

**Comments on OEHHA's
Draft Technical Support
Document for Cancer Potency
Factors of Cobalt and Cobalt
Compounds**

MAY 7, 2019

ToxStrategies

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Acronyms

BMD	benchmark dose
BMDL	benchmark dose lower bound
BMR	benchmark response
CSF	cancer slope factor
HEC	human equivalent concentration
IUR	inhalation unit risk
NTP	National Toxicology Program
OEHHA	Office of Environmental Health Hazard Assessment
RoC	Report on Carcinogens (Monograph on Cobalt and Cobalt Compounds that Release Cobalt Ions in Vivo [NTP, 2016b])
SCAQMD	South Coast Air Quality Management District
USEPA	U.S. Environmental Protection Agency

Executive Summary

The Office of Environmental Health Hazard Assessment (OEHHA) released a draft document detailing its assessment of the carcinogenic potency of cobalt and cobalt compounds, deriving cancer inhalation unit risk factors (IURs) and cancer potency factors (CPFs). OEHHA developed separate IURs for cobalt metal and water-insoluble cobalt compounds and for water-soluble cobalt compounds (normalized to cobalt) based on the rodent carcinogenicity bioassay studies of the National Toxicology Program (NTP) (NTP 1998, 2014). Previously, the U.S. Environmental Protection Agency (USEPA) and researchers from ToxStrategies also developed IURs based on the same NTP data (**Table 1**) (Suh et al. 2016; USEPA 2008), but the values differed from those developed by OEHHA by up to ~11-fold.¹ Moreover, the draft OEHHA IUR for cobalt metal and water-insoluble cobalt compounds is approximately an order of magnitude higher than that for water-soluble cobalt compounds, which is in the opposite direction of IURs for cobalt metal and cobalt sulfate heptahydrate developed previously. OEHHA is soliciting public comments on the draft document until May 7, 2019.

ToxStrategies conducted a comprehensive review of OEHHA's draft risk assessment of cobalt and cobalt compounds. ToxStrategies' comments focus on the categorization of cobalt metal with water-insoluble cobalt compounds, and quantitative risk assessment procedures, specifically dose-response modeling. Importantly, we find it problematic that cobalt in its most commonly used form—as alloys, including stainless steel, and super alloys—is not discussed more extensively, because this use constitutes the vast majority of water-insoluble cobalt produced. Cobalt alloy forms are insoluble in water and in most biological media (Hillwalker and Anderson 2014, Suh et al. 2019, ToxStrategies 2017). On the contrary, although it is not soluble in water, cobalt metal is highly soluble, bioaccessible, and bioavailable in biological media, including lung fluids (Hillwalker and Anderson 2014, NTP 2016b, Stopford et al. 2003).

Overall, substantial revisions to the draft document are recommended to ensure that the risk assessments of cobalt and cobalt compounds are based on the best available science and scientific methods, and to clarify and differentiate the different forms of water-insoluble cobalt so that the IURs are not misapplied in air toxics risk assessments. Pertinent data on bioaccessibility should be included in the draft document, and we recommend that OEHHA use the important risk assessment refinements developed by the USEPA for inhalation exposure to particles, to assess tissue dose and extrapolate from rodents to humans on a more refined basis than body weight.

OEHHA has indicated that “[t]he cobalt IURs do not apply to cobalt alloys (e.g., cobalt-tungsten hard metal dust) or the cobalt-containing essential nutrient vitamin B12.” We agree with this statement. However, we request that the text be clarified to explicitly state that the values are not applicable to cobalt in any alloys or forms that are not readily soluble or bioavailable in lung fluids. These alloys should be also considered separately from

¹ Based on comparison of USEPA (2008) provision peer-reviewed toxicity value (PPTRV) to that of the draft OEHHA IUR for water-soluble cobalt compounds (normalized to cobalt content).

cobalt metal and water-soluble cobalt compounds and excluded from IUR applications. This is consistent with the NTP findings regarding cobalt in alloys as assessed in the 2016 Report on Carcinogens (RoC) Monograph on Cobalt and Cobalt Compounds that Release Cobalt Ions in Vivo (NTP 2016b).

Table 1. Overview of IURs and inhalation cancer slope factors developed for cobalt and cobalt compounds

Agency/Author	Report/ Publication Year	Compound	Unit Risk Factor ($\mu\text{g}/\text{m}^3$) ⁻¹	Inhalation Slope Factor ($\text{mg}/\text{kg}\text{-day}$) ⁻¹	Data Used as the Basis
OEHHA	2019	Cobalt metal and water-insoluble cobalt compounds	7.8×10^{-3}	27	NTP (2014) 2-year bioassay of cobalt metal
		Water-soluble cobalt compounds (normalized to cobalt content)	8.0×10^{-4}	2.8	NTP (1998) 2-year bioassay of cobalt sulfate hexahydrate
Suh et al. (2016)	2016	Insoluble cobalt metal particulates	3×10^{-3}	Not calculated	NTP (2014) 2-year bioassay of cobalt metal
U.S. EPA*	2008	Indicated to be applicable to all forms of cobalt	9×10^{-3}	Not calculated	NTP (1998) 2-year bioassay of cobalt sulfate hexahydrate

* Provisional peer-reviewed toxicity value (PPRTV)

Comments

ToxStrategies scientists wrote the peer-reviewed paper by Suh et al. titled, “Inhalation cancer risk assessment of cobalt metal” published in *Regulatory Toxicology and Pharmacology* (2016), which provides a more detailed discussion of many of the points offered herein. Our comments cover three general topics: (1) characterization of cobalt metal with other water-insoluble forms of cobalt, (2) dosimetric adjustment and unit conversions, and (3) quantitative cancer risk assessment approaches.

1 Water solubility is not the correct measure for categorizing cobalt compounds.

The categorization of cobalt and cobalt compounds by water solubility is inappropriate and is not supported by inhalation bioaccessibility data for cobalt compounds. We are concerned that, without further differentiation and clarification in the OEHHA document, these categories will lead to significant confusion and errors in risk assessment, such that cobalt in steel will be confused with pure cobalt metal. We recommend that cobalt forms be differentiated based on lung fluid bioaccessibility rather than water solubility.

Cobalt metal, in its pure form such as that administered in the NTP (2014) study, should not be categorized with the vast majority of water-insoluble cobalt compounds. Notably, both cobalt metal and cobalt sulfate are readily accessible in artificial lung fluids, and they represent highly bioavailable substances. Categorization based on water solubility is likely to result in misclassifying other water-insoluble forms of cobalt, particularly cobalt in alloys such as stainless steel, and cobalt in ceramics, as being carcinogenic in the lung and incorrectly assessing them in air toxics risk assessments.

Uses of cobalt in the United States are shown in **Table 2** (re-created from data presented in NTP 2016b). Cobalt is used in various industrial applications as a colorant, catalyst, and as a drying agent for glass, ceramics, paint, inks, feed supplements, batteries; it is used to produce alloys or composites (NTP 2016b). However, as evidenced in **Table 2**, the primary use of cobalt is in steel-related alloy applications. Hence, cobalt is used primarily in forms that are water insoluble, but not nearly as bioaccessible and bioavailable as cobalt in the pure metal form. We are concerned that errors will result in applying the IURs to forms of cobalt that, like cobalt in stainless steel, are water insoluble but do not behave biologically in the same manner as pure cobalt metal.

Table 2. Use patterns for cobalt in 2012 for United States (recreated from Table 2-3 of NTP 2016b)

End Use	Consumption (Metric Tons Cobalt Content)	% Total Consumption
Super Alloys	4,040	48
Chemical and ceramic	2,300	27.3
Cemented carbides	774	9.2
Other alloys*	699	8.3
Steels	548	6.5
Miscellaneous and unspecified	63	0.7

*Includes magnetic, nonferrous, and wear-resistant alloys and welding materials

Cobalt in alloys is not bioavailable like cobalt metal or water-soluble cobalt compounds such as cobalt sulfate (Hillwalker and Anderson 2014). It should be noted that NTP’s 14th RoC lists cobalt sulfate and cobalt-tungsten carbide powders and hard metals as reasonably anticipated to be human carcinogens, and the RoC Monograph on cobalt and cobalt compounds reached the same conclusion based on animal and mechanistic data (NTP 2014, 2016a). Notably, cobalt-containing alloys were not classified with these compounds. On Page 2, OEHHA states, “The cobalt IURs do not apply to cobalt alloys (e.g., cobalt-tungsten hard metal dust) or the cobalt-containing essential nutrient vitamin B12.” We agree with this statement, but we request additional clarification that cobalt in steel and super alloys be specifically excluded or that the categorization of cobalt and cobalt compounds be based on lung bioaccessibility. This is an important clarification because cobalt-tungsten hard metals are not representative of the forms of cobalt that occur in stainless steel and super alloys.

1.1 Cobalt metal should be recognized as bioaccessible and bioavailable in the lung.

Cobalt metal is soluble in dilute acids and biological fluids, including lung cytosol, plasma, and intracellular lysosomal fluids. NTP stated, “Cobalt metal particles have been found to be 100% bioaccessible (i.e., dissolving to release cobalt ions) in both artificial gastric and lysosomal fluids” (NTP 2016b). Dissolution in lysosomal fluids is designed to represent intracellular solubility in the lung. Dissolution in lysosomal fluid is assessed to evaluate the potential for release of ions in the nucleus and is applicable for metals that are insoluble

in the neutral conditions of alveolar and interstitial fluids but may be transported into lung cells by means other than simple dilution.

It is critical to consider that bioaccessibility and bioavailability of metals depend on the micro-environment in which the metal compound resides. The insolubility of cobalt metal in water does not mean that it has limited bioaccessibility and bioavailability in biological fluids. As evidenced in Stopford et al. (2003), solubility of cobalt metal in lysosomal fluid is similar to that of cobalt sulfate heptahydrate (**Figure 1A**). This is contrary to the limited bioaccessibility of cobalt in alloys reported in Hillwalker and Anderson (2014) and ToxStrategies (2017) (**Figure 1B**); these data are discussed further in section 1.3. It is evident that both cobalt metal and cobalt sulfate heptahydrate represent highly bioavailable forms of cobalt unlike cobalt in alloys.

Moreover, water solubility is a poor surrogate for solubility of metals under physiological conditions, because solubility of cobalt compounds is highly influenced by pH, redox conditions, and the presence of organic species. NTP states, “The metals and poorly soluble compounds tended to be less bioaccessible in neutral biological fluids, which is consistent with the pH dependence for releasing cobalt ions in solution” (NTP 2016b). Therefore, water solubility should not be the measure by which to classify cobalt compounds. OEHHA’s categorization of toxicity and carcinogenic potential of cobalt compounds should be amended to be consistent with the current state of the science.

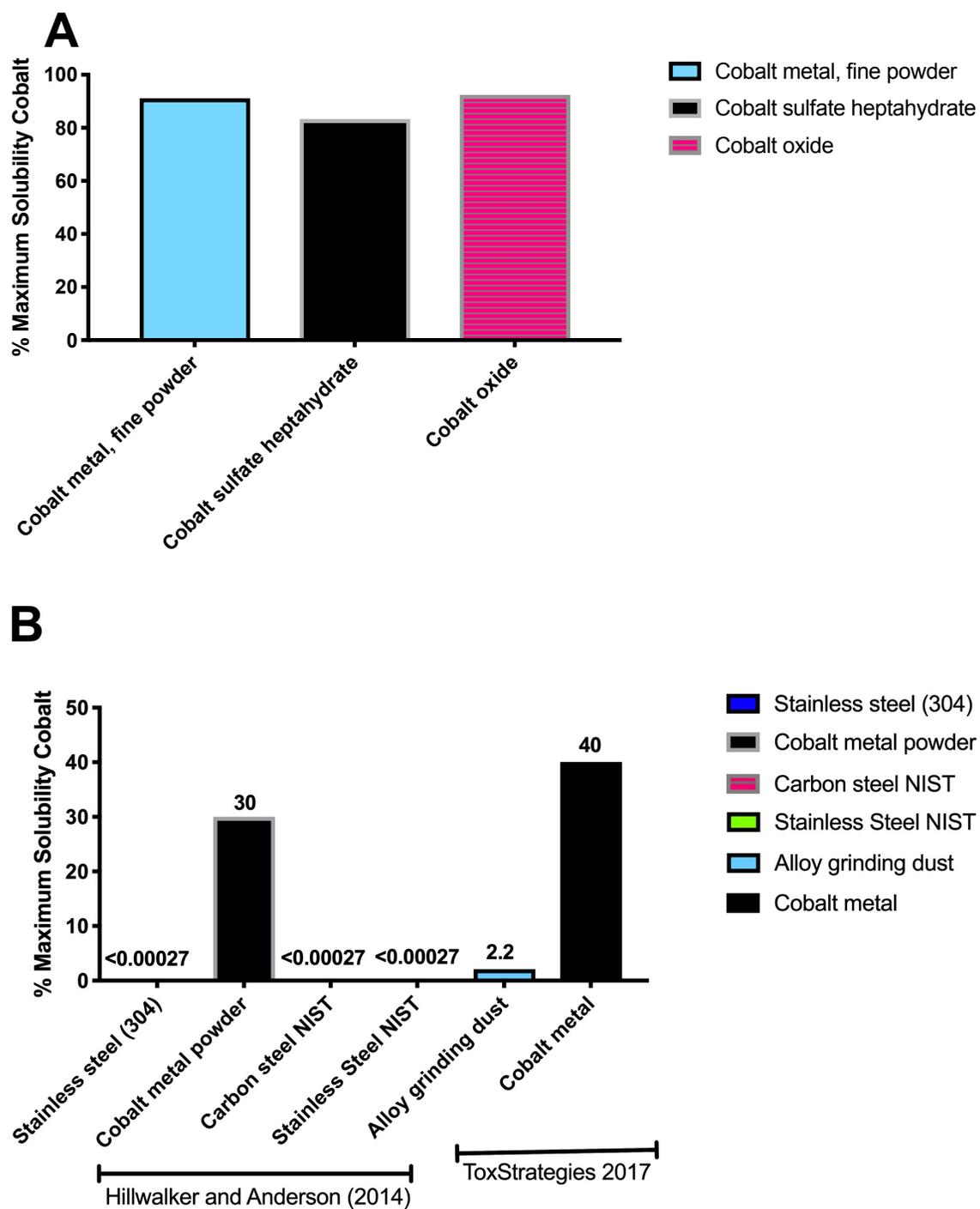


Figure 1. Solubility of cobalt compounds and cobalt containing alloys in lysosomal fluid (pH 4.5). Data adapted from: A) Stopford et al. 2003; B) Hillwalker and Anderson (2014) and ToxStrategies (2017)

1.2 The draft risk assessment document does not contain detailed evaluation of the inhalation bioaccessibility information for cobalt and cobalt compounds.

NTP states, “Evaluation of toxicological and carcinogenic effects of cobalt compounds depends largely on the release of cobalt ions that can either be transported to and taken up at target sites or released within cells from particles” (NTP, 2016b). However, the draft OEHHA (2019) risk assessment document does not contain a detailed section on inhalation bioavailability and bioaccessibility of cobalt and cobalt compound, to characterize cobalt ion release. Table 1 in OEHHA (2019) presents only qualitative descriptions of solubility for different cobalt compounds, but no quantitative data on inhalation bioaccessibility are presented. The body of published data for cobalt inhalation bioaccessibility is considerable (see **Table 3** as an example). Table 1 in OEHHA’s draft risk assessment document needs to be revised to present quantitative data. Additionally, current text in Section 3, Carcinogenicity, needs to be revised and expanded to consider inhalation bioaccessibility information on cobalt and cobalt compounds.

Table 3. Inhalation bioaccessibility data on cobalt and cobalt compounds

Citation	Compound	Fluid Type	Incubation Period (hours)	Bioaccessibility Results	
				Cobalt concentration (e.g., µg Co/mL) or rate (e.g., µg Co/mL/day)	% Cobalt Bioaccessibility
Stopford et al. (2003)	Cobalt metal fine powder	Alveolar	2, 5, 24, 72	Not reported	4.8
	Cobalt sulfate heptahydrate	Alveolar	2 or 24		>51.4
	Cobalt oxide	Alveolar	2, 5, 24, 72		2.4
	Cobalt metal fine powder	Lysosomal	2, 5, 24, 72		>91.1
	Cobalt sulfate heptahydrate	Lysosomal	2 or 24		>83.3
	Cobalt oxide	Lysosomal	2, 5, 24, 72		92.4
	Cobalt metal fine powder	Interstitial	2, 5, 24, 72		4
	Cobalt sulfate heptahydrate	Interstitial	2 or 24		82.8
	Cobalt oxide	Interstitial	2, 5, 24, 72		9.9
	Co-Cr alloy (powder)	Synovial	2, 5, 24, 72		0.0018
	Co-Cr alloy (rods)	Synovial	2, 5, 24, 72		0.0013
Brock and Stopford (2003)	Cobalt pigments in pastel dust (art supply)	Gamble's solution (interstitial fluid surrogate)	72	0.05 µg Co/mL/day	Not reported

Table 3. (cont.)

Citation	Compound	Fluid Type	Incubation period (hours)	Bioaccessibility Results	
				Cobalt concentration (e.g., µg Co/mL) or rate (e.g., µg Co/mL/day)	% Cobalt Bioaccessibility
Hillwalker and Anderson (2014)	Stainless steel (304)	Artificial lysosomal fluid	72	Not reported	<0.00027
	Cobalt metal powder	Artificial lysosomal fluid	72		30
	Carbon steel NIST 14g	Artificial lysosomal fluid	2 or 72		<0.00027
	Stainless steel NIST 101 g	Artificial lysosomal fluid	2 or 72		<0.00027
Huang et al. (2016)	TSP (containing Co)	Gamble's solution (interstitial fluid surrogate)	48	Not reported	15
	TSP (containing Co)	Artificial lysosomal fluid	48		44
Stefaniak et al (2011)	Cobalt metal particles	Alveolar macrophage phagolysosomal fluid	Not provided	2.8±0.8 x 10 ⁻⁵ g/cm ² /day	Not reported
	Cobalt metal particles	Airway lining fluid			

NIST — National Institute of Standards and Technology

TSP — Total Suspended Particles

1.3 Cobalt in alloys should be considered separately from pure cobalt compounds.

Corrosion- and heat-resistant metal alloys, used by several industries such as aerospace and nuclear, often use metals that include cobalt, nickel, and chromium (ATSDR 2004; IARC 2006). The chromium present in stainless steel forms an impervious oxide layer that limits the solubility of metals in the alloy matrix. Therefore, cobalt in alloys is considered distinctly from pure cobalt compounds, such as cobalt as pure metal and cobalt sulfate, because cobalt in alloys is generally not bioavailable, meaning that cobalt ions are not readily released from the alloy into biological fluids. As shown by Hillwalker and Anderson (2014), cobalt in chromium-enriched alloys is relatively insoluble in lysosomal fluid (**Table 3; Figure 1B**). The solubility of cobalt metal was 30%, whereas the solubility of cobalt in stainless steel and other metal alloys was <0.00027%.

ToxStrategies recently conducted inhalation bioaccessibility testing of cobalt in a baghouse dust sample collected from a metal processing facility in Paramount, California (ToxStrategies 2017). We also evaluated a pure cobalt metal sample for inhalation bioaccessibility. This facility conducts grinding of various metal alloys, and its cobalt emissions are water insoluble and also expected to be insoluble in lung fluids. The objective was to understand whether cobalt in the alloy forms generated from grinding the metal was bioaccessible/soluble in simulated lung fluids and how that compares to bioaccessibility of the pure cobalt metal.

Bioaccessibility in synthetic lysosomal lung fluid was tested in the laboratory using the experimental methods delineated in Henderson et al. (2014). The baghouse dust and cobalt metal samples were analyzed at Prima Environmental, Inc. Baghouse dust samples were filtered to less than 75 microns using a 200-mesh screen to test particles in the size range most likely to be inhaled. Lysosomal fluids were created using the specifications provided in Table 2 of Henderson et al. (2014). Two incubation time periods (24 hours and 72 hours) were used to understand how bioaccessibility in the lung fluids changes over time as particles are cleared from the lung over days or longer.

Similar to Hillwalker and Anderson (2014), we found that cobalt in alloys had limited bioaccessibility compared to pure cobalt metal (**Table 4; Figure 1B**). With 72-hour incubation in lysosomal fluid, cobalt metal had 40% solubility/bioaccessibility, compared to 2.2% in dust generated from grinding alloys. Cobalt in the alloy form in grinding dust is about 20 times less bioaccessible than cobalt metal in lysosomal fluids. It is clear that an alloy matrix effect is present that limits bioaccessibility of cobalt in an alloy form. Based on this work, the carcinogenic potency of cobalt in the metal dust emitted from the grinding facility was expected to have lower potential for carcinogenicity than pure cobalt metal, and it could be characterized as such. This trend is also observed with other metals in alloys and also in gastric fluids where pH is substantially lower (pH=1.5) compared to lysosomal fluid (pH=4.5) (Henderson et al. 2012, Hillwalker and Anderson 2014, Suh et al. 2019).

Table 4. Inhalation bioaccessibility results for cobalt in samples collected from a metal processing facility in California

Sample	Lysosomal 24-hour	Lysosomal 72-hour
Alloy grinding dust	1.8%	2.2%
Cobalt metal sample	28%	40%

Notably, in the 2016 RoC Monograph, NTP does not specifically address cobalt alloys, because cobalt ions are not released readily from alloys in biological conditions. Hence, consideration of inhalation bioaccessibility information is critical for evaluating cobalt in alloys. We agree with OEHHA that the draft IURs are not applicable to alloys (stated on page 2). However, we also recommend adding further clarification to indicate that all alloy forms are considered for exclusion, not just the cobalt-tungsten hard metal alloys.

2 Errors in unit and dosimetric conversions result in inaccurate conclusions regarding the relative carcinogenicity of cobalt sulfate and cobalt metal.

There are errors and unclear statements in OEHHA’s draft risk assessment document that create confusion and will likely result in inaccurate air toxics risk assessments when these values are applied. We recommend that OEHHA conduct a comprehensive review of the draft document and provide corrections and revisions of statements that are confusing, and review the NTP (1998) bioassay for cobalt sulfate heptahydrate in detail to better characterize the dose. Specific examples are provided below.

2.1 The conversion calculations for cobalt concentrations from cobalt sulfate heptahydrate concentrations are in error.

It is clear in the NTP (1998) cobalt sulfate heptahydrate study that doses are presented as cobalt sulfate heptahydrate. However, OEHHA converted doses to cobalt ion using the mass of cobalt sulfate, without the waters of hydration. As a result, the molecular weight of cobalt sulfate heptahydrate is underestimated, as is the carcinogenicity, because the mass of cobalt administered is overestimated. OEHHA states that the conversion was done to compare the NTP (1998) cobalt sulfate heptahydrate data to the NTP (2014) cobalt metal data:

To compare cancer potencies of the two cobalt forms, the exposure levels for the studies were calculated based on cobalt content alone (Behl et al., 2015). Thus, chamber concentrations of 0, 0.3, 1.0 and 3.0 mg/m³ cobalt sulfate

(CoSO₄) corresponds to 0, 0.11, 0.38 and 1.14 mg/m³ Co, respectively.” (page 43, OEHHA 2019)

However, the doses consisted of cobalt sulfate heptahydrate, not cobalt sulfate. This conversion is based on the ratio derived by dividing the molecular weight of cobalt into the molecular weight of cobalt sulfate ($58.9 \text{ g/mol Co} \div 154.996 \text{ g/mol CoSO}_4 = 0.38$).

In Behl et al. (2015) and NTP (1998), the authors indicate that cobalt exposures in the aerosol were primarily in the form of cobalt sulfate **hexahydrate** to add further confusion to these comparisons:

Exposure concentrations of cobalt sulfate heptahydrate in this study are expressed as mg cobalt sulfate/m³; however, it was determined that each mole of aerosol in the exposure chambers **contained an approximate 1:1:6 molar ratio of cobalt:sulfate:water, indicating that exposures were primarily to cobalt sulfate hexahydrate.** [emphasis added] (page 196, Behl et al. 2015)

The stability of aerosol concentrations in the 0.3 and 3.0 mg/m³ chambers was monitored by analyzing samples collected on Gelman A/E glass fibers using a calibrated flow sampler. X-ray diffraction analyses were performed by a Philips 3600 diffraction unit with Cu Ka radiation. **Results indicated that cobalt sulfate hexahydrate was the primary species delivered to the chambers.**” [Emphasis added] (page 215, NTP 1998)

It is apparent that OEHHA used the conversion calculations from Behl et al. (2015) without considering the cobalt form as described above. We recognize that Behl et al. (2015) also made this error. Perhaps additional confusion was created because the discussion of the predominant form of cobalt sulfate was brief in NTP (1998), and the heptahydrate form was indicated in the title and discussed throughout the report, although hexahydrate seems to have been the administered form.

Regardless, the conversion calculation should not have been based on cobalt sulfate, rather the mass of heptahydrate should have been included. Based on the ratio derived by dividing the molecular weight of cobalt into the molecular weight of cobalt sulfate heptahydrate ($58.9 \text{ g/mol Co} \div 281.1 \text{ g/mol CoSO}_4 \cdot 7\text{H}_2\text{O} = 0.2095$), the corrected cobalt content based on the chamber concentrations of 0, 0.3, 1.0, and 3.0 mg/m³ cobalt sulfate heptahydrate are 0, 0.063, 0.21, and 0.63 mg/m³ cobalt. These values should be used in the comparison, not the values used in the current draft.

OEHHA used the same approach to normalize the cobalt sulfate heptahydrate cancer slope factor (CSF) to the content of cobalt. A ratio derived by dividing the molecular weight of cobalt into the molecular weight of cobalt sulfate heptahydrate ($58.9 \text{ g/mol Co} \div 281.1 \text{ g/mol CoSO}_4 \cdot 7\text{H}_2\text{O} = 0.2095$) was multiplied by a human CSF of $13.41 \text{ (mg/kg-day)}^{-1}$ from cobalt sulfate heptahydrate (CoSO₄•7H₂O) to calculate a CSF of $2.8 \text{ (mg/kg-day)}^{-1}$.

In addition to the conversion of cobalt content, as discussed below, the concentration in air is not the determinant of target-tissue dose to the lung, and a molecular weight conversion,

even if done correctly, is inadequate to compare airborne particulate cobalt metal and cobalt sulfate heptahydrate potencies. See Comment 3 for the comprehensive discussion.

2.2 OEHHA compares inhalation exposures between rodents and humans without using a well-established extrapolation method, or whether the extremely high exposures of animal bioassays are environmentally relevant.

OEHHA (2019), notes that:

The mean cobalt levels of 0.06 to 0.10 mg/m³ the workers were exposed to were below the lowest cobalt sulfate heptahydrate concentration (0.3 mg/m³) used in the NTP (1998a) rodent studies - a concentration that did not result in a statistically significant increase at the p = 0.05 level in tumor incidence in the animals by pairwise comparison.

It is not appropriate to simply compare airborne exposure concentrations of particulates between rodents and humans. USEPA provides guidance for such extrapolations (USEPA 1994).

The more relevant comparison of airborne concentrations is that among workers with average exposures of 60,000 to 100,000 ng/m³ (0.06 to 0.10 mg/m³) to concentrations in California ambient air. For example, the average concentration of cobalt in the South Coast Air Quality Management District (SCAQMD) ranges from only 0.2 to 0.79 ng/m³ in the Multiple Air Toxics Exposure Study in the South Basin (MATES IV, SCAQMD 2015). Thus, among workers with exposure concentrations approximately 100,000-times higher than ambient air, no increased risk was observed. We recognize that there are differences in extrapolating results between workers and non-working populations. However, that extrapolation certainly is more noteworthy than comparison with animal data.

2.4 OEHHA should consider whether the mode of action for chemical carcinogenesis which resulted in rodent tumors is relevant at environmental exposure levels

Further, OEHHA should consider whether the mode of action for tumor formation in rodents in the NTP studies is relevant to environmental exposures. The mechanistic data provided in the NTP (2014) study for cobalt metal, as well as the data discussed in the OEHHA draft guidance, generally support a finding that tumor formation in the lung is secondary to tissue damage induced by extreme exposures that exceed the maximum tolerated dose in some cases, resulting in oxidative stress and oxidative DNA damage. This is also the finding of Suh et al. (2016). It is highly questionable whether this mode of action exists for environmental exposures to cobalt, which occur at levels that are many orders of magnitude lower. Further, the occupational epidemiology data, as cited by OEHHA, do not indicate that an increased risk of cancer exists in humans at exposure concentrations that are approximately 100,000 times higher than environmental exposures.

OEHHA should further consider the text on page 42, wherein it is stated:

The cancer hazard of cobalt inhalation was assessed by NTP in separate chronic rodent studies of the water-soluble cobalt compound, cobalt sulfate heptahydrate (NTP, 1998a), and cobalt metal (NTP, 2014a) in male and female rats and mice. Based on the results of these NTP studies, cobalt exhibits carcinogenicity in multiple species, which reflects the greatest potential to induce tumors in other species including humans (Tennant and Spalding, 1996; NTP, 2014a; Behl *et al.*, 2015).

It is certainly not surprising that doses of cobalt, in highly bioaccessible and bioavailable forms, that are sufficiently high to induce oxidative stress and oxidative DNA damage, will cause lung tumors in multiple species in a bioassay. However, the critical question is whether there is the potential for carcinogenicity at relevant human exposure levels and to the forms of cobalt to which people are exposed in ambient air. OEHHA should address this issue. The tumors induced in the bioassay are unlikely to be relevant to environmental human exposures based on both the delivered dose to the lung and the forms of cobalt that exist environmentally.

Application of OEHHA's draft cancer risk assessment, assuming linear extrapolation to the very high exposures that caused cancer in rodents to very low exposure range in ambient air, can have significant implications for environmental risk assessment. As an example, lifetime exposures to cobalt in the metal and insoluble forms, using OEHHA's draft risk assessment and the upper end of the average exposures measured in ambient air, results in a cancer risk of 6 in one million ($0.00079 \mu\text{g}/\text{m}^3 \times 7.8 \times 10^{-3} [\mu\text{g}/\text{m}^3]^{-1}$), which exceeds the *de minimus* risk level of 1 in one million. As is evident in this example, significant regulatory actions may result from OEHHA's risk assessment of cobalt metal, and it is vital to the regulated industry and to the public interest, that the forms of cobalt be characterized correctly and that the best scientific methods be used to calculate carcinogenic potency.

2.5 The discussion of solubility requires revision.

If OEHHA does not revise the discussion of solubility to be based on bioaccessibility, there is a high likelihood that the IUR for insoluble cobalt will be misused. Forms of cobalt that are insoluble in biological lung fluids should be treated differently from cobalt metal. For example,

- On Page 1, OEHHA states:
“Insoluble/poorly soluble cobalt compounds are defined here as having a water solubility of $\leq 100 \text{ mg}/\text{L}$ at 20°C and would use the IUR of $7.8 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$ for risk assessment. This definition of water solubility has been used by other organizations (MAK 2007, USP, 2015).”

First, these two reference citations do not support the use of water solubility for risk assessment. USP (2015) is a pharmacopeia defining solubility, but it is not directly applicable for use in risk assessment. Additionally, water solubility is not specified; rather, solubility is indicated in varying degrees (i.e., very slightly soluble, slightly soluble, sparingly soluble, soluble, freely soluble, and very soluble) (USP, 2015). In MAK (2007), cobalt solubility in serum is presented alongside cobalt solubility in water. It is also stated that “in the case of cobalt metal in powder form, cobalt(II) oxide and cobalt(III) oxide hydrate, a higher solubility was found in blood serum when compared with that in water” (MAK 2007). MAK recognizes the important difference between water solubility and solubility in biological fluids.

Since the release of MAK (2007), NTP published its RoC Monograph on cobalt and cobalt compounds (NTP, 2016b). In the Monograph, detailed discussions of cobalt inhalation bioaccessibility are presented. It is clear that, while cobalt metal powder is poorly soluble in water, it is soluble in all physiologically relevant fluids (NTP, 2016b). Given these factors and as described in Section 3, the rationale for using water solubility to categorize cobalt compounds should be revised and clarified.

2.6 OEHHA should compare the carcinogenicity of cobalt sulfate heptahydrate and cobalt metal using equivalent administered doses.

On Page 43, OEHHA’s discussion in the first full paragraph is confusing. First, cobalt sulfate concentrations were converted to “cobalt contents” for comparison with the NTP (2014) cobalt metal study concentrations. This totally ignores the property of the exposure material, including the size of the administered particle. At the end of the paragraph, it is stated that “cobalt metal appears to be more effective than cobalt sulfate at inducing lung tumors.” If it is indeed appropriate to compare the cobalt contents between the two forms, then the carcinogenic potential should be identical. The fact that the two forms appear to have different potencies based on applied dose is evidence that physical properties affecting dosimetry may be important. In this regard, Suh et al. (2016) converted the two forms of cobalt to human equivalent concentrations (HECs) using the EPA (1994) method and found the carcinogenicity to be similar (see Figure 3, reproduced here as **Figure 2**).

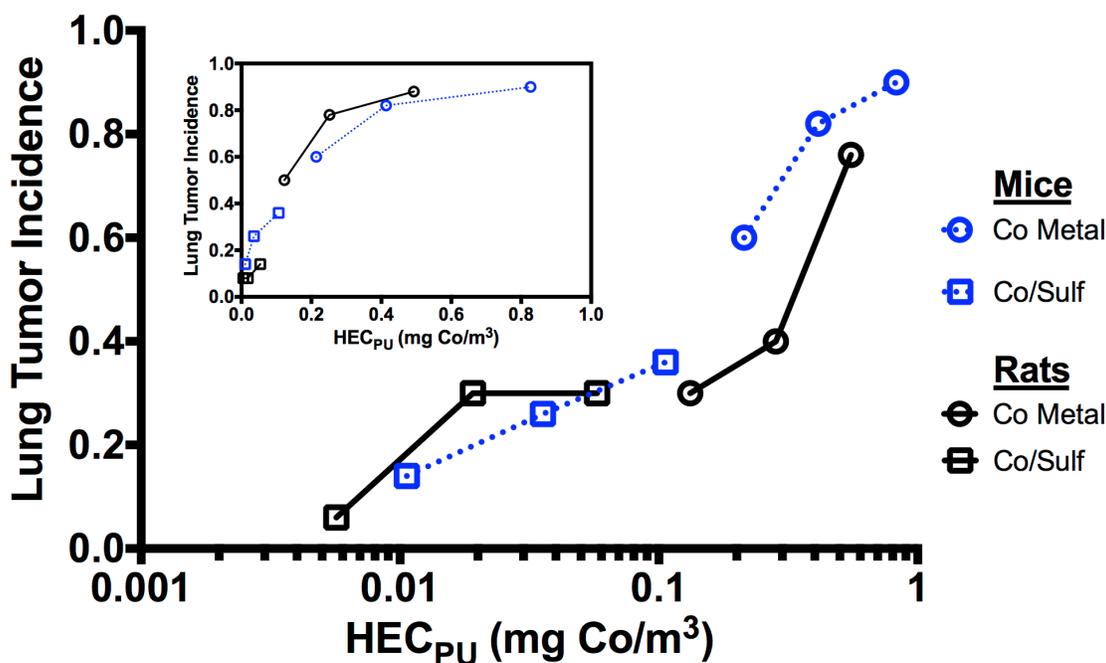


Figure 2. Replicated from Figure 3 of Suh et al. (2016).

The figure above provides lung tumor incidence data in rats and mice from the NTP cobalt metal and cobalt sulfate heptahydrate 2-year cancer bioassays. For the latter, particle size characterization data (e.g., mass median aerodynamic diameter [MMAD] and geometric standard deviation [GSD] of particle sizes) for cobalt sulfate heptahydrate were used assuming that water was included in the mass. The HEC was then adjusted to the cobalt fraction of cobalt sulfate heptahydrate. The main plot shows the data for male and female rats and mice on a log x-axis. The insert shows the data on a linear scale.

3 Refinements to the Cobalt Risk Assessment Methods Used by OEHHA

The Suh et al. (2016) paper, “Inhalation cancer risk assessment of cobalt metal,” published in *Regulatory Toxicology and Pharmacology*, is highly relevant to OEHHA’s IURs, yet it is cited only once, and not in the cancer risk assessment section.

On Page 20, OEHHA cites Suh et al. (2016) for the following statement:

Thus, the equivocal increased cancer risk noted by Tuchsén et al. may be related to the lack of significant *in vivo* release of cobalt ions from cobalt aluminate spinel (Suh et al. 2016).

In fact, Suh et al. does not make this statement, but we don't disagree with the statement. Aside from that, we are puzzled because OEHHA does not discuss the study in Section V, Quantitative Cancer Risk Assessment, where it is clearly most relevant. We recommend that OEHHA review the Suh study and revise the assessment.

We offer several specific refinements to improve the risk assessment methods of the OEHHA draft. As authors of the Suh et al. (2016) publication of a cobalt metal IUR, our comments focus on a comparison of the methods used by OEHHA as compared to our paper. **Table 5** compares selected IUR values derived by OEHHA with those published in Suh et al. (2016). Specifically, we show comparisons for male rats and mice, which resulted in the highest IURs for cobalt metal, as derived in OEHHA (2019). Overall, the recommended IURs determined by OEHHA and Suh et al. (2016) differ by 2.6-fold (IUR values of 7.8E-3 vs. 3.0E-3). As will be discussed, these values were derived using different approaches.

Table 5. Comparison of selected IUR values between OEHHA (2019) and Suh et al. (2016)

Endpoint	OEHHA (2019) Human CSF (mg/kg-day) ⁻¹	OEHHA (2019) Human IUR (µg/m ³) ⁻¹	Suh et al. (2016) Human IUR (µg/m ³) ⁻¹	Suh et al. (2016) ^b Human IUR (ALT) (µg/m ³) ⁻¹
Male rat A/B tumors	12.91	3.7E-3	5.8E-3	4.5E-3
Male rat pheochromocytomas	9.51	2.7E-3	6.3E-4	NC
Male rat pancreatic	1.71	4.9E-4	1.1E-4	NC
Combo: Male rat (all three)	22.17	6.3E-3	NC	NC
Combo: Male rat (lung & pancreas) ^a	14.1	4.0E-3	NC	NC
Male mouse A/B tumors	27.49	7.9E-3	5.7E-3	3.1E-3
Final proposed value	27	7.8E-3		3.0E-3 ^c

NC = not conducted

Shaded row for male mouse tumors was selected by OEHHA as the basis for an IUR

^a Analysis not conducted by OEHHA, but shown here for comparison (derived by ToxStrategies using OEHHA method)

^b Analysis conducted using custom benchmark response (BMR) approach (see Table 4 in Suh et al. 2016)

^c Final value was based on 3.4E-3 average of IURs for male and female rats and mice (rounded to one significant figure; see Table 4 in Suh et al. (2016))

3.1 OEHHA did not follow its own guidance on benchmark response (BMR) selection.

On page 50, OEHHA states, “For large datasets such as those by NTP, the BMD recommended by OEHHA (2008) is the 95% lower confidence bound on the effective dose producing 5% response (BMDL₀₅).”

The citation supporting the 5% BMR is OEHHA (2008), which is a document focusing on noncancer effects:

OEHHA. 2008. Air Toxics Hot Spots Program risk assessment guidelines. Technical support document for the derivation of noncancer reference exposure levels. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Oakland, CA. Online at: http://www.oehha.ca.gov/air/hot_spots/rels_dec2008.html.

It is unclear why OEHHA did not cite the more recent 2009 guidance on developing cancer potency factors:

OEHHA. 2009. Technical support document for cancer potency. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

In the (2009) guidance, OEHHA states:

The benchmark chosen is a point at the low end of the observable dose-response curve. Usually a dose at which the incidence of the tumor is 10% is chosen for animal studies, although lower effect levels may be appropriate for large epidemiological data sets. Because real experimental data include variability in the response of individual subjects, and measurement errors, likelihood methodology is applied in fitting the data. A lower confidence bound (usually 95%) of the effective dose (LED₁₀), rather than its maximum likelihood estimate (MLE), is used as the point of departure.

Importantly, neither the 5% nor the 10% response rate is near the observable range for the NTP cobalt metal bioassay, because NTP administered only very high doses of cobalt metal. Further, OEHHA did not follow its own guidance by selecting the 5% BMR.

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

USEPA uses the guidance document Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (USEPA 1994) for adjusting inhalation exposures to various regions of the body—depending on the location of the lesion of interest (including tumors). This method takes into account physicochemical characteristics of the test article (e.g., particle diameter), and well as the anatomy of the

target species. Overall, USEPA (1994) provides methods for estimating target-tissue dosimetry to the respiratory tract, as well as dosimetry beyond the respiratory tract. Instead, on page 49, OEHHA simply converted the duration-adjusted inhalation concentration to a rodent body burden using inhalation-rate data and bodyweights. This ignores the particle size information, as well as the target-tissue dosimetry.

3.3 OEHHA did not use dosimetric adjustments appropriate for each tumor site (i.e., inconsistent with U.S. EPA guidance).

By using the method described in USEPA (1994), exposures to rodents can be converted to human equivalent concentrations (HECs). Following duration and dose adjustment, the tumor data can be modeled in terms of HEC. Suh et al. (2016) modeled effects in the rodent lung, pancreas, and adrenal medulla in terms of HEC. These endpoints required different adjustments, because lung tumors were most likely a site-of-contact effect, whereas the pancreas effects were likely a result of systemic distribution. There is considerable uncertainty regarding the pheochromocytomas in rats, due to their questionable human relevance and evidence for pheochromocytomas arising secondary to lung effects in rodents (see Section 3.4). Together with the issues discussed in Section 3.2, OEHHA has not used standard methods for developing IUR values.

3.4 OEHHA failed to consider human relevance for certain rodent tumors.

OEHHA modeled pheochromocytomas in rats both independently and as part of a combined analysis. As will be discussed below, there is evidence that pheochromocytomas arise in inhalation studies where hypoxia is induced either as a consequence of exposure to particulate or lung lesions (including tumors). As stated in the NTP (2014) cobalt metal bioassay:

The results of several NTP inhalation studies with particulate compounds suggest that there may be an association between the occurrence of benign and malignant alveolar/bronchiolar neoplasms and variably extensive chronic pulmonary nonneoplastic lesions of the lung and significantly increased incidences of hyperplasias and benign and malignant pheochromocytomas of the adrenal medulla in exposed male and female rats...

This relationship can also be surmised by the tumor data. According to Table 8 in OEHHA (2019), the incidence of pheochromocytomas in untreated male rats was 17/46, whereas the incidence of lung tumors was 2/47. This indicates a vast difference in the background incidence in these tumors. Yet, in all the treatment groups, the numbers of male rats with pheochromocytomas were slightly *lower* than those with lung tumors. If the pheochromocytoma tumor responses were independent of lung tumors, one would expect to see more animals with pheochromocytomas, due to systemic exposure to cobalt, than lung tumors among the exposed animals.

NTP (2014) also states:

Agents that induce adrenal medullary neoplasia tend to be nongenotoxic and seemingly induce carcinogenesis through an indirect mechanism (Strandberg, 1995). In NTP studies, the mechanism(s) responsible for the induction of pheochromocytoma in rats is not understood. However, it is thought that reduced gas exchange induced by extensive space-occupying neoplasms and nonneoplastic lung lesions such as fibrosis and chronic inflammation leads to systemic hypoxemia that chronically stimulates catecholamine secretion from the adrenal medulla. This chronic hypersecretory activity may lead to medullary hyperplasia and neoplasia (Ozaki *et al.*, 2002).

The NTP (2014) report notes that abnormal breathing was observed in rats in shorter-term studies as well as the chronic bioassay, indicating that exposure to cobalt metal particulate induced breathing issues in rats with or without the presence of lung tumors. Thus, there was evidence for treatment-related hypoxia in the NTP cobalt metal study.

Critically, experts in clinical toxicology have concluded that pheochromocytomas in rats “have little or no relevance to human safety” (Greaves 2012). Therefore, 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 tumor) is present, and combining the tumors is not appropriate because pheochromocytomas are dependent on lung tumors and other respiratory damage.

3.5 OEHHA used model results with large amounts of uncertainty due to extrapolation below the range of observation.

The BMD and BMDL values that OEHHA used for deriving slope factors for lung tumors in rats and mice were highly uncertain due to the BMD and BMDL values being well below the lowest exposure dose in the study. Because OEHHA ultimately derived their IUR based on the male mouse lung tumors, we focus here on those modeling results.

Using OEHHA’s approach of converting inhaled dose to body burden, we were able to replicate several values reported in Table 11 of OEHHA (2019). Although the BMD modeling results in BMDS v2.7 indicated an acceptable p-value for model fit, the BMD₅ is well below the range of observation. Dividing the lowest exposure dose (0.26 mg/kg-day) by the BMD₅ (0.0145 mg/kg-day) results in extrapolation ~18-fold below the range of observation (note: the BMDL₅ is even further below the range of observation at ~23-fold).

We further ran these data in the latest version of BMDS 3.1 (USEPA 2019), which now contains recommendations (and warnings) for model selection, results in recommendations for all models used by OEHHA to be flagged as “Unusable” or “Questionable.” All three Multistage cancer models result in “Questionable” due to warnings about (1) “BMD 3x lower than lowest non-zero dose,” and (2) “BMDL 10x lower than lowest non-zero dose.”

Notably, Suh *et al.* (2016) modeled the lung tumor data without such extrapolations below the observable range by deriving a custom BMR that would result in the BMD being within

the range of observation. This method has been used previously by USEPA wherein the standard BMR of 10% results in BMD/BMDL values far below the range of observation (USEPA 2011). In USEPA’s method, the custom BMR is calculated as follows:

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

Again, using OEHHA’s approach of converting inhaled dose to body burden, but using a custom BMR of 78%, returns Multistage models with recommendations of “Viable – Alternate” and BMDL₇₈ values of 0.3311 mg/kg-day². The resulting rodent CSF is 2.36 per mg/kg-day (0.78/0.3311), and the human CSF is 14.5 per mg/kg-day. As shown in **Table 6**, OEHHA would have derived an IUR similar to that proposed by Suh et al. (2016) if BMD modeling had been conducted using methods that did not require extrapolation below the range of observation. This suggests that OEHHA’s use of BMD/L values well below the range of observation results in an IUR ~2-fold higher than that proposed by Suh et al. (2016). However, we reiterate that OEHHA’s method of converting inhaled dose to body burden without considering the methods described in USEPA (1994) is also problematic (see Sections 3.3 and 3.4).

Table 6. Comparison of select IUR values between OEHHA (2019) and Suh et al. (2016)

Endpoint	OEHHA (2019) Human CSF (mg/kg-day)⁻¹	OEHHA (2019) Human IUR (µg/m³)⁻¹	Suh et al. (2016) Human IUR (µg/m³)⁻¹
Male mouse A/B tumors (BMR=5%)	27.49	7.9E-3	ND
Hypothetical OEHHA analysis ^a : Male mouse A/B tumors (BMR=78%) ^b	14.5	4.2E-3	3.1E-3

^a Analysis not conducted by OEHHA, but shown here for comparison (derived by ToxStrategies using OEHHA method)

^b Analysis conducted using custom BMR approach (see Table 4 in Suh et al. 2016)

3.6 OEHHA’s use of the MS_Combo model is inappropriate due to likely interdependence of tumors

OEHHA conducted modeling for the combined tumor incidence in male rats, as well as female rats. We replicated the combined modeling results for male rats using MS_Combo model in BMDS 3.1. While the numbers appear correct, the analysis is flawed, because MS_Combo assumes that the tumors modeled arise independent of one another. In fact, as

² Notably, the new Bayesian model-averaged BMDL in BMDS v3.1 results in a similar BMDL₇₈ of 0.288 mg/kg.

discussed above, researchers recognize that pheochromocytomas arise secondary to lung tumors. On page 51, OEHHA acknowledges that there is some evidence that pheochromocytomas of the adrenal medulla in rodents might be “dependent on tumor formation in the lungs.” More specifically, it is hypothesized that tumor formation and/or particle overload can lead to hypoxia-related catecholamine secretion from the adrenal medulla and stimulation of medullary hyperplasia that ultimately leads to adrenal pheochromocytomas (NTP 2014; Suh et al. 2016). Notably, medullary hyperplasia was observed in the NTP (2014) cobalt metal study but not the NTP (1998) cobalt sulfate heptahydrate study.

3.7 OEHHA’s use of the MS_Combo model is inappropriate due to differences in target-tissue dosimetry.

The combined modeling was based on OEHHA’s conversion of inhaled doses to body burden (mg/kg-day). It seems highly unlikely that lung tumors, pancreatic tumors, and pheochromocytomas are the result of the same dose metric. Lung tumors are likely the result of direct site-of-contact effects, whereas pancreatic tumors may arise from either systemic effects or ingestion of cobalt metal. As mentioned above, it is conceivable that the pheochromocytomas are secondary to hypoxia-induced effects on oxygen absorption in the lung. Therefore, combining risks based on body burden is unwarranted. As stated in Dr. Kenny Crump’s analysis of MS_Combo³:

USEPA generally prefers to utilize pharmacokinetic data on the dose to the target organ in its risk assessments. However, different tumor sites will have different internal doses and it will not be possible to take these differences into account properly with the current implementation of MS-COMBO. Conceptually, accounting for target organ doses would require incorporation of a quantitative physiologically-based pharmacokinetic (PBPK) model into the analysis... Consistent with the manner in which EPA normally uses PBPK data to convert from animals to humans, the animal tumor data would be modeled using tumor site-specific internal doses estimated from the animal PBPK model, and the BMD calculation would use the human PBPK model (implemented using the simple linear approximation) to calculate the human external BMD corresponding to these internal doses.

According to the USEPA RfC approach, lung tumors should be modeled as a pulmonary effect, whereas the pancreas is an extrapulmonary (i.e., systemic) tumor site. As noted above, the pheochromocytomas have questionable human relevance and may arise secondary to lung lesions. Without additional information, body burden might be a suitable dose metric for the pancreatic tumors and pheochromocytomas, but not for lung tumors. Unless each tumor response can be modeled in terms of its tissue-specific dosimetry, it makes little sense to model the tumors on a single exposure metric using MS_Combo.

³ Versar. 2011. External peer review of EPA’s MS-COMBO multi-tumor model and test report. Contract No. EP-C-7-025.

In summary, OEHHA should not use MS_Combo to model pheochromocytomas with lung tumors; OEHHA should use dosimetric adjustments for particle deposition in the lung consistent with EPA guidance, to calculate and model HECs; and OEHHA should use a custom BMR in the observable range, rather than extrapolating over a 20-fold dose range. Both EPA's BMD and OEHHA's cancer risk assessment guidance recognize the importance of selecting a BMR within or close to the observable range.

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