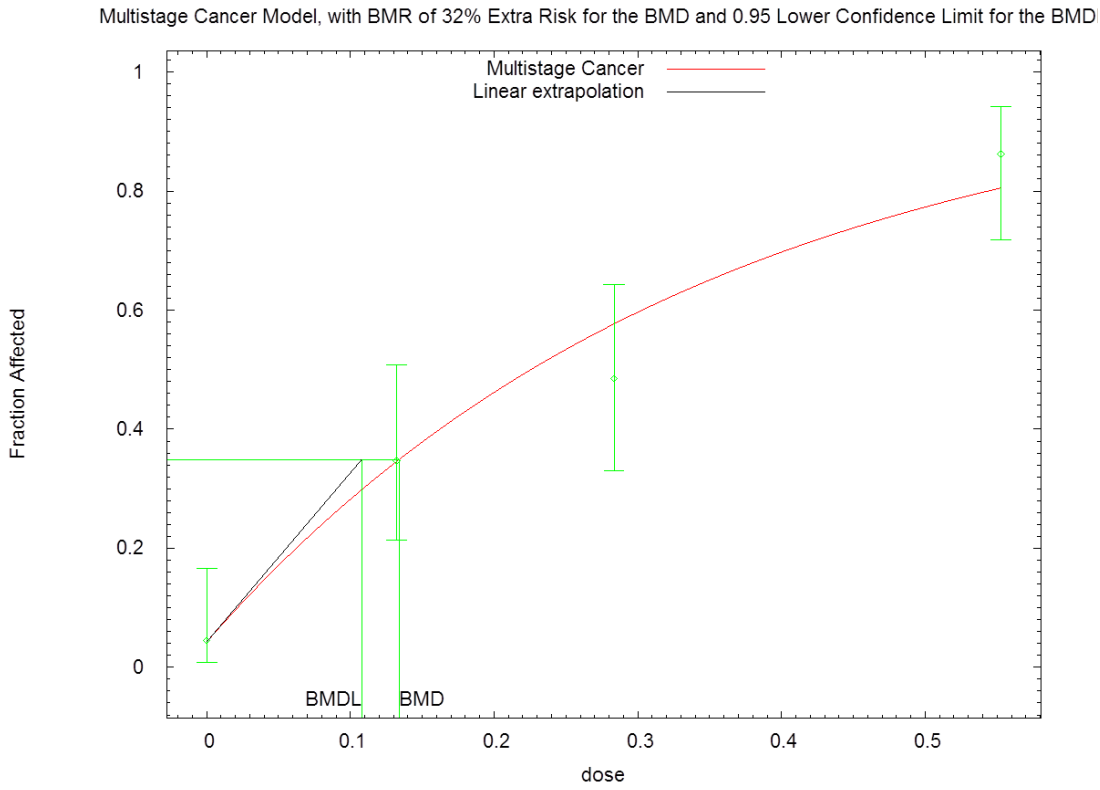


Figure 3. Multistage Model Fit to Female Rat Lung Adenoma/Carcinoma Data from NTP (2014a)

Importantly, all BMDLAlt-HEC values are within 1.2-fold of the lowest non-zero, duration-adjusted HEC doses (see Tables 10 and 11), resulting in a greater confidence in the estimation of a POD.

4.2.3.1.2.3 URF based on NTP (2014a)

As shown in Table 11, calculated $BMDL_{Alt\text{-}HEC}$ values are within a factor of 2.3 of each other. Based on these $BMDL_{Alt\text{-}HEC}$ values, Suh et al. propose the average URF of 3E-03 per µg/m^3 (3.4E-03 per µg/m^3 rounded to one significant figure) in their paper. Moreover, the TCEQ notes that female rats had the best model fit at the low dose (i.e., lowest scaled residual, visual inspection) and the lowest dataset-specific BMR_{Alt} (32%), which is more similar to the default BMR of 10% for low dose extrapolation and derivation of a URF. Accordingly, a URF based on the $BMDL_{Alt\text{-}HEC}$ value for female rats would be calculated as follows:

URF = 0.32 / $BMDL_{Alt\text{-}HEC}$ = 0.32 / 108 µg Co/m^3 = 2.96E-03 per µg Co/m^3

This URF (3.0E-03 per µg Co/m^3 rounded to two significant figures) is almost identical to that which would be based on the $BMDL_{10\text{-}HEC}$ (0.10 / 29.5 µg Co/m^3 = 3.4E-03 per µg Co/m^3) and is identical to that proposed by Suh et al. (2016), although the TCEQ rounds toxicity factors to two significant figures (TCEQ 2015). *Thus, the TCEQ URF for cobalt based on NTP (2014a) is 3.0E-03 per µg Co/m^3.*

4.2.3.2 Evaluating Susceptibility from Early-Life Exposures

USEPA (2008) indicates that because a mutagenic MOA cannot be established for the carcinogenicity of inhaled cobalt, the application of age-dependent adjustment factors (ADAFs) as described in USEPA (2005b) is not recommended. The TCEQ concurs with this conclusion. Therefore, ADAFs will not be applied at this time, consistent with both TCEQ and USEPA guidelines (USEPA 2005b; TCEQ 2015). This determination may be revisited in the future if and when significant new carcinogenic MOA data become available for cobalt.

4.2.3.3 Final URF and $^{chronic}ESL_{nonthreshold(c)}$

The TCEQ URFs for cobalt based on NTP (1998) and NTP (2014a) are 9.1E-03 per µg Co/m^{3}and 3.0E-03 per µg Co/m^3, respectively, and show excellent agreement as to the excess risk potentially associated with chronic exposure to high concentrations of cobalt sulfate and cobalt metal. In the absence of source-specific information as to the form of cobalt emitted that identifies one of the URFs as clearly more appropriate, the TCEQ will use the midpoint of these URFs for the final URF (e.g., similar to USEPA 1987). Thus, the final TCEQ URF for cobalt is 6.0E-03 per µg Co/m^3, based on the midpoint of the URFs derived for the two forms of cobalt (i.e., cobalt sulfate and metal) evaluated by NTP (1998, 2014a). Available source-specific information, however, may indicate that use of either URF is more scientifically defensible for a particular purpose (e.g., the URF of 3.0E-03 per µg Co/m^3 along with an air concentration of 0.0033 µg Co/m^3 corresponding to the no significant excess risk level of 1 in 100,000 would be appropriate when evaluating representative long-term, public exposure air concentrations resulting from cobalt metal emissions). As the TCEQ considers cobalt and cobalt compounds as a group to be *Likely to Be Carcinogenic to Humans* via inhalation, the TCEQ's inhalation URF will be applied to all forms of cobalt. This URF represents an important regulatory carcinogenic

assessment update as USEPA does not have a URF for cobalt on IRIS (only as a PPRTV). Based on the final URF, the air concentration corresponding to the no significant excess risk level of 1 in 100,000 is 0.0017 µg Co/m^3 when rounded to two significant figures (i.e., 0.00001 / 6.0E-03 per µg Co/m^3). Therefore, the $^{chronic}ESL_{nonthreshold(c)}$ is 0.0017 µg Co/m^3.

4.3 Welfare-Based Chronic ESL

No useful data were found regarding potential adverse vegetative effects due to direct exposure to airborne cobalt.

4.4 Chronic Values for Air Permitting and Air Monitoring Evaluations

The chronic evaluation resulted in the derivation of the following chronic values:

- chronic ReV = 0.063 µg Co/m^3
- $^{chronic}ESL_{threshold(nc)}$ = 0.019 µg Co/m^3
- $^{chronic}ESL_{nonthreshold(c)}$ = 0.0017 µg Co/m^3

The chronic ESL for air permit evaluations is the $^{chronic}ESL_{nonthreshold(c)}$ of 0.0017 µg Co/m^3 as it is lower than the $^{chronic}ESL_{threshold(nc)}$ of 0.019 µg Co/m^3 (Table 2). For evaluation of long-term ambient air monitoring data, the $^{chronic}ESL_{nonthreshold(c)}$ of 0.0017 µg Co/m^3 is lower than the chronic ReV of 0.063 µg Co/m^3 (Tables 1 and 2). However, both values may also be used for the evaluation of long-term air data. The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) value is not used to evaluate ambient air monitoring data.

4.5 Subchronic and Chronic IOAELs

4.5.1 Subchronic Noncarcinogenic IOAEL

The inhalation toxicity database indicates that respiratory effects are the most sensitive endpoints of long-term exposure (ATSDR 2004). More specifically, respiratory irritation (i.e., eye, nose, and throat irritation, cough) and reduced lung function are the critical effects and occurred in workers subchronically exposed to 15.1 µg Co/m^3 (Nemery et al. 1992).Thus, the POD_{HEC} of 15.1 µg Co/m^3 will be used as the subchronic IOAEL. As the basis for development of IOAELs is limited to available data, future studies may identify a lower POD for this purpose. This value represents a concentration at which it is probable that similar effects could occur in some individuals exposed subchronically to this level (or greater). Importantly, adverse effects are not a certainty due to potential intraspecies differences in sensitivity. The subchronic IOAEL of 15.1 µg Co/m^3 is provided for informational purposes only (TCEQ 2015).

The MOE between the subchronic IOAEL of 15.1 µg Co/m^3 and the chronic ReV of 0.063 µg Co/m^3 is a factor of approximately 240.

4.5.2 Chronic Carcinogenic IOAEL

A chronic (i.e., lifetime) carcinogenic IOAEL may be estimated based on an evaluation of the dose-response data. In this case, Table 8 identifies 0.032 mg Co/m^3, or 32 µg Co/m^3, as the lowest duration-adjusted POD_{HEC} corresponding to a laboratory animal (i.e., female rat) exposure that statistically increased the incidence of lung neoplasms (i.e., adenoma and/or carcinoma in NTP 1998). However, TCEQ guidance suggests avoiding duration adjustments when determining IOAELs since the resulting concentrations are not representative of those where excess risk was induced by the exposure (TCEQ 2015). Accounting for the duration adjustment (i.e., reversing it by multiplying the duration-adjusted POD_{HEC} by 7/5 days $\times$ 24/6 h = 5.6), the POD_{HEC} is 179 µg Co/m^3, which represents a chronic (i.e., lifetime) concentration at which it is possible that individuals exposed chronically could experience an increased risk of lung neoplasms. Thus, 179 µg Co/m^3 will be used as the chronic (i.e., lifetime) carcinogenic IOAEL. Increased risk is not a certainty due to potential interspecies and intraspecies differences in sensitivity. For example, the value would be 325 µg Co/m^3 if female mice in NTP (1998) were a more appropriate carcinogenicity animal model for humans than female rats, and the value would be 560 µg Co/m^3 if male rats were a more appropriate animal model (Table 8). The chronic carcinogenic IOAEL of 179 µg Co/m^3 is over 100,000 times greater than the $^{chronic}ESL_{nonthreshold(c)}$ of 0.0017 µg Co/m^3, and is provided for informational purposes only (TCEQ 2015).

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