Air Toxics Hot Spots Program

Inhalation Cancer Unit Risk (IUR)

Cobalt and Cobalt Compounds

Office of Environmental Health Hazard Assessment

October 4, 2019 SRP Review

Cobalt and Cobalt Compounds

- **Elemental cobalt: #27 on the Periodic Table**
- **Transition metal: can generate reactive oxidant species in biological systems**

Uses

- **Cobalt metal powder - used as alloying component in "hard metal"**
- **Cobalt oxides and salts – used as pigments in glass and ceramics**
- **A primary component in lithium- and nickel-based rechargeable batteries**

Cobalt and Cobalt Compounds

Ambient air levels of cobalt:

- **0.0005 to 0.005 nanograms per cubic meter (ng/m^3) in rural and wilderness areas of California**
- **Mean 2017 air concentrations in urban Southern California: 1.3 to 1.97 ng/m^3, with maximum levels of 2.9 – 5.6 ng/m^3**

Cobalt and Cobalt Compounds

- **Bioaccessibility of cobalt ion (Co^{+2}) is an important factor for carcinogenicity**
  - **Inhaled cobalt compound particles that are water-soluble (>100 mg/L) will dissolve in the alveolar lining fluid and release the cobalt ion**
  - **Water-insoluble cobalt compound particles (≤100 mg/L) reaching distal airways and alveoli may be uptaken by macrophages and other pulmonary cells by endocytosis, then dissolve intracellularly in the acidic environment of lysosomes (pH 4.5 to 5)**

Cobalt and Cobalt Compounds

Some Commercially important cobalt compounds

Molecular Formula	Molecular Weight	Cobalt Compound	CAS #	Water Solubility
Co	58.9	Cobalt metal particles	7440-48-4	2.9 mg/l
$CoSO_4$	281.1	Sulfate (heptahydrate)	10026-24-1	604,000 mg/l
$CoCl_2$	129.9	Chloride (hexahydrate)	7646-79-9	450,000 mg/l
CoO	74.9	Oxide (II)	1307-96-6	4.9 mg/l
Co_3O_4	240.8	Oxide (II,III)	1308-06-1	1.6 mg/l

Cobalt and Cobalt Compounds Toxicokinetics

- **Human acute inhalation studies - see multiphasic elimination of inhaled cobalt metal or oxides from lungs:**
  - **Rapid, initial phase - $t_{1/2}$ 2-44 hrs (mucociliary clearance)**
  - **Intermediate phase $t_{1/2}$ 10-78 days (macrophage-mediated clearance)**
  - **Fraction of inhaled cobalt retained long term (cobalt bound to cellular components in the lung)**
- **With short term exposure, cobalt did not translocate or accumulate appreciably in other tissues**

Cobalt and Cobalt Compounds Toxicokinetics

National Toxicology Program (NTP) conducted 13-week and 2-year inhalation studies with cobalt metal dust in rats and mice.

- **Cobalt concentrations and burdens in exposed rats and mice increased in lung and all tissues examined, indicating absorption and systemic distribution occurs following inhalation.**
- **lung cobalt concentrations and burdens in rats and mice increased with increasing cobalt concentrations, but appeared to reach steady state by day 26.**
- **Lung burden steadily decreased following cessation of cobalt exposure.**

Cobalt and Cobalt Compounds Toxicokinetics

NTP 13-week and 2-year inhalation studies in rats and mice

- **Cobalt concentrations (µg Co/g tissue) in rats showed the following order: lung > liver > kidney > femur > heart > serum > blood.**
- **Overall, normalized lung tissue burdens measured as the ratio of tissue burden (µg Co/total lung) to exposure concentration (mg Co/m^3) did not increase with increasing exposure**

Cobalt and Cobalt Compounds Carcinogenicity

NTP performed an inhalation cancer bioassay in rats and mice for cobalt sulfate heptahydrate in 1998, and for cobalt metal dust in 2014

- **Carcinogenicity findings for cobalt metal dust used by OEHHA as basis of cancer potency factors for insoluble cobalt compounds (water solubility of ≤100 mg/L)**
- **Carcinogenicity findings for cobalt sulfate heptahydrate used by OEHHA as the basis of cancer potency factors for soluble cobalt compounds (water solubility of >100 mg/L)**

Cobalt and Cobalt Compounds Carcinogenicity

Cobalt metal exposures

- **F-344/NTac rats and B6C3F1/N mice (50 group/sex/species)**
- **0, 1.25, 2.5, 5 mg/m^3 for 6.2 hrs/day, 5 days/week for 105 weeks**

Cobalt sulfate heptahydrate exposures

- **F-344/N rats and B6C3F1 mice (50 group/sex/species)**
- **0, 0.3, 1.0 or 3.0 mg/m^3 for 6.2 hrs/day, 5 days/week for 105 weeks**

Cobalt Metal Dust
Tumor Incidence - Rats

Increased lung tumor incidences in male and female rats

Sex, species	Tumor type	Exposed dose (mg/m^3)	Tumor incidence
Male rats	Alveolar/bronchiolar adenoma or carcinoma (combined)	0 1.25 2.5 5.0	2/50‡ 25/50** 39/50** 44/50**
Female rats		0 1.25 2.5 5.0	2/50‡ 15/50** 20/50** 38/50**

** $p < 0.01$ **difference from controls, poly-3 test**

‡ $p < 0.01$ **positive trend for tumor type**

Cobalt Metal Dust
Tumor Incidence - Rats

Increased adrenal medulla tumor incidences in male and female rats

Sex, species	Tumor type	Exposed dose (mg/m^3)	Tumor incidence
Male rats	Benign or malignant pheochromocytoma (combined)	0 1.25 2.5 5.0	17/50‡ 23/50 38/50** 41/50**
Female rats		0 1.25 2.5 5.0	6/50‡ 13/50 23/50** 40/50**

** ***p*** **< 0.01 difference from controls, poly-3 test**

‡ ***p*** **< 0.01 positive trend for tumor type**

Cobalt Metal Dust
Tumor Incidence - Rats

Increased pancreatic islet tumor incidences in male rats, and increased incidence of mononuclear cell leukemia in female rats

Sex, species	Tumor type	Exposed dose (mg/m^3)	Tumor incidence
Male rats	Pancreatic islet cell adenoma or carcinoma (combined)	0 1.25 2.5 5.0	2/50‡ 2/50 10/48* 9/49*
Female rats	Mononuclear cell leukemia	0 1.25 2.5 5.0	16/50 29/50** 28/50* 27/50*

*** $p < 0.05$, ** $p < 0.01$ difference from controls, poly-3 test**

† $p < 0.05$, ‡ $p < 0.01$ positive trend for tumor type (Cochran-Armitage trend test)

Cobalt Metal Dust
Tumor Incidence - Mice

Increased lung tumor incidences in male and female mice

Sex, species	Tumor type	Exposed dose (mg/m^3)	Tumor incidence
Male mice	Alveolar/bronchiolar adenoma or carcinoma (combined)	0 1.25 2.5 5.0	16/50‡ 41/49** 43/50** 47/50**
Female mice		0 1.25 2.5 5.0	8/49‡ 30/50** 41/50** 45/50**

**** $p < 0.01$ difference from controls, poly-3 test**

‡ $p < 0.01$ positive trend for tumor type (Cochran-Armitage trend test)

Cobalt Sulfate Heptahydrate Tumor Incidence - Rats

Increased lung tumor incidences in male and female rats

Sex, species	Tumor type	Exposed dose (mg/m^3)	Tumor incidence
Male rats	Alveolar/bronchiolar adenoma or carcinoma (combined)	0 0.3 1.0 3.0	1/50† 4/50 4/48 7/50*
Female rats		0 0.3 1.0 3.0	0/50‡ 3/49 16/50** 16/50**

*** $p < 0.05$, ** $p < 0.01$ difference from control group**
† $p < 0.05$, ‡ $p < 0.01$ positive trend for tumor type (logistic regression test)

Cobalt Sulfate Heptahydrate Tumor Incidence - Rats

Increased adrenal medulla tumor incidences in female rats

Sex, species	Tumor type	Exposed dose (mg/m^3)	Tumor incidence
Male rats**	Benign or malignant pheochromocytoma (combined)	0 0.3 1.0 3.0	15/50 19/50 25/49* 20/50
Female rats		0 0.3 1.0 3.0	2/48‡ 1/49 4/50 10/48*

** **equivocal evidence for tumor incidence**

* ***p* < 0.05 difference from controls**

‡ ***p* < 0.01 positive trend for tumor type (logistic regression test)**

Cobalt Sulfate Heptahydrate Tumor Incidence - Mice

Increased lung tumor incidences in male and female mice

Sex, species	Tumor type	Exposed dose (mg/m^3)	Tumor incidence
Male mice	Alveolar/bronchiolar adenoma or carcinoma (combined)	0 0.3 1.0 3.0	11/50‡ 14/50 19/50 28/50**
Female mice		0 0.3 1.0 3.0	4/50‡ 7/50 13/50* 18/50**

*** $p < 0.05$, ** $p < 0.01$ difference from controls**

‡ $p < 0.01$ positive trend for tumor type (logistic regression test)

Cobalt and Cobalt Compounds Epidemiological Studies

Limited data for worker exposure to cobalt

- **Retrospective study by Sauni et al. (2017) at Finnish cobalt plant (n = 995)**
- **Employed at plant at least 1 year, mean follow-up 26.2 years.**
- **Airborne cobalt (mostly sulfate or metal dust) measured several times per year - 0.1 to <0.02 mg/m^3 (depending on job type)**
- **No increased cancer risk with 5 years of employment: Standardized Incidence Ratio (SIR) = 1.08 for total risk; 0.52 for lung cancer incidence – compared to regional Finnish cancer database**
- **Low SIR for lung cancers not due to smoking differences**

Issues: Respirators available, but not mandatory- unclear what actual exposure to cobalt was; no mean exposure time

Soluble Cobalt and Cobalt Oxide Compounds Genotoxicity

Considerable database of genotoxicity studies for soluble cobalt compounds and cobalt oxides:

- **DNA damage assay (comet assay)**
- **Oxidative DNA damage assay**
- ***In vivo* DNA adduct assay**
- **Bacterial & mammalian gene mutation assays**
- **Chromosomal aberration assay**
- **Micronucleus assay**

Mostly positive findings for genotoxicity- with exception of bacterial & mammalian gene mutation assays

Cobalt Metal Dust Genotoxicity

Cobalt metal particle genotoxicity tested using:

- **DNA damage assay (Comet)**
- ***In vivo* oxidative DNA damage assay**
- **Gene mutation analysis**
- **Bacterial & mammalian gene mutation assays**
- **Chromosomal aberration assay**

Positive genotoxicity findings for Comet assay, oxidative DNA damage and gene mutation analysis

Cobalt and Cobalt Compounds Cancer Hazard Evaluation

Based on lifetime NTP inhalation studies for both cobalt metal and cobalt sulfate heptahydrate:

- **Carcinogenic in multiple species (rats and mice).**
- **Induced lung tumors that were of the same histogenic type in both species**
- **Induced tumors at one or more sites in both rats and mice**
- **Numerous positive genotoxicity studies**

Combined, these factors point to a strong potential for cobalt to induce tumors in humans.

Cobalt and Cobalt Compounds Cancer Slope Factor Derivation

First step in CSF derivation is converting the NTP tumor incidence into "effective tumor incidence"

- **Effective Tumor Incidence - The number of tumor-bearing animals over the number of animals alive at time of first occurrence of the tumor.**
- **Removes animals from the assessment that died before they are considered at risk for tumor development.**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

Comparison of NTP tumor incidence with effective tumor incidence for rodents exposed to cobalt metal dust

Sex, species	Tumor type	Exposure Level (mg/m^3)	NTP Incidence	Effective Tumor Incidence
Male rats	Alveolar/bronchiolar adenoma or carcinoma (combined)	0	2/50†	2/47†
		1.25	25/50**	25/48**
		2.5	39/50**	39/50**
		5.0	44/50**	44/49**
Female rats				
		0	2/50†	2/48†
		1.25	15/50**	15/49**
		2.5	20/50**	20/48**
		5.0	38/50**	38/50**
Male mice				
		0	16/50†	16/50†
		1.25	41/49**	41/49**
		2.5	43/50**	43/49**
		5.0	47/50**	47/49**

Fisher exact test pairwise comparison with controls: ** $p < 0.01$
Cochran-Armitage trend test for dose response: † $p < 0.01$

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **Survival was significantly reduced in some animal groups exposed to cobalt metal - 2.5 mg/m^3 female rats, 2.5 and 5.0 mg/m^3 male mice**
- **However, a poly-3 survival correction was not applied because survival differences did not occur until week 85 or later.**
- **Most died with treatment-related tumors, many of which were considered the primary cause of death.**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **To determine cancer potency, need to convert cobalt air concentration to average daily dose, in mg/kg BW-day:**

Dose (mg/kg BW-day) = IR × C / BW

Where:

C = time-adjusted annual average concentration

(6.2 hrs / 24 hrs x 5 days / 7 days)

BW = body weight – average over 2-year exposures

IR = inhalation rate – equation based on BW of animal

IR calculation:

- **rats: IR (m^3/day) = 0.702 × $(BW)^{2/3}$ (OEHHA, 2018)**
- **mice: IR (m^3/day) = 0.0345 m^3/day × $(BW / 0.025\ kg)^{2/3}$ (Anderson, 1983)**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

Dose (mg/kg BW-day) = IR × C / BW

Species sex	Cobalt Metal Chamber Concentration (mg/m^3)			
	0	1.25	2.5	5.0
	Daily Exposed Dose (mg/kg-day)			
Rats				
Males	0	0.21	0.42	0.84
Females	0	0.25	0.50	1.00
Mice				
Males	0	0.26	0.51	1.02
Females	0	0.25	0.50	0.99

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

We now have the fraction affected (effective tumor incidences) and the dose (in mg/kg BW-day)

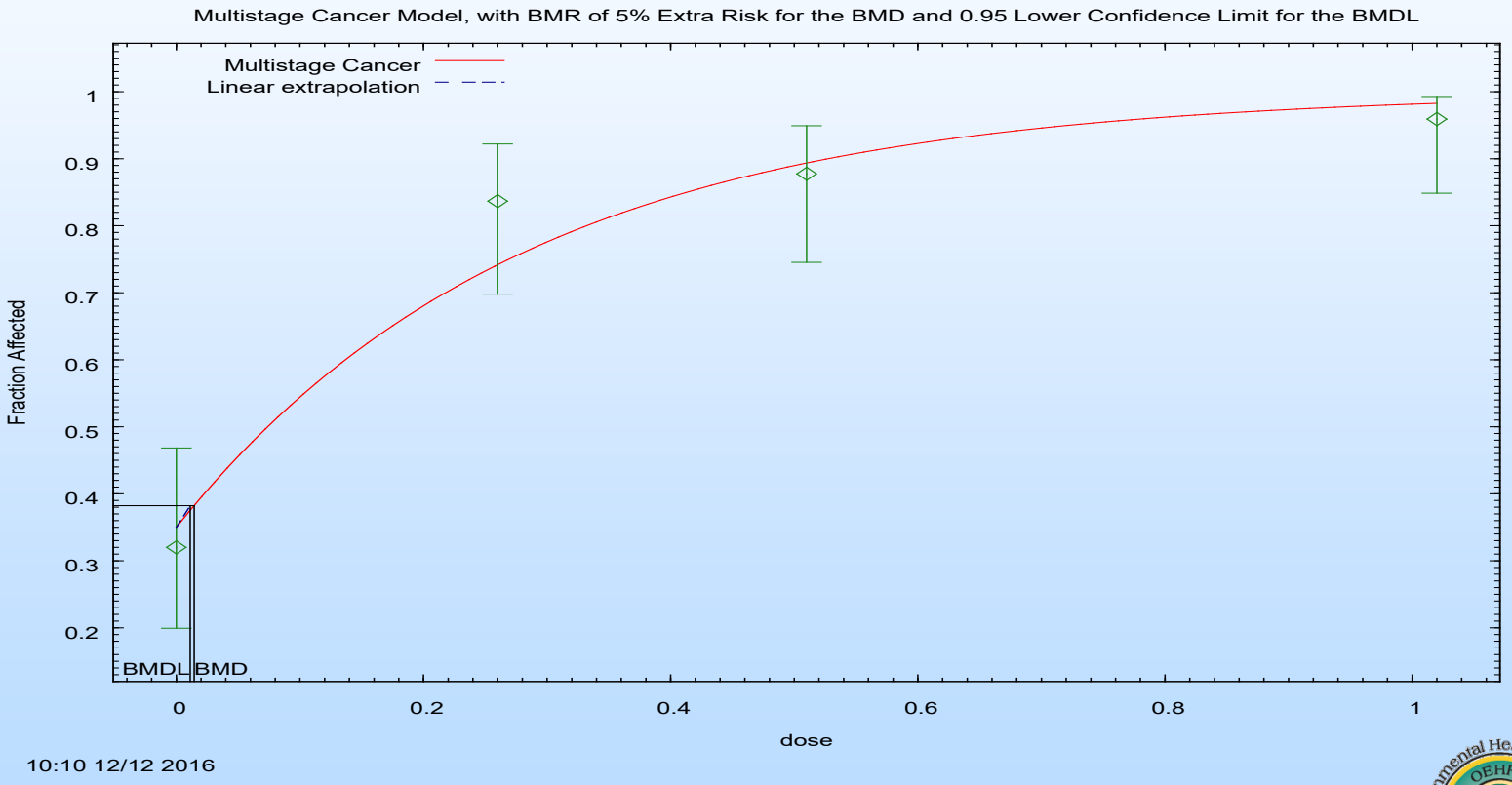
- **Can now run the Multistage Cancer Model in the Benchmark Dose Software (U.S. EPA, 2017) to determine the cancer potency**
- **Potency values derived using a Benchmark Response (BMR) of 5% (5% extra risk) to calculate the Benchmark Dose (BMD)**
- **The 95% lower confidence bound on the effective dose producing 5% response ($BMDL_{05}$) is used to calculate cancer potency**
- **$0.05 / BMDL_{05}$ = Cancer Slope Factor (CSF)**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **Cancer slope factors were calculated for tumors with a statistically significant tumor incidence and positive trend**
  - **Alveolar/bronchiolar adenoma or carcinoma (all rats and mice)**
  - **Benign or malignant pheochromocytoma (male and female rats)**
  - **Pancreatic Islets adenoma or carcinoma (male rats)**
  - **Mononuclear cell leukemia (female rats)**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

BMDS Multistage Cancer Model plot fit for alveolar/bronchiolar lung tumors in male mice exposed to cobalt metal



Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **Rats developed tumors in more than one organ system**
- **Basing cancer risk on only one tumor type may underestimate tumor risk**
- **Multi-site tumor CSFs were calculated using the MS Combo Model (US EPA, 2017):**
  - **Male rats – lung, adrenal medulla, and pancreatic islet tumors combined**
  - **Female rats – lung and adrenal medulla tumors, and leukemia combined**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **Final calculation is to convert the animal CSF values (CSF(a)) to CSF human equivalents (CSF(h)) using body weight ($BW^{3/4}$) scaling:**

$$CSF(h) = CSF(a) \times (BW(h) / BW(a))^{1/4}$$

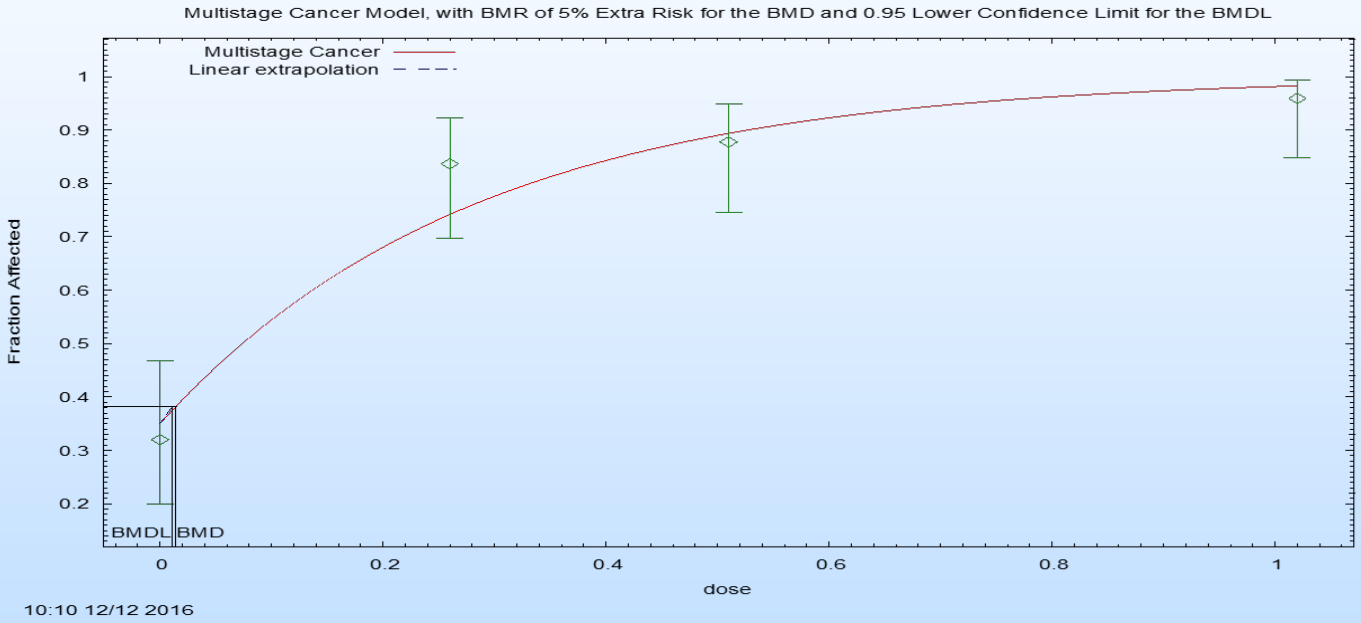
- **This interspecies scaling factor is used to account for pharmacokinetic differences (*e.g.*, metabolism), and for pharmacodynamic considerations (*i.e.*, tissue responses to chemical exposure).**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

Tumor type	AIC	*p*-value	BMD_{05} (mg/kg-day)[a]	$BMDL_{05}$ (mg/kg-day)	CSF - Rodent $(mg/kg\text{-}day)^{-1}$	CSF - Human $(mg/kg\text{-}day)^{-1}$
Male Rats						
Multisite: lung-adrenal-pancreatic tumors combined	NA	NA	0.009291	0.007947	6.29	22.17
Female Rats						
Multisite: lung-adrenal-leukemia combined	NA	NA	0.02828	0.01867	2.68	10.70
Male Mice						
Lung Tumors	167.47	0.12	0.01446	0.01122	4.46	**27.49**
Female Mice						
Lung Tumors	188.20	0.57	0.01868	0.01506	3.32	20.04

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

BMDS Multistage Cancer Model plot fit for alveolar/bronchiolar lung tumors in male mice exposed to cobalt metal (BMR = 5% response)



- BMD is more than 3x lower than lowest non-zero dose
- BMDL is 10x lower than lowest non-zero dose
- BMD model recommendation: “Questionable”

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **When a BMR = 5% yields a "questionable" CSF, OEHHA uses the exact formula for the calculation of the cancer slope factor (upper bound on β_1):**

$$\text{CSF (upper bound on } \beta_1) = -\ln(1-\text{BMR})/\text{BMDL}$$

This conservative estimate is derived by solving for β_1 in the risk equation and inserting the result into the log-likelihood equation for β_1 to use it to profile the BMD and obtain the BMDL.

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **What we found was the exact formula**

  (CSF = -ln(1-BMR)/BMDL)

  is constant over a range of values of the BMR (5 to 15%) and this approach appropriately accounts for the increased curvature in the dose response relationship at higher doses and BMRs

- **A BMR of 15% was considered "viable" (the BMD resulted in a BMDL that was within 10x of the lowest non-zero dose)**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

Results from BMDS 3.1 using the approximation (BMR/BMDL) and use of the exact formula

BMDS output using the approximation					Exact formula -ln(1-BMR)/BMDL
Model	**BMDL**	**CSF_a**	**BMDS "Recommen-dation"**	**BMDS "Recommendation notes"**	
BMR05 1st degree polynomial	0.01122	**4.46**	Questionable	BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose	= -ln(1-0.05)/0.01122 = **4.57 (mg/kg-day)-1**
BMR10 1st degree polynomial	0.02304	**4.34**	Questionable	BMD 3x lower than lowest non-zero dose BMDL 10x lower than lowest non-zero dose	= -ln(1-0.10)/0.02304 = **4.57(mg/kg-day)-1**
BMR15 1st degree polynomial	0.03554	**4.22**	Viable - Recommended	BMD 3x lower than lowest non-zero dose **BMDL now within 10x of lowest non-zero dose**	= -ln(1-0.15)/0.03554 = **4.57 (mg/kg-day)-1**

Cobalt Metal and Insoluble Cobalt Compounds Cancer Slope Factor Derivation

- **The animal CSF values (CSF(a)) are converted to CSF human equivalents (CSF(h)) using body weight ($BW^{3/4}$) scaling:**

$$CSF(h) = CSF(a) \times (BW(h) / BW(a))^{1/4}$$

$$CSF(h) = 4.57\ (mg/kg\text{-}day)^{-1} \times (70\ kg / 0.0485\ kg)^{1/4}$$

$$CSF(h) = 28\ (mg/kg\text{-}day)^{-1}$$

Soluble Cobalt Compounds
Cancer Slope Factor Derivation

- **Cancer slope factors for cobalt sulfate heptahydrate were calculated for tumors with a statistically significant tumor incidence and positive trend**
  - **Alveolar/bronchiolar adenoma or carcinoma (all male/female rats and male/female mice)**
  - **Benign or malignant pheochromocytoma (female rats only)**
  - **Multi-site tumor CSFs were calculated using the MS Combo Model (US EPA, 2017) for female rats – lung and adrenal medulla tumors combined**

Soluble Cobalt Compounds
Cancer Slope Factor Derivation

Comparison of NTP tumor incidence with effective tumor incidence for rodents exposed to cobalt sulfate heptahydrate

Sex, species	Tumor type	Exposure Level (mg/m^3)	NTP Incidence	Effective Tumor Incidence
Female rats	Alveolar/bronchiolar adenoma, carcinoma or squamous cell carcinoma (combined)	0 0.3 1.0 3.0	0/50† 3/49 16/50** 16/50**	0/44† 3/41 16/42** 16/46**
	Benign, complex or malignant pheochromocytoma	0 0.3 1.0 3.0	2/48† 1/49 4/50 10/48*	2/39† 1/37 4/38 10/39*

Fisher exact test pairwise comparison: * $p < 0.05$ ** $p < 0.01$

Cochran-Armitage trend test for dose response: † $p < 0.01$

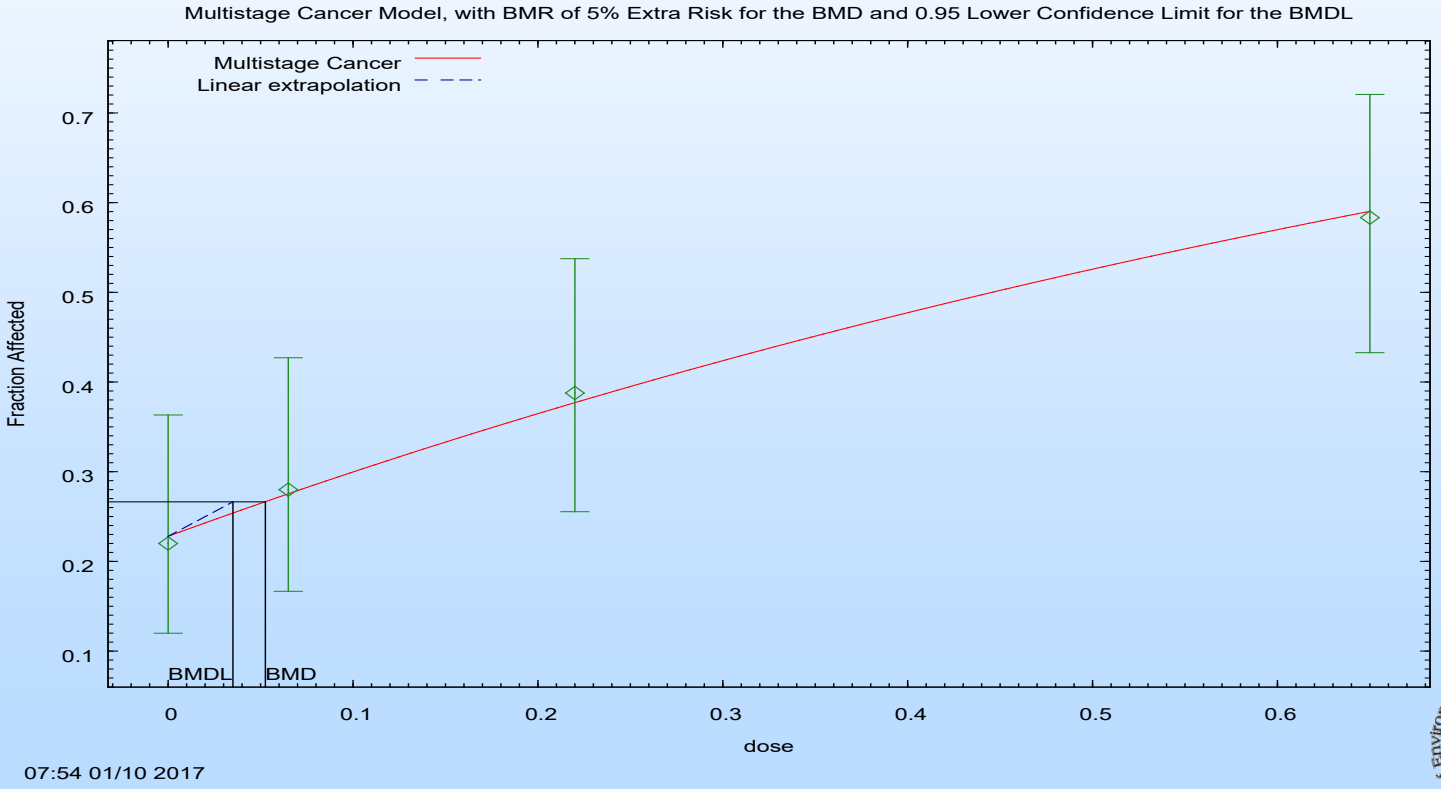
Soluble Cobalt Compounds
Cancer Slope Factor Derivation

Dose (mg/kg BW-day) = IR × C / BW

Species **sex**	**Cobalt Sulfate Heptahydrate Chamber Concentration (mg/m^3)**			
	0	**0.3**	**1.0**	**3.0**
	Daily Exposed Dose (mg/kg-day)			
Rats				
Males	0	0.051	0.17	0.51
Females	0	0.061	0.20	0.61
Mice				
Males	0	0.064	0.21	0.64
Females	0	0.065	0.22	0.65

Soluble Cobalt Compounds Cancer Slope Factor Derivation

- **BMDS Multistage Cancer Model plot fit for alveolar/bronchiolar lung tumors in male mice exposed to cobalt sulfate heptahydrate**



Soluble Cobalt Compounds
Cancer Slope Factor Derivation

Tumor type	AIC	*p*-value	BMD_{05} (mg/kg-day)[a]	$BMDL_{05}$ (mg/kg-day)	CSF - Rodent $(mg/kg\text{-}day)^{-1}$	CSF - Human $(mg/kg\text{-}day)^{-1}$
Male Rats						
lung tumors	105.27	0.53	0.1644	0.08383	0.60	2.14
Female Rats						
Multisite: lung-adrenal tumors combined	NA	NA	0.02064	0.01504	3.32	**13.41**
Male Mice						
Lung Tumors	246.71	0.96	0.05161	0.03435	1.46	9.35
Female Mice						
Lung Tumors	189.87	0.70	0.07258	0.04819	1.04	6.72

Soluble Cobalt Compounds Cancer Slope Factor Derivation

- **Cobalt sulfate CSF (normalized to cobalt content)**

  = 3.0 (mg Co/kg-day)$^{-1}$

- **Because the cobalt ion is considered to be the primary factor for cancer risk, the cobalt sulfate heptahydrate CSF was normalized to the content of cobalt:**

- **(58.9 Co / 263.1 $CoSO_4$ × 6H_2O) × 13.41 (mg/kg-day)$^{-1}$**

  = 3.0 (mg Co/kg-day)$^{-1}$

  (Note that under the conditions of the NTP exposures, animals were actually exposed to cobalt sulfate hexahydrate, not the heptahydrate)

Cobalt & Cobalt Compounds Inhalation Unit Risk (IUR) Derivation

- **Cobalt unit risk factor = IUR** $= \left(\frac{CSF \times BR}{BW \times CV}\right)$
  - **Human breathing rate (BR) of 20 m^3/day**
  - **Average human body weight (BW) of 70 kg**
  - **mg to µg conversion (CV) of 1000**
- **Cobalt metal IUR = 7.8×10^{-3} $(\mu g/m^3)^{-1}$**
- **Cobalt sulfate IUR = 8.0×10^{-4} $(\mu g\ Co/m^3)^{-1}$**
  - **Lifetime exposure to 1 µg/m^3 cobalt metal results in 7.8 chances in one thousand, or 7800 in a million**
  - **Lifetime exposure to 1 µg/m^3 of cobalt from cobalt sulfate heptahydrate: 800 chances in a million**

Questions?

Comments and Responses

During the public comment period, OEHHA received comments from:

- ToxStrategies, Inc.
- Cobalt Institute
- Color Pigments Manufacturers Association

Comments and Responses

Comment #1 (ToxStrategies)

Clarify that cobalt alloys in addition to cobalt-tungsten hard metals (e.g., stainless steel, super alloys) should be excluded from the Cobalt and cobalt compounds categories.

Response to #1

OEHHA agrees that cobalt alloys should not be included in the cobalt CSF categories, and we say this in the document: Cobalt alloys have different chemical and physical properties compared to cobalt compounds:

1) Some alloys are carcinogenic with a greater potency, such as cobalt-tungsten hard metals, and thus have a different CPF
2) Other cobalt alloys are essentially insoluble even in weak acids, and likely present no cancer risk.

Comments and Responses

Comment #2 (ToxStrategies/Cobalt Institute)

Water solubility is a poor surrogate for solubility of metals under physiological conditions

Response to Comment #2

1) Solubility appears to play a role in cobalt induced lung cell genotoxicity and suggests soluble and insoluble forms of cobalt may have different carcinogenicity potentials.

2) Categorization based on water solubility works well because insoluble cobalt metal and compounds appear to be largely internalized by cells as particles.

3) Keeping the classification information simple, based on water solubility (< or > than 100 mg/L), is adequate for determining which cobalt IUR to use.

Comments and Responses

Comment #3 (ToxStrategies)

Comparison of cobalt sulfate heptahydrate cancer potency to that of cobalt metal should be based on 1) content of cobalt in cobalt sulfate heptahydrate, not the content of cobalt sulfate, and 2) NTP actually found rodents were exposed to cobalt sulfate hexahydrate, not the heptahydrate.

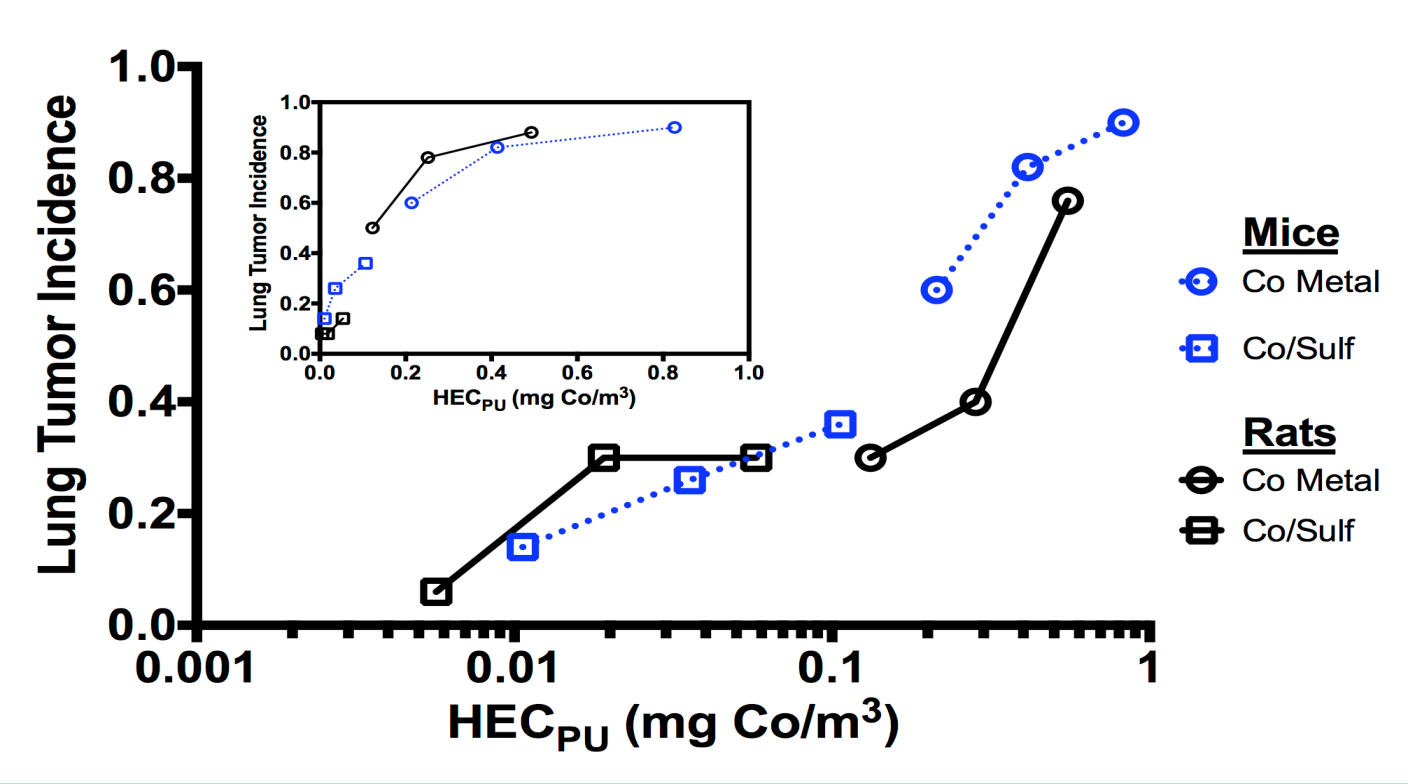
Response to Comment #3

1) OEHHA corrected the comparison of cobalt metal based on content of cobalt in cobalt sulfate heptahydrate in Section IV (Cancer Hazard Evaluation)
2) OEHHA corrected cobalt content based on cobalt sulfate "hexahydrate" in the final assessment (i.e., at the end of the CSF derivation). This change results in the CSF adjusted up to **3.0 (mg/kg-day)$^{-1}$** based on the hexahydrate form, compared to **2.8 (mg/kg-day)$^{-1}$** when based on the heptahydrate form.

Comments and Responses

Comment #4 (ToxStrategies/Cobalt Institute)

Suh et al. (2016) converted the two forms of cobalt to human equivalent concentrations (HECs) using the EPA (1994) [RDDR] method and found the carcinogenicity [potency] to be similar:



Comments and Responses

Response to Comment #4

ToxStrategies suggests that a line could be drawn through the combined cobalt metal and cobalt sulfate heptahydrate data points of the log-dose graph in Figure 2 to suggest a monotonic dose-response is produced.

If lines were drawn through the cobalt metal and cobalt sulfate heptahydrate data separately, the cobalt metal slopes are steeper compared to the cobalt sulfate slopes. The steeper slopes indicate that cobalt metal is a more potent carcinogen. This is what the OEHHA-derived CSF values show – that cobalt metal is nearly 10-fold more potent a carcinogen than cobalt sulfate heptahydrate.

In vitro data supports this finding – that insoluble cobalt particles are more genotoxic than soluble cobalt compounds

Comments and Responses

Comment #5 (ToxStrategies)

OEHHA did not use dosimetric adjustments appropriate for each tumor site, which is inconsistent with US EPA guidance and ignores the importance of variable lung deposition by particle size and species.

Response to Comment #5

Because there is evidence of systemic distribution of inhaled cobalt resulting systemic tumors, we used body weight ($BW^{3/4}$) scaling to convert to human equivalents. This is a method used by OEHHA for extrapolating from rodents to humans in CPF derivations. Using this interspecies scaling factor is preferred by OEHHA because it is assumed to account not only for pharmacokinetic differences (e.g., metabolism), but also for pharmacodynamic considerations, i.e., tissue responses to chemical exposure (US EPA, 2005).

Comments and Responses

Comment #6 (ToxStrategies)

The latest version of BMDS 3.1 (USEPA 2019) now contains recommendations (and warnings) for model selection of the BMR. A BMR of 5% for lung tumors in male mice resulted in a "Questionable" recommendation because the 5% response rate is not within the observable range.

The custom BMR method is recommended, which has been used previously by USEPA (2011). In US EPA's method, the custom BMR is calculated as follows:

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

This method results in a BMR of 78% and is within the observable range

Comments and Responses

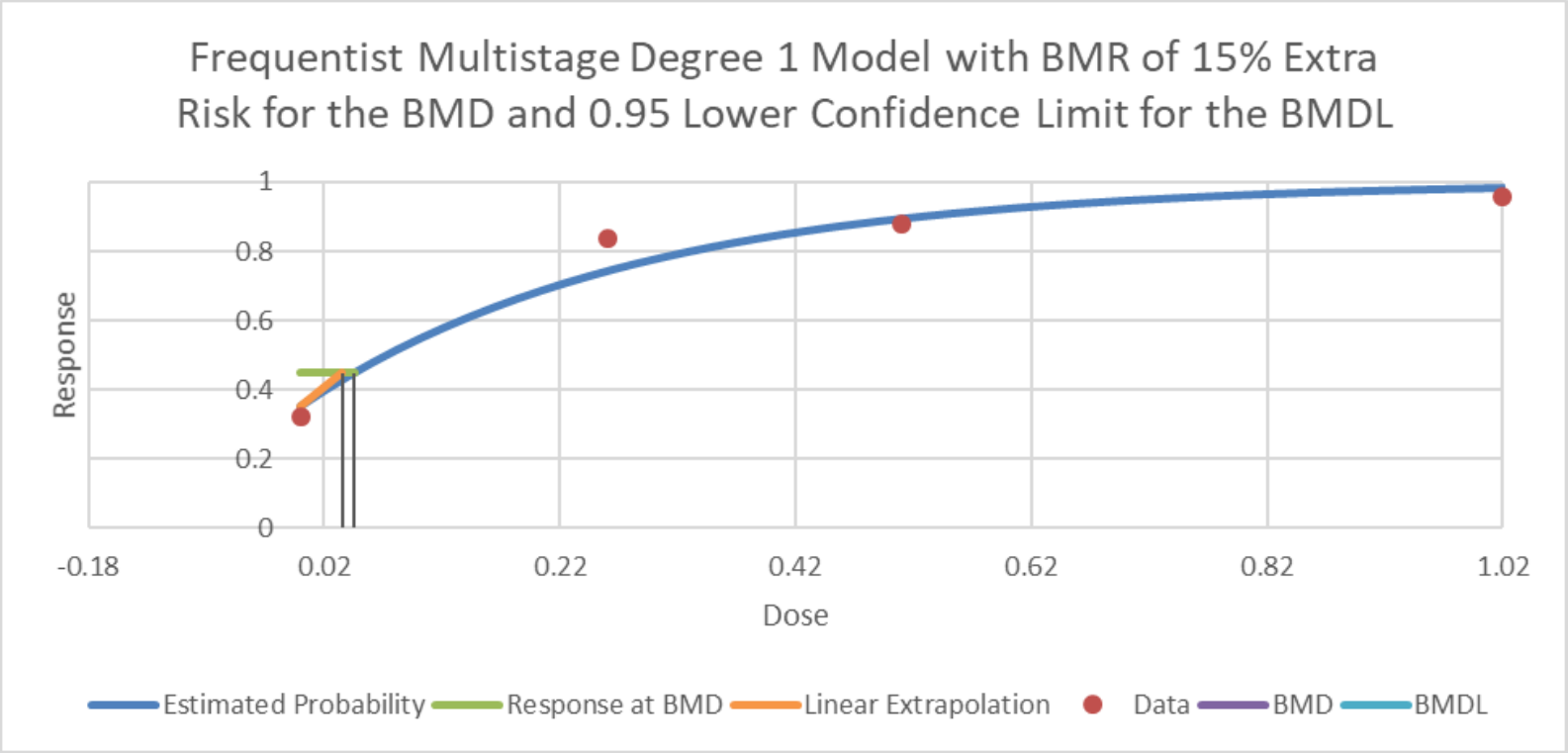
Response to Comment #6

As noted earlier, OEHHA recommends using the exact formula (CSF = -ln(1-BMR)/BMDL) when the BMR = 5% yields a BMD that is not in the observable range:

- US EPA BMD version 3.1 software shows that a BMR = 15% gives a "viable" recommendation for the model:
- The exact formula shows that the CSF (4.57 $(mg/kg\text{-}day)^{-1}$) is the same regardless of whether the BMR = 5% or the BMR = 15%

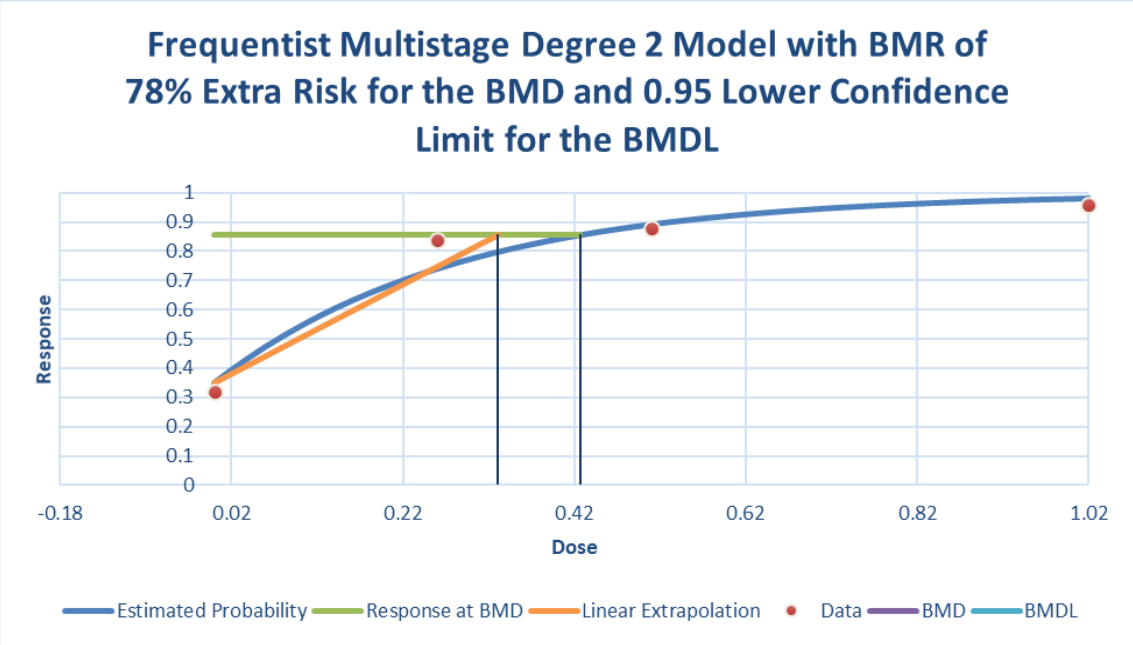
Comments and Responses

Response to Comment #6 continued:



Comments and Responses

Response to Comment #6 continued:



- Using the BMR custom equation to derive a BMR by ToxStrategies, which raises the BMR to 78% response rate, is unnecessary and not as health protective as OEHHA's approach.
- The custom BMR method proposed by ToxStrategies is from a 2011 EPA external review draft document that has never been finalized

Comments and Responses

Comment #7 (ToxStrategies/Cobalt Institute)

OEHHA modeled pheochromocytomas in rats both independently and as part of a combined analysis. There is evidence that pheochromocytomas arise in inhalation studies where hypoxia is induced as a consequence of exposure to particulate producing lung lesions (including tumors).

Thus, it is unnecessary for pheochromocytomas to serve as a basis for any CSF or IUR (alone or in combination) when a more relevant site-of-contact tumor (i.e., lung tumors) is present.

Comments and Responses

Response to Comment #7

1) Due to the lack of confidence by NTP and other researchers have for the cause of the rat pheochromocytomas, as suggested by ToxStrategies, OEHHA has chosen a health protective approach by assuming that pheochromocytomas arise independently from the lung cancer and noncancer effects.

2) A number of NTP carcinogenicity studies observed pheochromocytomas resulting from a carcinogenic chemical in feed or administered by gavage, in which no pulmonary effects were found. Therefore, OEHHA cannot ignore the possibility that inhaled cobalt metal and cobalt compounds that are absorbed systemically and reach the adrenal glands could be a direct cause of pheochromocytoma.

Comments and Responses

Comment #8 (Cobalt Institute):

Due to the increasing morbidity (i.e., declining fertility, sporadic seizure activity, and chylothorax) of the F344/NTac rat colony and the lack of historical control data, the occurrence of the systemic tumors in the cobalt metal study in rats cannot be conclusively interpreted.

Response to Comment #8

1) NTP did not express concern that the strain of rat used in the cobalt metal study would affect the carcinogenicity incidence. Some non-cancer endpoints may be affected, but not the cancer endpoints.

2) OEHHA ultimately derived a cancer potency factor for cobalt metal based on the lung tumor incidence in male mice.

Comments and Responses

Comment #9 (Cobalt Institute)

The combination of both Co compounds into one dose response curve results in very good model fit, and the indication that the model is able to predict exposure-responses at relevant (low) exposures. A detailed report on benchmark dose (BMD) modeling of the complete animal dataset (Co metal powder and Co sulfate) is appended to these comments.

Response to Comment #9

Cobalt Institute combines both the cobalt metal and cobalt sulfate heptahydrate lung tumor incidence data in male rats to derive a single cobalt BMDL value of 0.12 mg/kg-day. This value translates to a rodent CSF of 0.42 $(mg/kg\text{-}day)^{-1}$

The BMR chosen was 5%, with a 90% confidence interval around the BMD ($BMDL_{10}$). Typically, OEHHA would have chosen a 95% confidence interval around the BMD.

Comments and Responses

Response to Comment #9 Continued:

For comparison, based on the methods described in the draft OEHHA Cobalt TSD, OEHHA derived rodent CSFs of 4.57 and 0.74 $(mg/kg\text{-}day)^{-1}$ for cobalt metal and cobalt sulfate heptahydrate (normalized to content of cobalt), respectively.

As outlined in an earlier response, the lung tumor incidence slopes for cobalt metal appear steeper than the lung tumor incidence slopes for cobalt sulfate heptahydrate in both rats and mice. Thus, OEHHA chose to calculate CSFs separately for the two forms of cobalt.

Comments and Responses

Comment #10 (Cobalt Institute)

Cobalt compounds such as Co_3O_4 and CoS with negligible solubility (~1%) in biological fluids (e.g., artificial alveolar and lysosomal lung fluids) should not be grouped with cobalt metal powder for the endpoint inhalation toxicity.

Response to Comment #10

1) Up to 50% solubility of Co_3O_4 particles within cells have been observed in lung cell cultures
2) A number of *in vitro* studies in lung cells observed genotoxicity and cytotoxicity resulting from Co_3O_4 exposure

Therefore, cobalt compounds of low solubility are grouped with cobalt metal.

Comments and Responses

Comment #11 (CPMA)

It is inappropriate for OEHHA to categorize all compounds with solubilities lower than 100 mg/L as essentially the same for inhalation risk assessment. Complex inorganic color pigments (e.g., cobalt aluminum chrome spinel) do not yield significant amounts of bioavailable cobalt.

Response to Comment #11

OEHHA agrees that cobalt spinels should not be included in the cobalt CPFs, and we now say this in the document:

1) The calcining process at high temps forms an interdiffused crystalline spinel matrix, which has similarities to alloying process. Cobalt alloys are not included in the CPF definition
2) Spinels have very low solubility, even in lysosomal fluid (0.089%)
3) IARC (2006) concluded there is currently inadequate evidence for the carcinogenicity of cobalt-aluminum chromium spinel