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IRIS Assessment Plan
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IRIS Assessment Plan and Protocol for Assessing Cancer Risk from Inhalation Exposure to Cobalt and Cobalt Compounds

(Scoping and Problem Formulation Materials)

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Integrated Risk Information System
Center for Public Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
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ABBREVIATIONS

ADAF	age-dependent adjustment factors
ADME	absorption, distribution, metabolism, and excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BMR	benchmark response
BMDS	Benchmark Dose Software
CAA	Clean Air Act
CalEPA	California Environmental Protection Agency
CASRN	Chemical Abstract Services Registry Number
CPAD	Chemical and Pollutant Assessment Division
CPHEA	Center for Public Health and Environmental Assessment
EPA	Environmental Protection Agency
HAWC	Health Assessment Workspace Collaborative
HERO	Health and Environmental Research Online
IAP	IRIS Assessment Plan
IARC	International Agency for Research on Cancer
ICD – 8	International Classification of Diseases (8th revision)
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
NTP	National Toxicology Programs
MOA	Mode of Action
OAR	Office of Air and Radiation (EPA)
ORD	Office of Research and Development (EPA)
PAC	protective action criteria
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
POD	point of departure
RIS	Research Information Systems
RfC	reference concentration
ROS	reactive oxygen species
SEM	systematic evidence map
SWIFT	Sciome Workbench for Interactive Computer-facilitated Text-mining
TIAB	title and abstract
TCEQ	Texas Commission on Environmental Quality
URE	unit risk estimates
URF	unit risk factor

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1. INTRODUCTION

IRIS assessments provide high quality, publicly available information on the toxicity of environmental chemicals and pollutants to which the public might be exposed. These assessments provide an important source of toxicity information used by the Environmental Protection Agency (EPA), state and local health agencies, other federal agencies, tribes, and international health organizations. Specifically, IRIS assessments provide rigorous scientific evaluations addressing the first two steps of the 4-step risk assessment process, hazard identification and dose-response analysis.

As part of the initial steps in assessment development, the IRIS Program undertakes scoping and initial problem formulation activities. During scoping activities, the IRIS Program consults with EPA programs and regional offices to identify the nature of the hazard characterization needs, the most important exposure pathways, and the timeframe to inform Agency decisions. A broad, preliminary literature survey (referred to as a systematic evidence map, or SEM) may also be conducted to assist in identifying the extent of the evidence and health effects that have been studied for the chemical of interest. Based on the SEM and the scope defined by EPA, the IRIS Program undertakes problem formulation activities to frame the scientific questions that will be the focus of the assessment. A summary of the IRIS Program's scoping and problem formulation conclusions are contained in the IRIS Assessment Plan (IAP). Based on the IAP, an IRIS Protocol is developed to describe the methods that will be used to address the defined scope and identified problem formulation considerations during IRIS assessment development.

This document presents the draft IAP for the "IRIS Assessment of Cancer risk from Inhalation Exposure to Cobalt and Compounds." The IRIS Protocol outlining the methods for conducting the assessment is also included because the results of problem formulation indicated the proposed analysis will be targeted, focusing on dose-response analyses of studies identified from the SEM as being most suitable for deriving cancer inhalation toxicity values.

2. SCOPING AND PROBLEM FORMULATION

2.1. BACKGROUND

Section 2.1 provides a summary of background information for contextual purposes only. This brief overview emphasizes reviews and other summary information that, unless otherwise specifically noted, are derived from NTP (2016), TCEQ (2017), OEHHA (2020), and Slack et al. (2017); it is not intended to be a comprehensive description of the available information.

Cobalt is a metallic element that is naturally occurring as several different substances and oxidation states, often in association with nickel, silver, lead, copper, and iron ores. Cobalt compounds are used in a variety of industrial applications, including as catalysts, in feed supplements, in batteries, as colorants for glass, ceramics, and paint, and as driers for inks and paints. Cobalt is also used in alloys or composites, such as cobalt-tungsten carbide, and in cobalt-containing prosthetics. Nanomaterials containing cobalt are used in medical tests and treatments as well as in the textile and electronics industries. Cobalt also forms part of the structure of vitamin B12, which plays essential roles in red blood cell formation, cell metabolism, nerve function and DNA synthesis Osman et al. (2021); Mayo Clinic (2021).

Elemental cobalt (limited natural occurrence, generally produced during smelting) is a hard, silvery grey metal. Cobalt reacts with other elements, such as oxygen (cobalt oxide), sulfur (cobalt sulfate), and arsenic (cobalt arsenide). Cobalt compounds represent a large group of substances. For example, EPA's Substance Registry Services - the central system for information about substances that are tracked or regulated by EPA or other sources - contains over 400 cobalt containing compounds U.S. EPA (2014b). These compounds can be organometallic or inorganic as well as water-soluble or -insoluble. The most common oxidation states of cobalt (Co) are +2 and +3; for most simple cobalt compounds, the valence is +2, designated as Co (II), while Co (III) substances are generally strong oxidizers. There is only one stable isotope of cobalt, ^{59}Co, and there are about 26 known radioactive isotopes of cobalt, of which only two are of commercial importance, ^{60}Co and ^{57}Co.

2.2. SCOPING SUMMARY

EPA's Office of Air and Radiation (OAR) nominated a cancer assessment of water-soluble and water-insoluble cobalt compounds to the IRIS Program. The nomination focused on inhalation exposure and those forms most pertinent to implementing the Clean Air Act (CAA) by informing decisions related to potential carcinogenic risks due to emissions to air of cobalt compounds during industrial processes (Appendix A.1). This assessment activity was added to the IRIS Program Outlook in June 2022.

Cobalt compounds represent a very large and diverse set of substances. Some uses of cobalt compounds may result in their emissions to air. Cobalt compounds most pertinent to OAR's implementation of the Clean Air Act (CAA) are primarily water-soluble forms [such as cobalt aluminate, cobalt bromide, cobalt carbonate, cobalt chloride, cobalt hydrocarbonyl, cobalt naphtha, cobalt nitrate, cobalt oxide (II, III), and hexanoic acid, 2-ethyl-, cobalt (2+) salt] and some water-insoluble forms [such as cobalt metal and cobalt carbonyl]. These compounds were identified based on currently available emission data U.S. EPA (2020a). Only a few cobalt compounds identified to date have cancer toxicity data. Thus, those cobalt compounds that do have evidence for cancer due to inhalation exposure (e.g., hydrated cobalt sulfates) are being evaluated within the scope of this review for potential use as surrogates for other water-soluble and water-insoluble forms of cobalt. See Appendix A for a summary of chemical and physical properties, obtained largely from the EPA CompTox Chemicals Dashboard and PubChem, for the key compounds identified during scoping[1]. If supported by the available data, EPA may develop separate cancer values for water-soluble and water-insoluble cobalt compounds. Note that the chemicals included in Appendix A do not represent an exhaustive list of water-soluble and water-insoluble cobalt compounds of interest to OAR that will be addressed in the dose-response assessment. However, certain cobalt containing substances are considered out of scope for this assessment: nanomaterials containing cobalt, radioactive isotopes (i.e., ^{60}Co), and vitamin B12, because their chemical and physical properties are quite different from the forms identified during scoping as most pertinent to the CAA, and hence, their toxicological characteristics are also expected to be different. Forms pertinent to the CAA are those that are detected and reported in air quality monitoring.

Table 2-1. EPA Program Office Interest in a Cancer Assessment of Cobalt Compounds.

EPA program or regional office	Oral	Inhalation	Statutes/regulations	Anticipated uses/interest
OAR		✓	Clean Air Act (CAA)	Cobalt compounds are listed as a hazardous air pollutant (HAP) under section 112 (b) (42 U.S.C.§ 7412) of the CAA. CAA Section 112 has a number of regulatory requirements, including the requirement

[1] The physicochemical properties in the summary tables are based on information from a variety of sources, primarily from the EPA CompTox Chemicals Dashboard and PubChem. The data obtained from the EPA CompTox Chemicals Dashboard are of varying quality and include both experimental and predicted data. The data associated with the chemical substances in the CompTox Chemicals Dashboard database have been compiled from public sources, databases and peer-reviewed literature and have varying levels of reliability and accuracy. Predicted data in particular have significant limitations in terms of the predictions of properties for salts, inorganic and organometallic substances. Links to many external resources are provided. Expansion, curation, and validation of the content are ongoing. The tables presented in the Appendix were reviewed by chemists for obvious errors and the most appropriate values available were selected.

EPA program or regional office	Oral	Inhalation	Statutes/regulations	Anticipated uses/interest
				that EPA promulgate emission standards for sources emitting HAP. Eight years after promulgation of emission standards, EPA must perform risk and technology reviews of emission standards that require maximum achievable control technology (MACT). Cobalt toxicological information developed for this cancer assessment may be used to inform CAA section 112 regulatory decisions. The toxicological information may also be used for non-regulatory purposes, such as the annual national screening-level assessments of air toxics (i.e., AirToxScreen). Some cobalt containing substances are considered out of scope for this assessment, because their chemical and physical properties are quite different from the cobalt forms identified as most pertinent to the CAA during scoping, and hence, their toxicological characteristics are also expected to be different: nanomaterials containing cobalt, radioactive isotopes (i.e., ^{60}Co), and vitamin B12.

2.3. PROBLEM FORMULATION

Multiple health agencies, including the U.S. EPA, National Toxicology Program (NTP), International Agency for Research on Cancer (IARC), California EPA, and Texas Commission on Environmental Quality (TCEQ), have concluded that cobalt and certain cobalt compounds are likely to cause cancer (Table 2-2). The IRIS database does not contain a cancer classification, oral slope factor or inhalation unit risk for cobalt. An EPA Provisional Peer Reviewed Toxicity (PPRTV) assessment published in 2008 concluded under EPA's Guidelines for Carcinogen Risk Assessment U.S. EPA (2005a) that water-soluble cobalt compounds are "likely to be carcinogenic to humans by the inhalation route" U.S. EPA (2008). This was based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals (rats and mice) treated with a water-soluble form of cobalt (cobalt sulfate heptahydrate[2], often referenced as "cobalt sulfate" in existing assessments) in a 2-year inhalation cancer bioassay Bucher et al. (1999); NTP (1998).[3] Since publication of the PPRTV assessment, the NTP has released a 2-year inhalation cancer bioassay of cobalt metal NTP (2014), which was used by the CalEPA to develop an inhalation unit risk estimate for cobalt metal and water-insoluble cobalt compounds (Table 2-2). CalEPA also developed an inhalation unit risk estimate for water-soluble cobalt compounds based on the 1998 NTP cancer bioassay study of cobalt sulfate NTP (1998). Both the 1998 and 2014 NTP cancer bioassays were used by TCEQ to develop an inhalation unit risk estimate for cobalt and cobalt compounds. The unit risk factor derived by TCEQ was based on the midpoint of the unit risk factors of cobalt sulfate and metal. Additional details on derivation of the various unit risk factors are presented in Appendix B along with a summary of non-cancer reference values for cobalt and cobalt compounds.

[2] $CoSO_4 \cdot 7H_2O$, CAS No. 10026-24-1, molecular weight 281.13. It should be noted that the experimental conditions dehydrated the compound to cobalt sulfate hexahydrate ($CoSO_4 \cdot 6H_2O$, molecular weight 263.09), and that this was the chemical rodents were exposed to NTP (1998). See Section 4.2.1 for additional information on dose standardization for NTP (1998).

[3] NTP analyses Bucher et al. (1999) described statistically significant increased incidence of alveolar/bronchiolar tumors in both sexes of rats and mice, pheochromocytomas in female rats, and hemangiosarcomas in male mice. NTP (2014) concluded that there was clear evidence of carcinogenic activity of cobalt metal in male rats (lung, adrenal medulla, pancreas), female rats (lung, adrenal medulla, mononuclear cell leukemia), and male and female mice (lung); NTP (1998) concluded that there was clear evidence of carcinogenic activity of cobalt sulfate heptahydrate in female rats (lung, adrenal medulla) and male and female mice (lung), and some evidence of carcinogenic activity in male rats (lung).

Table 2-2. Summary of Existing Cancer Hazard Conclusions for cobalt by the inhalation route

Agency/Organization (year)	Cancer Characterization[a]	Cobalt substance(s)	Inhalation unit risk[b] and study on which its based
Provisional Peer-Reviewed Toxicity Value (PPRTV) U.S. EPA (2008)	Likely to Be Carcinogenic to Humans	Soluble cobalt sulfate	9.0 $(mg/m^3)^{-1}$ NTP (1998) Lung tumors
California Office of Environmental Health Hazard Assessment OEHHA (2019); OEHHA (2020)	Listed as under Proposition 65 as causing cancer	Cobalt metal and water-insoluble compounds	8.0 $(mg/m^3)^{-1}$ NTP (2014) Multisite tumor analysis
		Water-soluble cobalt compounds	0.86 $(mg/m^3)^{-1}$ NTP (1998) Multisite tumor analysis
Texas Commission on Environmental Quality TCEQ (2017)	Likely to Be Carcinogenic to Humans	Cobalt and compounds	6.0 $(mg/m^3)^{-1}$ NTP (1998); NTP (2014) [c] Lung tumors
International Agency for Research on Cancer Karagas et al. (2022)	Group 2A: Probably Carcinogenic to Humans	Cobalt metal	NA
		Cobalt sulfate and other soluble Co(II) salts	
European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC) ECHA (2017)	Category 1B for Carcinogenicity: Presumed to Cause Cancer to Humans	Cobalt and compounds	NA
National Toxicology Program NTP (2016)	Reasonably Anticipated to Be Human Carcinogens	Cobalt and cobalt compounds that release cobalt ions *in vivo*	NA
American Conference of Governmental Industrial Hygienists ACGIH (2001a)	Group A3: Confirmed Animal Carcinogen with Unknown Relevance to Humans	Inorganic cobalt	NA

[a] Cancer hazard conclusions expressed using the phrasing of the specific agency or organization that conducted the assessment and reflects terminology used at the time of the published report.

[b] All values normalized to cobalt content (see Section 4.2.1). It should be noted that some agencies may have used the molecular weight of cobalt sulfate hexahydrate to convert from chemical concentrations listed in NTP (1998) to mg/m^3 elemental cobalt. This is because analysis of the chamber samples indicated that exposures were to cobalt sulfate hexahydrate, and that the parent compound (cobalt sulfate heptahydrate) dehydrated. However, based on a review of the assessment analytical details in the NTP report and Behl et al. (2015), it was determined that the chemical concentrations listed in NTP (1998) were units of mg/m^3 anhydrous cobalt sulfate Bucher et al. (In Press). As a result, dose-response modeling results for soluble cobalt based on data from NTP (1998) may contain a bias due to an error in units conversion. Assuming a lower percentage of elemental cobalt in the exposure compound would result in an overestimation of toxicity.

[c] TCEQ derived unit risk factors of 9.1 $(mg/m^3)^{-1}$ (based on NTP (1998)) and 3.0 $(mg/m^3)^{-1}$ (based on NTP (2014)). The final unit risk factor was the midpoint of these two values.

The focus of the present task is to carry out a cancer dose-response assessment and develop values for inclusion in the IRIS database. EPA anticipates this cancer dose-response assessment will derive an inhalation unit risk (IUR) based on previous work indicated in this document. In addition, analyses will be undertaken to evaluate support for a non-linear MOA, and, if deemed necessary, a nonlinear approach for the dose-response will be presented. Currently, EPA does not anticipate deriving any noncancer inhalation values. This assessment will adopt the PPRTV cancer hazard conclusion that under EPA's *Guidelines for Carcinogen Risk Assessment* U.S. EPA (2005a), cobalt is "likely to be carcinogenic to humans by the inhalation route," a conclusion consistent with other authoritative bodies (Table 2). EPA's PPRTV concluded soluble cobalt is likely to be carcinogenic to humans by the inhalation route. Subsequently peer reviewed assessments from other authoritative bodies have reached this conclusion for both soluble and insoluble forms. Accordingly, this assessment will not undertake a hazard assessment but will apply this designation to all the cobalt forms identified within its scope. As shown in Table 2, the NTP 1998 and 2014 cancer bioassays NTP (1998); NTP (2014) have consistently been considered most suitable for developing inhalation unit risk estimates in prior assessments. A systematic evidence map (SEM, see Appendix C) was developed to determine whether any more recent studies have been published that could plausibly be used for dose-response. No human epidemiology or experimental animal studies were identified that were considered at least as suitable as the NTP bioassays. Thus, for dose-response analysis, the IRIS assessment will focus on the 1998 and 2014 NTP studies as representative of water-soluble and water-insoluble compounds of cobalt, similar to the approach taken by CalEPA. Methods for adjusting observed inhaled particulate exposure effect levels for interspecies dosimetric differences will be performed according to EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* U.S. EPA (1994), and implementation further refined using EPA's *MPPD Technical Support Documentation and User's Guide* U.S. EPA (2022).

2.4. KEY SCIENCE ISSUES

Based on the preliminary literature survey and review of past assessments on inhalation exposure to cobalt, the following key scientific issues related to the mechanistic evidence for cobalt were identified. Evaluation of these key science issues may inform facets of the dose-response assessment, potential dependencies between different tumor types, and application of age-dependent adjustment factors (ADAF) as appropriate in accordance with EPA's Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA (2005b). The evaluation of these cobalt-related science issues will be informed by conclusions from prior assessments U.S. EPA (2008); OEHHA (2019); OEHHA (2020); TCEQ (2017) and supplemented by evidence obtained from new mechanistic studies identified since these assessments were completed.

- Tumor dependencies: Carcinogenicity studies in rats and mice conducted by NTP show significant dose-related increases in incidences of lung tumors (alveolar/bronchiolar adenomas and carcinomas) following 2-year inhalation exposures to insoluble cobalt metal NTP (2014); Behl et al. (2015) and soluble cobalt sulfate heptahydrate NTP (1998); Bucher et al. (1999). NTP (2014) and NTP (1998) also report tumor formation at sites distal to the lung. Specifically, both cobalt compounds also caused treatment-related increases in neoplasms of the adrenal gland in female rats. In male rats, adrenal gland tumors were also reported with cobalt metal, but findings were equivocal in males exposed to cobalt sulfate heptahydrate. Inhalation exposures to cobalt metal at a higher dose range also elicited a greater spectrum of systemic tumors in rats than did cobalt sulfate heptahydrate, including mononuclear leukemia, and tumors of the pancreas and kidneys. Assessment of dependence or independence of the different tumor types will help to determine whether a combined tumor analysis can be performed (i.e., combined tumor analysis is considered invalid if it is judged that the tumors do not form independently U.S. EPA (2020b).

- Cellular uptake and tissue disposition: The kinetics and tissue disposition of inhaled cobalt may be affected by the specific cobalt-containing chemical compound and associated physical-chemical properties, including solubility and particle size. Insoluble cobalt metal and soluble cobalt sulfate heptahydrate are shown in vivo and in vitro to elicit similar respiratory and inflammatory responses but may exhibit differing pharmacokinetics and pharmacodynamics that can influence cobalt dosimetry and biological activity NTP (2014); NTP (1998). Although cobalt bioavailability and its influence on carcinogenicity are not fully understood, it is known that cellular uptake of free cobalt ion and particles occur by differing processes U.S. EPA (2008); Lison et al. (2018); NTP (2016); NTP (2021); OEHHA (2020). Water insoluble cobalt compounds could be absorbed into the cell via endocytosis processes where they are solubilized in lysosomes and released in ionic form inside the cell. As a result, some compounds that are poorly soluble in water (such as cobalt metal, cobalt (II) oxide, and cobalt (III) oxide) have higher solubilities in serum and biological media MAK-Commission (2007). In addition, even for sparingly soluble compounds that are commonly termed insoluble, solubility limits may be higher than relevant biological levels of cobalt. In which case information about the *rate* of solubilization could inform assessment of toxicity. Solubilized cobalt compounds release ions outside the cell after which they are taken up into the cell through membrane-bound ion channels. Thus, many

water-soluble and sparingly water-soluble cobalt compounds can result in the cellular uptake or release of cobalt ions in vivo. The differences between uptake and intracellular release rates of water-soluble and water-insoluble cobalt compounds could lead to distinct target sites, as well as variations in systemic and intracellular concentrations. Therefore, mechanistic information regarding cellular uptake and tissue deposition will be updated and may inform selection and application of dosimetric adjustments or modeling approaches Behl et al. (2015); Colognato et al. (2008); Ponti et al. (2009); Smith et al. (2014).

- Cobalt particle toxicity: The release of cobalt ion intracellularly in lysosomes by water-insoluble cobalt compounds is suggested to be largely responsible for mediating their biological activity IARC (2006); NTP (1998); NTP (2014); NTP (2016); NTP (2021). However, in addition to potential differences in particle ion uptake and distribution that might influence tissue dosimetry, cobalt is a redox-active transition metal, and as such, it has been suggested that cobalt particles may have a greater effect than ions in catalyzing production of reactive oxygen species (ROS) IARC (2006); NTP (2016). Updating the mechanistic evidence concerning whether cobalt particles may elicit direct toxicity contributing to carcinogenesis will help inform the choice of the particle lung dose metric used for rodent-to-human extrapolation and dose-response.

- Proposed MOA of cobalt carcinogenicity: While not fully understood, there is evidence that cobalt-induced neoplastic development likely involves pathways of genotoxicity, oxidative stress (and generation/scavenging of ROS), and stabilization of hypoxia-inducible factor 1α (HIF-1α) U.S. EPA (2008); IARC (2006); NTP (2016); NTP (2021); Ton et al. (2021). Evidence with differing water-insoluble and water-soluble cobalt compounds suggests cobalt genotoxicity involves primarily clastogenic effects, as well as direct and indirect DNA damage and inhibition of DNA repair U.S. EPA (2008); IARC (2006); NTP (2016). Previous assessments have found the evidence generally inconsistent on whether inhaled cobalt carcinogenicity involves a mutagenic MOA, and do not apply age-dependent adjustment factors (ADAF) in unit risk estimates U.S. EPA (2008); OEHHA (2020); TCEQ (2017). Updating the current evidence in the proposed cobalt cancer MOA, including capturing any new evidence of mechanistic responses beyond those previously described, will help inform the dose-response analyses, pharmacokinetic evaluations, and animal-to-human extrapolation methodologies U.S. EPA (2020c).

- Cobalt compounds are a large and diverse group of substances. To the extent possible, the assessment will try to describe the types of cobalt compounds for which use of this IRIS assessment would not be appropriate. Substances that can release cobalt ions in vivo[4], both water soluble and insoluble, likely define the domain of applicability. Substances where cobalt atoms are tightly bound and not bioavailable, such as Vitamin B12, are unlikely to present the same carcinogenicity hazards.

[4] Release of cobalt ions can involve the solubilization of Co(II) ions or, for metallic materials, reflect both surface corrosion and release of Co(II) ions.

3. OVERALL OBJECTIVE AND SPECIFIC AIMS

3.1. OVERALL OBJECTIVE

The overall objective is to carry out a dose-response assessment for water soluble and water insoluble compounds of cobalt. The evaluation conducted in this assessment will use relevant EPA guidelines.[5]

3.2. SPECIFIC AIMS

- Utilize the SEM (presented in Appendix C) to identify studies most suitable for the dose-response modeling for water-soluble and water-insoluble compounds of cobalt.
    - Based on the SEM and assessments conducted by others, the NTP inhalation cancer bioassay studies for cobalt sulfate and cobalt metal NTP (1998); NTP (2014) were considered most appropriate for dose-response analysis.
    - As supported by the available data, EPA will consider developing separate estimates for water-soluble and water-insoluble cobalt compounds.
- As supported by the available data, mechanistic information obtained from new studies (see section 4.1.1) and prior assessments will be evaluated to inform existing conclusions on the MOA and whether there are any new MOA considerations for dose-response analysis U.S. EPA (2005a); U.S. EPA (2005b); Karagas et al. (2022).
    - MOA considerations will inform methods for deriving inhalation unit risk values for water soluble and water insoluble compounds of cobalt, statistical analyses of dose-response data, common dependencies between different tumor types, and application of ADAF. See Section 2.4 for details.
- As supported by the available data, endpoints will be modeled using EPA's Benchmark Dose Software[6] and associated statistical dose-response methods (e.g., time-to-tumor modeling).
    - MOA considerations will inform methods for combining multiple tumor types.
    - Statistical considerations will inform which dose-response methods can be used for each tumor type.

[5]The EPA guidelines have been developed over time and address the state of the science at the time they were developed. Thus, evaluation methods may be updated as new science emerges, or when existing guidelines are updated. EPA guideline documents can be found at: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/

[6] Information on model fitting, model selection, and reporting of decisions and results are outlined in the *Benchmark Dose Technical Guidance Document* U.S. EPA (2012b).

- Points-of-departure derived from animal data will be converted to human equivalent concentrations for derivation of the IUR(s).
    - MOA and pharmacokinetic considerations will inform choice of internal dose metrics, and methods for performing animal-to-human extrapolations[7].

[7] Methods for lung dosimetry are described in Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry U.S. EPA (1994), and in EPA's MPPD Technical Support Documentation and User's Guide U.S. EPA (2022).

4. ASSESSMENT PROTOCOL

4.1. ORGANIZATIONAL APPROACH FOR SUPPLEMENTAL MATERIAL

Studies tagged as supplemental material during preparation of the SEM were grouped by the specific category of supplemental material content (e.g., mechanistic, ADME, etc.) (Table C-2, Figure 4-1). Additional more granular sub-tagging is undertaken in Health Assessment Workspace Collaborative (HAWC), a web-based data content management system for human health assessments, during draft assessment development to help address the key science issues and inform dose-response. Full-text retrieval is reserved for studies that most directly address the key science issues. The degree of sub-tagging depends on the extent of content for a given type of supplemental material and needs of the assessment with respect to deriving the IUR(s). For the cobalt assessment, more granular tagging will be conducted for supplemental content classified as mechanistic, ADME, PK/PBPK models, and susceptibility.

Supplemental material studies identified from other assessments U.S. EPA (2008); OEHHA (2019); OEHHA (2020); TCEQ (2017); NTP (2016); ATSDR (2004) were also tagged. Tagging judgments in HAWC are made by one assessment member and confirmed during preparation of draft assessment by another member of the assessment team. The same study could have multiple tags. The overall approach for supplemental material content is presented in Figure 4-1, with details on subsequent sub-tagging presented in the following sections under the specific type of supplemental content (i.e., mechanistic, ADME and PK/PBPK).

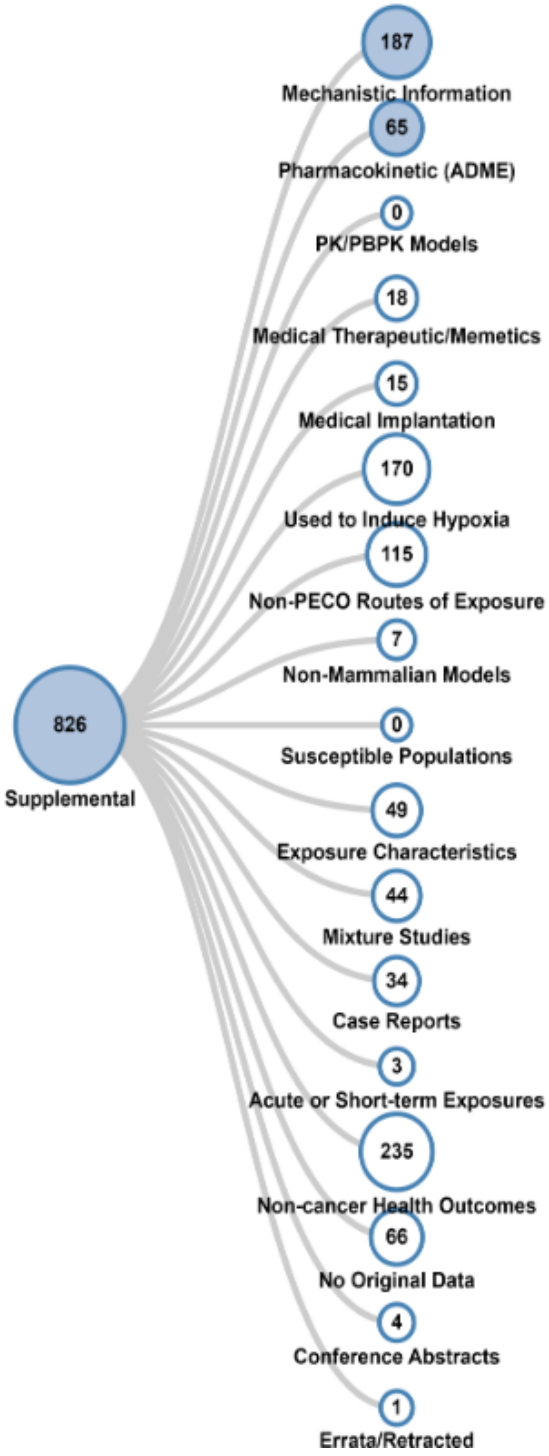

Figure 4-1. Studies identified as supplemental during literature screening. Click here to view interactive version.

4.1.1. Organization of Mechanistic Information

For detailed sub-tagging of mechanistic carcinogenesis evidence, studies are organized by the 10 key characteristics of carcinogens (1. electrophilic or can be metabolically activated to an electrophile; 2. genotoxic; 3. alters DNA repair/causes genomic instability; 4. induces epigenetic alterations; 5. induces oxidative stress; 6. induces chronic inflammation; 7. immunosuppressive; 8. modulates receptor-mediated effects; 9. causes cellular immortalization; 10. alters cell proliferation, death, or nutrient supply) Smith et al. (2016). See Figure 4-2 for organizational structure.

Similarly, sub-tagging will be undertaken for additional types of mechanistic evidence. This sub-tagging is not based on an a priori construct. Instead, it is based on the content of the available studies.

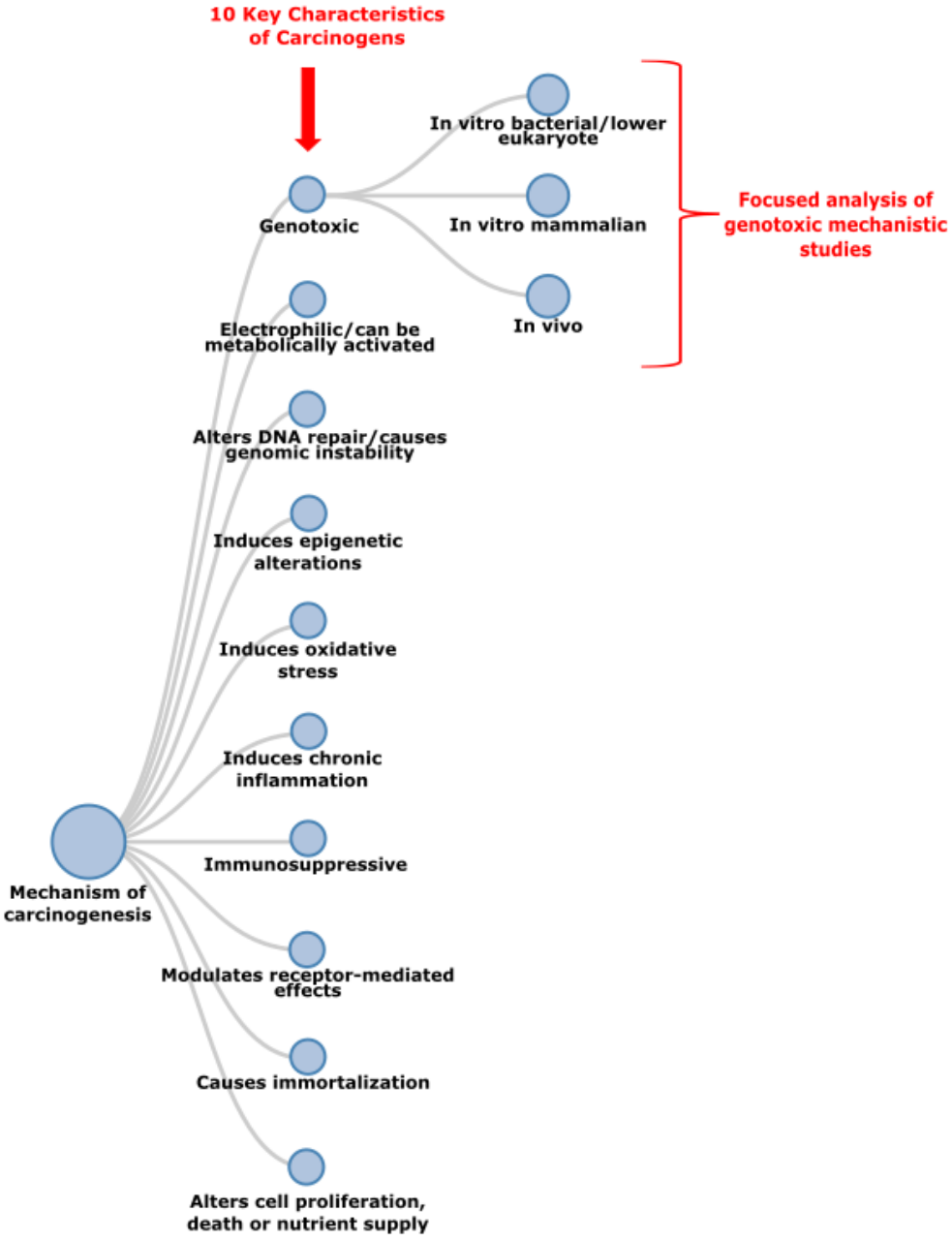

Figure 4-2. Visual summary of overall tagging structure for mechanistic studies related to carcinogenesis.

4.1.2. Organization of ADME and PK/PBPK Model Information

Primary data ADME studies are tagged as absorption, distribution, metabolism, or elimination (using a tag all that apply approach). PK/PBPK models are tagged according to species applicability, i.e., animal, human, or multiple species (to include human). See Figure 4-3 for organizational structure.

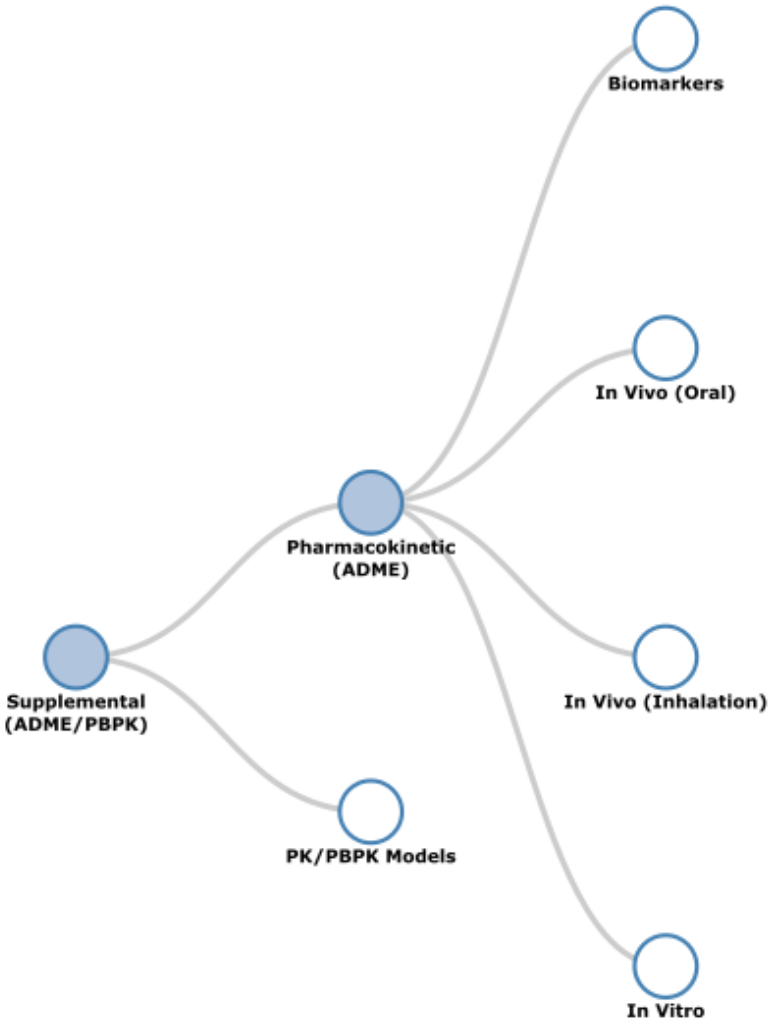

Figure 4-3. Visual summary of tagging structure for ADME and PK/PBPK studies.

4.2. METHODS FOR DOSE-RESPONSE ASSESSMENT

4.2.1. Selecting Endpoints for Dose-Response Assessment

Based on the SEM (Appendix C) and assessments conducted by others, the NTP inhalation cancer bioassay studies for cobalt sulfate and cobalt metal NTP (1998); NTP (2014) were considered most appropriate for dose-response analysis. Key scientific issues related to MOA and the dose response assessment are outlined in Section 2.4. In addition, statistical and biological information will be used to try to identify BMR levels, and the appropriate dose metrics for animal-to-human extrapolation. If supported by the available data, EPA may develop separate IURs for water-soluble and water-insoluble cobalt compounds, as was done by other agencies (Table 2-2). If this is done, EPA will define a water solubility limit to guide IRIS users as to which IUR to apply

for their specific needs. EPA may also develop additional IURs for certain subsets of cobalt compounds or develop a single IUR to address all cobalt compounds.

Also considered is whether there are opportunities to quantitatively integrate the evidence. Tumors of the lung and other tissues were reported in both male and female rats and mice by NTP (2014), and NTP (1998). Examples of quantitative integration include (1) combining results for an outcome across sex (within a study); (2) characterizing effects that occur on a continuum (e.g., precursors and benign tumors that progress to malignant tumors); (3) conducting a meta-analysis or meta-regression of multiple studies; and (4) estimating the risk of getting one or more tumors for any combination of tumors observed in a single bioassay. In addition, mechanistic evidence that influences the dose-response analyses will be highlighted. This includes evidence related to susceptibility or evidence informing the potential shape of the dose-response curve (i.e., linear, or nonlinear dose response as described in the EPA Guidelines for Carcinogen Assessment U.S. EPA (2005a)). Mode(s) of action information relevant to dose-response analysis will be summarized, including any pathway interactions relevant to understanding overall risk. For cancer dose-response of animal data, relevant biological considerations are:

- Is there evidence for direct mutagenicity?
- Is there evidence of a nonlinear mechanism at low dose?
- Does tumor latency decrease with increasing exposure?
- If there are multiple tumor types, which cancers have longer/shorter latency periods?
- Are incidence data or individual-level available?
- While benign and malignant tumors of the same cell or tissue of origin are generally evaluated together, was there an increase only in malignant tumors?

4.2.1.1. *Data Extraction and Dose Standardization*

Data will be extracted from the NTP inhalation cancer bioassay studies for cobalt sulfate and cobalt metal NTP (1998);NTP (2014) into EPA's version of Health Assessment Workspace Collaborative (HAWC, https://hawcprd.epa.gov/), a web-based software application designed to manage and facilitate the process of conducting health assessments. Because the focus of the current assessment is to develop one or more cancer IURs for inclusion in the IRIS database, tumor data (along with any other data relevant to dose-response, such as animal survival rates and individual-level data) will be prioritized for data extraction. Raw data for NTP studies are available in the Chemical Effects in Biological Systems database (https://cebs.niehs.nih.gov/cebs/). In addition to HAWC, data will be stored in other formats necessary for dose-response modeling and assessment data presentation (i.e., Excel, BMDS, Word). For quality control, data extraction is to be performed by one member of the evaluation team and independently verified by at least one other

member. Discrepancies in data extraction will be resolved by discussion or consultation with a third member of the evaluation team.

For the dose-response assessment, exposures will be standardized to common units of mg/m^3 elemental cobalt. This involves performing a molecular weight conversion from the parent compound to cobalt. The 2-year inhalation cancer bioassay of cobalt metal NTP (2014) does not require unit conversion since concentration was measured in units of elemental cobalt. However, the air concentrations presented in the NTP (1998) 2-year inhalation cancer bioassay of cobalt sulfate heptahydrate were in units of mg/m^3 anhydrous cobalt sulfate ($CoSO_4$), and not the heptahydrate or hexahydrate (which it was shown to dehydrate to under the experimental conditions). This conclusion was based on a review of the assessment analytical details in the NTP report and Behl et al. (2015), and correspondence with study authors Bucher et al. (In Press). To convert from concentrations presented in NTP (1998) to concentrations of elemental cobalt, the molecular weight ratio of Co (MW=58.933) to $CoSO_4$ (MW=154.996) will be applied.

All assumptions used in performing dose conversions will be documented in the assessment. Dosimetry adjustments, including converting to continuous chronic exposure from workday/workweek exposure used in the bioassays and application of model-derived lung dosimetry factors, will also be documented.

4.2.2. Conducting Dose-Response Assessments

EPA uses a two-step approach for dose-response assessment that distinguishes analysis of the dose-response data in the range of observation from any inferences about responses at lower, potentially more environmentally relevant exposure levels U.S. EPA (2012b); U.S. EPA (2005a, §3):

1) The first step is an analysis of dose and response in the range of observation of the experimental or epidemiologic studies. The preferred approach for the first step is to use dose response modeling to incorporate as much of the data set as possible into the analysis to derive a point of departure (POD) near the lower end of the observed dose range without significant extrapolation.

2) The second step is extrapolation to lower doses. The extrapolation approach considers what is known about the agent's mode of action. When multiple estimates can be developed, the strengths and weaknesses of each are presented. In some cases, they may be combined in a way to best represent human cancer risk.

When sufficient and appropriate human and laboratory animal data are both available for the same outcome, human data are generally preferred for the dose response assessment because their use eliminates the need to perform interspecies extrapolations. Findings from human studies were evaluated but considered less suitable for dose-response primarily due to lack of well-characterized quantitative exposure estimates and certain study evaluation concerns (e.g., limited duration and confounding from other exposures). Therefore, the results of the cobalt SEM (see Appendix C) indicate that animal data represent the most appropriate evidence available for

estimating an IUR(s) and these data will be used for dose-response analysis. When there are multiple tumor types, the final IUR(s) will attempt to address overall cancer risk.

4.2.2.1. *Dose-Response Analysis in the Range of Observation*

For conducting a dose-response assessment, pharmacodynamic ("biologically based") modeling can be used when there are sufficient data to ascertain the mode of action and quantitatively support model parameters that represent rates and other quantities associated with the key precursor events of the modes of action. If an applicable pharmacodynamic model is not available to assess health effects associated with inhalation exposure to cobalt, empirical dose-response modeling will be used to fit the data (on the apical outcomes or a key precursor events) in the range of the observed data. For this purpose, EPA has developed a software tool (Benchmark Dose Software, BMDS) that includes a standard set of models (http://www.epa.gov/ncea/bmds) that can be applied to typical data sets, including those that are nonlinear. In situations where there are alternative models with significant biological support, the users of the assessment can be informed by the presentation of these alternatives along with the models' strengths and uncertainties. The EPA has developed guidelines on modeling dose-response data, assessing model fit, selecting suitable models, and reporting modeling results [see the *EPA Benchmark Dose Technical Guidance* U.S. EPA (2012b)].

U.S. EPA BMDS is designed to help model dose-response datasets in accordance with *EPA Benchmark Dose Technical Guidance* U.S. EPA (2012b). With the nonlinear approach of cancer data analysis based on *Guidelines for Carcinogen Risk Assessment* U.S. EPA (2005a)), a BMCL (for inhalation exposure data, as is the case for this assessment) is computed using a model selected from the BMDS suite of models using statistical and graphical criteria. Linear analysis of cancer datasets generally uses the multistage model, with degree selected following a U.S. EPA Statistical Workgroup technical memo available on the BMDS website (https://cfpub.epa.gov/ncea/bmds/recordisplay.cfm?deid=308382). Modeling of cancer data may in some cases involve additional, specialized methods, particularly for multiple tumors or early removal from observation. For example, when survivals are different across exposure groups and individual-level data are available, models that include time-to-tumor information may be useful. Also, additional judgment or alternative analyses may be used if these procedures fail to yield results in reasonable agreement with the data. For example, modeling may be restricted to the lower exposure levels, especially if there is competing toxicity at higher concentrations.

For each modeled response, a POD from the observed data should be estimated to mark the beginning of extrapolation to lower exposure levels. The POD is an estimated exposure level (expressed in human equivalent terms, e.g., POD_{HEC} for inhalation data) near the lower end of the observed range without significant extrapolation to lower concentrations. For linear extrapolation of cancer risk, the POD is used to calculate an inhalation unit risk (IUR), and for nonlinear extrapolation, the POD is used in calculating an RfC. The response level at which the POD is

calculated is guided by the severity of the endpoint. If linear extrapolation is used, selection of a response level corresponding to the POD is not highly influential, so standard values near the low end of the observable range are generally used (for example, 10% extra risk for cancer bioassay data, 1% for epidemiologic data, lower for rare cancers). Nonlinear approaches consider both statistical and biologic considerations. For dichotomous data, a response level of 10% extra risk is generally used for minimally adverse effects, 5% or lower for more severe effects in experimental animals. For continuous data, a response level is ideally based on an established definition of biologic significance. In the absence of such definition, one control standard deviation from the control mean is often used for minimally adverse effects, one-half standard deviation for more severe effects. The point of departure is the 95% lower bound on the dose associated with the selected response level.

EPA has developed standard approaches for determining the relevant exposure level to be used in the dose-response modeling in the absence of appropriate pharmacokinetic modeling. These standard approaches (limited here to inhalation cancer) also facilitate comparison across exposure patterns and species:

- Intermittent study exposures will be standardized to a daily average over the duration of exposure. For chronic effects, daily exposures are averaged over the lifespan. Exposures during a critical period, however, are not averaged over a longer duration U.S. EPA (2005a , §3.1.1);U.S. EPA (1991, §3.2). Note that this will typically be done after modeling because the conversion is linear.

- Exposure concentrations will be standardized to equivalent human terms (via a common internal dose metric for animals and humans) to facilitate comparison of results from different species. Inhalation exposures are scaled using dosimetry models that apply species-specific physiologic and anatomic factors and consider whether the effect occurs at the site of first contact or after systemic circulation U.S. EPA (2012a); U.S. EPA (1994, §3). The preferred approach for dosimetry extrapolation from animals to humans is through PBPK modeling. Methods for lung dosimetry are described in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* U.S. EPA (1994), and in EPA's *MPPD Technical Support Documentation and User's Guide* U.S. EPA (2022).

  In the absence of study specific data on, for example, inhalation rates or body weight, the EPA has developed recommended values for use in dose response analysis U.S. EPA (1988).

For additional dose-response considerations specific to this assessment, see Studies that Meet SEM PECO Criteria.

4.2.2.2. *Extrapolation: Unit Risk*

An IUR is calculated to facilitate estimation of human cancer risks when low-dose linear extrapolation for cancer effects is supported, particularly for chemicals with direct mutagenic activity or those for which the data indicate a linear component below the POD. Low-dose linear

extrapolation is also used as a default when the data are insufficient to establish the mode of action U.S. EPA (2005a). If the currently available data on cobalt compounds (or specific tumors resulting from cobalt exposure) are judged as sufficient to "ascertain the MOA[s] and conclude that it is not linear at low doses and the agent [cobalt] does not demonstrate mutagenic or other activity consistent with linearity at low doses…Where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach, [the] assessment may present results based on more than one approach (e.g., both low-dose linear and reference concentration approaches)" U.S. EPA (2005a). Both approaches may also be used when there are multiple MOAs identified. When multiple approaches are presented, the assessment will describe the strengths and uncertainties of each before selecting and justifying a final estimate.

4.2.2.3. *Extrapolation: Reference Concentrations*

Reference value derivation is EPA's most frequently used type of nonlinear extrapolation method. Although it is most commonly used for noncancer effects, this approach is also used for cancer effects if there are sufficient data to ascertain the MOA and conclude that it is not linear at low doses. For these cases, reference values for each relevant route of exposure are developed following EPA's established practices U.S. EPA (2005a , §3.3.4); in general, the reference value is based not on tumor incidence, but on a key precursor event in the MOA that is necessary for tumor formation. If a reference value approach is presented as an alternative to the IUR, reference value derivation will be performed in accordance with current EPA guidelines U.S. EPA (1998); U.S. EPA (1996); U.S. EPA (1994); U.S. EPA (1991); U.S. EPA (2002); U.S. EPA (2011); U.S. EPA (2014a).

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APPENDIX A. CHEMICAL AND PHYSICAL PROPERTIES OF INCLUDED FORMS

A.1. KEY COMPOUNDS IDENTIFIED DURING SCOPING

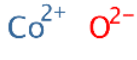
Table A-1. Chemical identity and physicochemical properties of cobalt

Characteristic or property	Value[a]	Reference
Chemical structure	Co	U.S. EPA (2021)
CASRN	7440-48-4	U.S. EPA (2021)
Synonyms	cobalt element	U.S. EPA (2021)
Color/form	hard, lustrous, silver-gray metal	U.S. EPA (2021)
Molecular formula	Co	U.S. EPA (2021)
Molecular weight (g/mol)	58.933	U.S. EPA (2021)
Density (g/cm^3)	8.9 at 20°C	ATSDR (2004)
Boiling point (°C)	3,000	U.S. EPA (2021)
Melting point (°C)	1,500	U.S. EPA (2021)
Heat of formation (kJ/mol)	427.7 (gas)	NCBI (2021)
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant ($atm\text{-}m^3/mol$)	ND	NA
Solubility in water (g/L)	2.9×10^{-3}	OEHHA (2020)
Vapor pressure (mmHg)	1 at 1,910 °C	ATSDR (2004)

NA = not applicable; ND = no data.

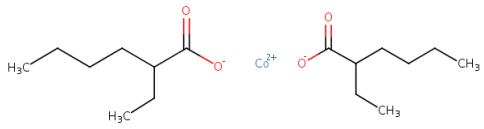
[a] When available, average experimental values are reported from U.S. EPA (2021) Chemicals Dashboard (Cobalt DTXSID1031040): https://comptox.epa.gov/dashboard/chemical/details/DTXSID1031040 .

Table A-2. Chemical identity and physicochemical properties of cobalt oxide

Characteristic or property	Value	Reference
Chemical structure		U.S. EPA (2021)
CASRN	1307-96-6	U.S. EPA (2021)
Synonyms	cobalt(II) oxide, cobaltous oxide, FCO 178, (oxido)cobalt, Zaffre, C.I. 77322, C.I. Pigment Black 13, cobalt black, cobalt monoxide, cobaltoxid	U.S. EPA (2021)
Color/form	olive-green or gray solid	U.S. EPA (2021)
Molecular formula	CoO	U.S. EPA (2021)
Molecular weight (g/mol)	74.932	U.S. EPA (2021)
Density (g/cm^3)	6.45	ATSDR (2004)
Boiling point (°C)	ND	NA
Melting point (°C)	1,935	NCBI (2021)
Heat of formation (kJ/mol)	-237.9	NCBI (2021)
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	4.88 × 10^{-3} at 20°C	NCBI (2021)
Vapor pressure (mmHg)	ND	NA

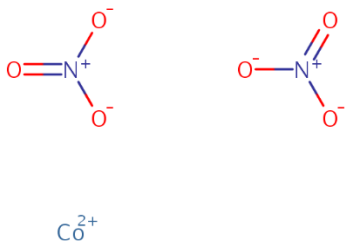
NA = not applicable; ND = no data.

Table A-3. Chemical identity and physicochemical properties of hexanoic acid, 2-ethyl-, cobalt(2+) salt

Characteristic or property	Value[a]	Reference
Chemical structure		U.S. EPA (2021)
CASRN	136-52-7	U.S. EPA (2021)
Synonyms	cobalt(2+) bis(2-ethylhexanoate); 2-ethylhexanoic acid cobalt(2+) salt; bis(2-ethylhexanoate) de cobalt; cobalt 2-ethylhexanoate; cobalt bis(2-	U.S. EPA (2021)

Characteristic or property	Value[a]	Reference
	ethylhexanoate); cobalt(II) 2-ethylhexanoate; cobalt octoate; cobaltous 2-ethylhexanoate; cobaltous octoate; hexanoate, 2-ethyl-, cobalt; Octlife Co 12; Octlife Co 8; Versneller NL 49	
Color/form	blue liquid	NCBI (2021)
Molecular formula	$C_{16}H_{30}CoO_4$	U.S. EPA (2021)
Molecular weight (g/mol)	345.345	U.S. EPA (2021)
Density (g/cm^3)	1.01	NTP (2016)
Boiling point (°C)	decomposes at 90	NCBI (2021)
Melting point (°C)	53 - 84 at 100.5 - 101.325 kPa	ECHA (2022)
Heat of formation (kJ/mol)	ND	NA
Log K_{OW}	2.96 at 20°C	ECHA (2022)
K_{OC} (L/kg)	ND	NA
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	40.3 at 20°C	ECHA (2022)
Vapor pressure (Pa)	5	ECHA (2022)
NA = not applicable; ND = no data.		

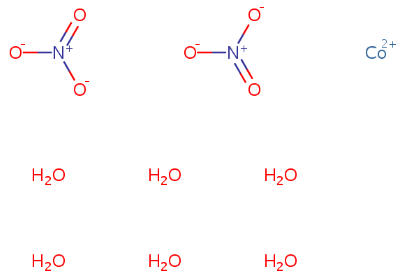
Table A-4. Chemical identity and physicochemical properties of cobalt nitrate

Characteristic or property	Value	Reference
Chemical structure		U.S. EPA (2021)
CASRN	10141-05-6	U.S. EPA (2021)
Synonyms	cobalt(II) nitrate; cobalt dinitrate; cobalt bis(nitrate); cobaltous nitrate; nitric acid, cobalt(2+) salt	U.S. EPA (2021)
Color/form	red solid	ATSDR (2004)
Molecular formula	$Co(NO_3)_2$	U.S. EPA (2021)
Molecular weight (g/mol)	182.941	U.S. EPA (2021)

Characteristic or property	Value	Reference
Density (g/cm^3)	2.49	ATSDR (2004)
Boiling point (°C)	NA	NA
Melting point (°C)	decomposes at 100-105	ATSDR (2004)
Heat of formation (kJ/mol)	-420.5	NCBI (2021)
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	670	OEHHA (2020)
Vapor pressure (mmHg)	ND	NA

NA = not applicable; ND = no data.

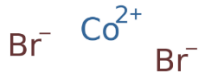
Table A-5. Chemical identity and physicochemical properties of cobalt nitrate hexahydrate

Characteristic or property	Value	Reference
Chemical structure		U.S. EPA (2021)
CASRN	10026-22-9	U.S. EPA (2021)
Synonyms	cobalt(2$^+$) nitrate--water	U.S. EPA (2021)
Color/form	red solid	NCBI (2021)
Molecular formula	$Co(NO_3)_2 \times 6\ H_2O$	U.S. EPA (2021)
Molecular weight (g/mol)	291.031	U.S. EPA (2021)
Density (g/cm^3)	1.88	NCBI (2021)
Boiling point (°C)	decomposes at 74	NCBI (2021)
Melting point (°C)	55	NCBI (2021)
Heat of formation (kJ/mol)	ND	NA
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA

Characteristic or property	Value	Reference
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	1,338 at 0°C	NCBI (2021)
Vapor pressure (mmHg)	ND	NA

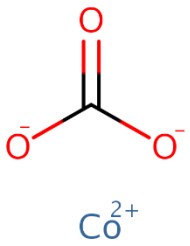
NA = not applicable; ND = no data.

Table A-6. Chemical identity and physicochemical properties of cobalt bromide

Characteristic or property	Value	Reference
Chemical structure		U.S. EPA (2021)
CASRN	7789-43-7	U.S. EPA (2021)
Synonyms	cobalt(II) bromide, cobalt dibromide, cobaltous bromide	U.S. EPA (2021)
Color/form	green solid	U.S. EPA (2021)
Molecular formula	$CoBr_2$	U.S. EPA (2021)
Molecular weight (g/mol)	218.741	U.S. EPA (2021)
Density (g/cm^3)	4.909	NCBI (2021)
Boiling point (°C)	927	AR.TEAM (2022)
Melting point (°C)	678	NCBI (2021)
Heat of formation (kJ/mol)	-220.9	NCBI (2021)
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	1,132 at 20°C	NCBI (2021)
Vapor pressure (mmHg)	ND	NA

NA = not applicable; ND = no data.

Table A-7. Chemical identity and physicochemical properties of cobalt carbonate

Characteristic or property	Value	Reference
Chemical structure		U.S. EPA (2021)
CASRN	513-79-1	U.S. EPA (2021)
Synonyms	carbonic acid, cobalt(2^+) salt (1:1), cobalt(II) carbonate	U.S. EPA (2021)
Color/form	reddish paramagnetic solid	U.S. EPA (2021)
Molecular formula	$CoCO_3$	U.S. EPA (2021)
Molecular weight (g/mol)	118.941	U.S. EPA (2021)
Density (g/cm^3)	4.13	CADENAS (2022)
Boiling point (°C)	ND	NA
Melting point (°C)	decomposes at 427	CADENAS (2022)
Heat of formation (kJ/mol)	-722.6	CADENAS (2022)
Log K_{OW}	-1.192	RSC (2022)
K_{OC} (L/kg)	ND	NA
Henry's law constant ($atm\text{-}m^3/mol$)	ND	NA
Solubility in water (g/L)	11.4×10^{-3}	OEHHA (2020)
Vapor pressure (mmHg)	ND	NA

NA = not applicable; ND = no data.

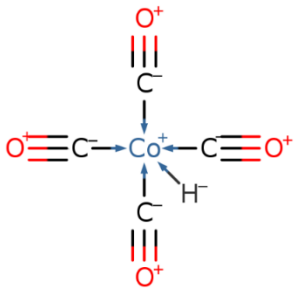
Table A-8. Chemical identity and physicochemical properties of cobalt chloride

Characteristic or property	Value[a]	Reference
Chemical structure	Cl^- Co^{2+} Cl^-	U.S. EPA (2021)
CASRN	7646-79-9	U.S. EPA (2021)
Synonyms	cobalt(II) chloride, cobalt dichloride, cobaltous chloride	U.S. EPA (2021)
Color/form	blue solid	ATSDR (2004)
Molecular formula	$CoCl_2$	U.S. EPA (2021)
Molecular weight (g/mol)	129.83	U.S. EPA (2021)
Density (g/cm^3)	3.4	NCBI (2021)
Boiling point (°C)	1,050	U.S. EPA (2021)
Melting point (°C)	411	U.S. EPA (2021)
Heat of formation (kJ/mol)	-311.07	Lavut et al. (1989)
Log K_{OW}	0.8494	Alpha Chemicals (2020)
K_{OC} (L/kg)	23.74	Alpha Chemicals (2020)
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	450	OEHHA (2020)
Vapor pressure (mmHg)	75 at 818°C	NCBI (2021)

NA = not applicable; ND = no data.

[a] When available, average experimental values are reported from U.S. EPA (2021) Chemicals Dashboard (Cobalt chloride DTXSID9040180): https://comptox.epa.gov/dashboard/chemical/details/DTXSID9040180.

Table A-9. Chemical identity and physicochemical properties of cobalt hydrocarbonyl

Characteristic or property	Value	Reference
Chemical structure		U.S. EPA (2021)
CASRN	16842-03-8	U.S. EPA (2021)

Characteristic or property	Value	Reference
Synonyms	carbon monooxide--cobalt	U.S. EPA (2021)
Form	flammable gas with offensive odor	ACGIH (2001c)
Molecular formula	C_4HCoO_4	U.S. EPA (2021)
Molecular weight (g/mol)	171.981	U.S. EPA (2021)
Relative gas density	5.93	NIOSH (2019)
Boiling point (°C)	10	DOE (2018)
Melting point (°C)	-26	ACGIH (2001c)
Heat of formation (kJ/mol)	-569.2	NIST (2021a)
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	0.5	ACGIH (2001c)
Vapor pressure (atm)	>1	NIOSH (2019)

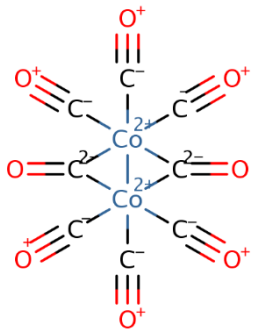
NA = not applicable; ND = no data.

Table A-10. Chemical identity and physicochemical properties of cobalt oxide (II, III)

Characteristic or property	Value	Reference
Chemical structure	**$CoO.Co_2O_3$**	NCBI (2021)
CASRN	1308-06-1	U.S. EPA (2021)
Synonyms	cobaltic-cobaltous oxide, cobalto-cobaltic oxide, cobalto-cobaltic tetroxide, cobaltosic oxide, cobalt tetraoxide, tricobalt tetraoxide	U.S. EPA (2021)
Color/form	black antiferromagnetic solid	U.S. EPA (2021)
Molecular formula	Co_3O_4	U.S. EPA (2021)
Molecular weight (g/mol)	240.797	NCBI (2021)
Density (g/cm^3)	6.07	ATSDR (2004)
Boiling point (°C)	decomposes at 900	ScholAR Chemistry (2009)
Melting point (°C)	895	ScholAR Chemistry (2009)
Heat of formation (kJ/mol)	ND	NA
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant (atm-m^3/mol)	ND	NA
Solubility in water (g/L)	1.6×10^{-3}	OEHHA (2020)
Vapor pressure (mmHg)	ND	NA

NA = not applicable; ND = no data.

Table A-11. Chemical identity and physicochemical properties of cobalt carbonyl

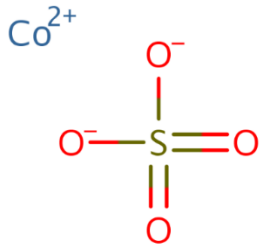
Characteristic or property	Value	Reference
Chemical structure		U.S. EPA (2021)
CASRN	10210-68-1	U.S. EPA (2021)
Synonyms	dicobalt octacarbonyl	U.S. EPA (2021)

Characteristic or property	Value	Reference
Color/form	orange solid, white when pure	ATSDR (2004)
Molecular formula	$Co_2(CO)_8$	U.S. EPA (2021)
Molecular weight (g/mol)	341.946	U.S. EPA (2021)
Density (g/cm^3)	1.73 at 18°C	ATSDR (2004)
Boiling point (°C)	decomposes at 52	ACGIH (2001b)
Melting point (°C)	51	ACGIH (2001b)
Heat of formation (kJ/mol)	-1,249.3	NIST (2021b)
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant ($atm\text{-}m^3/mol$)	ND	NA
Solubility in water	insoluble	ACGIH (2001b)
Vapor pressure (torr)	1.5	ACGIH (2001b)

NA = not applicable; ND = no data.

A.2. ADDITIONAL COBALT COMPOUNDS USED TO SUPPORT DERIVATION OF INHALATION UNIT RISK ESTIMATES

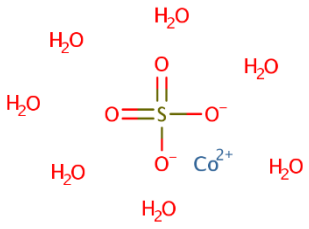
Table A-12. Chemical identity and physicochemical properties of cobalt sulfate

Characteristic or property	Value[a]	Reference
Chemical structure		U.S. EPA (2021)
CASRN	10124-43-3	U.S. EPA (2021)
Synonyms	cobalt(II) sulfate, cobalt monosulfate, cobalt sulphate, cobaltous sulfate, sulfuric acid, cobalt (2+) salt	U.S. EPA (2021)
Color/form	red or pink solid	NCBI (2021)
Molecular formula	$CoSO_4$	U.S. EPA (2021)
Molecular weight (g/mol)	154.99	U.S. EPA (2021)
Density (g/cm^3)	3.71	NCBI (2021)
Boiling point (°C)	735 – decomposition temperature[a]	NCBI (2021)
Melting point (°C)	97[a]	NCBI (2021); U.S. EPA (2021)
Heat of formation (kJ/mol)	-888.3	NCBI (2021)
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant ($atm\text{-}m^3/mol$)	ND	NA
Solubility in water (g/L)	383	NCBI (2021)
Vapor pressure (mmHg)	ND	NA

NA = not applicable; ND = no data.

[a] Several online databases, including PubChem and the Hazardous Substances Databank, contain conflicting data including that 735 °C is the melting point and decomposition temperature for cobalt (II) sulfate (while also reporting 97 °C as a melting point).

33 **Table A-13. Chemical identity and physicochemical properties of cobalt sulfate heptahydrate**

Characteristic or property	Value[a]	Reference
Chemical structure		U.S. EPA (2021)
CASRN	10026-24-1	U.S. EPA (2021)
Synonyms	cobalt(II) sulfate heptahydrate; cobalt monosulfate heptahydrate; cobaltous sulfate heptahydrate; sulfuric acid, cobalt(2+) salt, heptahydrate	U.S. EPA (2021)
Color/form	pink or red crystalline solid	NCBI (2021)
Molecular formula	$CoSO_4 \times 7\ H_2O$	NCBI (2021)
Molecular weight (g/mol)	281.09	U.S. EPA (2021)
Density (g/cm^3)	1.95	NCBI (2021)
Boiling point (°C)	Becomes anhydrous at 420 (°C), turning into cobalt sulfate[b]	NCBI (2021)
Melting point (°C)	ND[b]	NA
Heat of formation (kJ/mol)	ND	NA
Log K_{OW}	ND	NA
K_{OC} (L/kg)	ND	NA
Henry's law constant ($atm\text{-}m^3/mol$)	ND	NA
Solubility in water (g/L)	604 at 3°C	NCBI (2021)
Vapor pressure (mmHg)	ND	NA

NA = not applicable; ND = no data.

[a] When available, average experimental values are reported from U.S. EPA (2021) Chemicals Dashboard (Cobalt sulfate heptahydrate DTXSID7020340): https://comptox.epa.gov/dashboard/chemical/details/DTXSID7020340.

[b] Several online databases, including PubChem and the Hazardous Substances Databank, contain conflicting data including that 735 °C is the melting point and decomposition temperature for cobalt (II) sulfate (while also reporting 97 °C as a melting point).

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APPENDIX B. SURVEY OF EXISTING TOXICITY VALUES

B.1. METHODS

Table B-1 lists websites which were searched for relevant human health reference values for various compounds of cobalt, along with indications of the results of the search. In addition to these sources, the ToxVal database on the Chemicals Dashboard (https://comptox.epa.gov/dashboard/chemical_lists/TOXVAL_V5) was also searched for both reference values and potential points of departure (PODs) for development of values.

Table B-1. Sources searched for human health reference values for cobalt and cobalt forms

Source	Search Results	Query and/or link
ACGIH	See table of non-cancer values in HAWC	ACGIH. 2001. 2001 TLVs and BEIs: Based on documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.
AIHA	See table of non-cancer values in HAWC	AIHA. 2019. 2019 ERPG/WEEL Handbook. Fairfax, VA: American Industrial Hygiene Association. [Latest list of values.] AIHA. 2002 (and updates). 2002 Emergency Response Planning Guidelines. Fairfax, VA: American Industrial Hygiene Association. [Details used in deriving values.]
ATSDR	See table of non-cancer values in HAWC	http://www.atsdr.cdc.gov/toxprofiles/index.asp
		https://www.atsdr.cdc.gov/mrls/mrllist.asp
EPA CompTox Chemicals Dashboard	See table of non-cancer values in HAWC and Table B-2	https://comptox.epa.gov/dashboard
CT DEEP	See table of non-cancer values in HAWC	https://eregulations.ct.gov/eRegsPortal/Browse/getDocument?guid={00D6A654-0300-CC47-9B95-397D2AD21304}
DFG	No values found	https://series.publisso.de/sites/default/files/documents/series/mak/lmbv/Vol2021/Iss2/Doc002/mbwl_2021_eng.pdf
EPA/NRC AEGL	No values found	https://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values#chemicals
Health Canada	No values found	https://publications.gc.ca/collections/collection_2021/sc-hc/H129-108-2021-eng.pdf

Source	Search Results	Query and/or link
		https://www.canada.ca/en/services/health/publications/healthy-living.html
		http://publications.gc.ca/site/archivee-archived.html?url=http://publications.gc.ca/collections/Collection/H46-2-96-194E.pdf
HSA	See table of non-cancer values in HAWC	https://www.hsa.ie/eng/publications_and_forms/publications/chemical_and_hazardous_substances/chemical_agents_and_carcinogens_code_of_practice_2021.html
IDEM	See table of non-cancer values in HAWC	https://www.in.gov/idem/toxic/2343.htm
ID DEQ	24-h acceptable ambient concentrations for cobalt (0.0025 mg/m^3), cobalt carbonyl, and cobalt hydrocarbonyl (0.005 mg/m^3)	https://adminrules.idaho.gov/rules/current/58/580101.pdf
IFA	See table of non-cancer values in HAWC	https://limitvalue.ifa.dguv.de/WebForm_gw2.aspx
IRIS	No values found	http://www.epa.gov/iris/
JSOH	No values found	https://www.sanei.or.jp/?mode=view&cid=328
MassDEP	No values found	https://www.mass.gov/service-details/massdep-ambient-air-toxics-guidelines
MDH	No values found	https://www.health.state.mn.us/communities/environment/risk/guidance/air/table.html
MI EGLE	See table of non-cancer values in HAWC	https://www.michigan.gov/documents/deq/deq-rrd-chem-CleanupCriteriaTSD_527410_7.pdf
NATICH	Compendium of state values based on prior occupational exposure limits, last updated in 1993	https://nepis.epa.gov/Exe/ZyPDF.cgi/2000NS7S.PDF?Dockey=2000NS7S.PDF
NC DEQ	No values found	https://files.nc.gov/ncdeq/Air%20Quality/rules/rules/D1104.pdf
NDEP	See table of non-cancer values in HAWC and Table B-2	https://ndep.nv.gov/resources/risk-assessment-and-toxicology-basic-comparison-levels
NIOSH	See table of non-cancer values in HAWC	http://www.cdc.gov/niosh/npg/npgdcas.html
		https://www.cdc.gov/niosh/pubs/criteria_date_desc_nopubnumbers.html
		https://www.cdc.gov/niosh/idlh/intridl4.html
NYSDEC	No values found	https://www.dec.ny.gov/docs/remediation_hudson_pdf/techsuppdoc.pdf
OAQPS	No unique results	https://www.epa.gov/fera/dose-response-assessment-assessing-health-risks-associated-exposure-hazardous-air-pollutants

Source	Search Results	Query and/or link
OEHHA	See table of non-cancer values in HAWC and Table B-2	http://www.oehha.ca.gov/tcdb/index.asp
		https://oehha.ca.gov/air
Ontario MOL	See table of non-cancer values in HAWC	https://www.labour.gov.on.ca/english/hs/pubs/oel_table.php
OR DEQ	See table of non-cancer values in HAWC	https://www.oregon.gov/deq/FilterDocs/airtox-abc.pdf
OSHA	See table of non-cancer values in HAWC	https://www.osha.gov/chemicaldata/
PAC Database	See table of non-cancer values in HAWC	https://edms.energy.gov/pac/Search
PPRTV	See table of non-cancer values in HAWC and Table B-2	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments
Publications Quebec	See table of non-cancer values in HAWC	http://legisquebec.gouv.qc.ca/en/showdoc/cr/S-2.1,%20r.%2013?csi_scan_9222d36c6a354dc6=BO9xyrMZ+270UP3j0MGuOD0kZjgFAAAAXrM3HA==&bcsi_scan_filename=S-2.1,%20r.%2013&bcsi_scan_9222d36c6a354dc6=KXzmpPueuN0L1AjnJOB1Zerr85YMAAAAyhrPTg==&bcsi_scan_filename=S-2.1,%20r.%2013
RI DEM	See table of non-cancer values in HAWC	http://www.dem.ri.gov/programs/benviron/air/pdf/airtoxgl.pdf
RIVM	No values found	https://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
		https://www.rivm.nl/bibliotheek/rapporten/609021044.pdf
	See table of non-cancer values in HAWC	https://www.rivm.nl/bibliotheek/rapporten/711701025.pdf
Safe Work Australia	See table of non-cancer values in HAWC	https://www.safeworkaustralia.gov.au/exposure-standards#exposure-standards-in-australia
SWCAA	24-h acceptable source impact levels for cobalt metal (0.00017 mg/m^3), cobalt carbonyl, and cobalt hydrocarbonyl (0.00033 mg/m^3)	http://www.swcleanair.org
TCEQ	See table of non-cancer values in HAWC and Table B-2	https://www.tceq.texas.gov/toxicology/dsd/final
		https://www.tceq.texas.gov/remediation/trrp/trrppcls.html
USAPHC	Critical, marginal, and negligible military exposure guidelines based on other agencies' values	https://phc.amedd.army.mil/topics/envirohealth/hrasm/Pages/TG230.aspx
VT DEC	See table of non-cancer values in HAWC	https://dec.vermont.gov/sites/dec/files/aqc/laws-regs/documents/AQCD%20Regulations%20ADOPTED_Dec132018.pdf#page=127

Source	Search Results	Query and/or link
WA State Dept. of Ecology	24-h acceptable source impact level of 0.0001 mg/m^3	https://apps.leg.wa.gov/WAC/default.aspx?cite=173-460-150
Worksafe	See table of non-cancer values in HAWC	https://worksafe.govt.nz/topic-and-industry/work-related-health/monitoring/exposure-standards-and-biological-exposure-indices/

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Levels; AIHA = American Industrial Hygiene Association; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure index; CT DEEP = Connecticut Department of Energy & Environmental Protection; DFG = *Deutsche Forschungsgemeinschaft*, German Research Foundation; EPA = Environmental Protection Agency; ERPG = Emergency Response Planning Guideline; HSA = Health and Safety Authority; IDEM = Indiana Department of Environmental Management; ID DEQ = Idaho Department of Environmental Quality; IFA = *Institut für Arbeitsschutz, The Institute for Occupational Safety and Health;* IRIS = Integrated Risk Information System; JSOH = Japan Society for Occupational Health; MassDEP = Massachusetts Department of Environmental Protection; MDH = Minnesota Department of Health; MI EGLE = Michigan Environment, Great Lakes & Energy; MOL = Ministry of Labour; NATICH = National Air Toxics Information Clearinghouse; NC DEQ = North Carolina Department of Environmental Quality; NDEP = Nevada Division of Environmental Protection; NIOSH = National Institute for Occupational Safety and Health; NRC = National Research Council; NYSDEC = New York State Department of Environmental Conservation; OAQPS = Office of Air Quality Planning and Standards; OEHHA = California Office of Environmental Health Hazard Assessment; OR DEQ = Oregon Department of Environmental Quality; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PPRTV = Provisional Peer-Reviewed Toxicity Value; RI DEM = Rhode Island Department of Environmental Management; RIVM = *Rijksinstituut voor Volksgezondheid en Milieu,* The Netherlands Institute for Public Health and the Environment; SWCAA = Southwest Clean Air Association; TCEQ = Texas Commission on Environmental Quality; TERA – Toxicology Excellence for Risk Assessment; TLV = threshold limit value; USAPHC = United States Army Public Health Center; VT DEC = Vermont Department of Environmental Conservation; WEEL = Workplace Environmental Exposure Level.

B.2. SUMMARY OF EXISTING TOXICITY VALUES

A summary of inhalation reference values and cancer risk ranges is presented in Figure B-1. Details on the derivation of the inhalation cancer toxicity values are presented in Table B-2. Details on the available non-cancer values displayed in Figure B-1 can be found in HAWC, see "Non-cancer reference values for inhalation exposure to cobalt and compounds" under "Attachments."

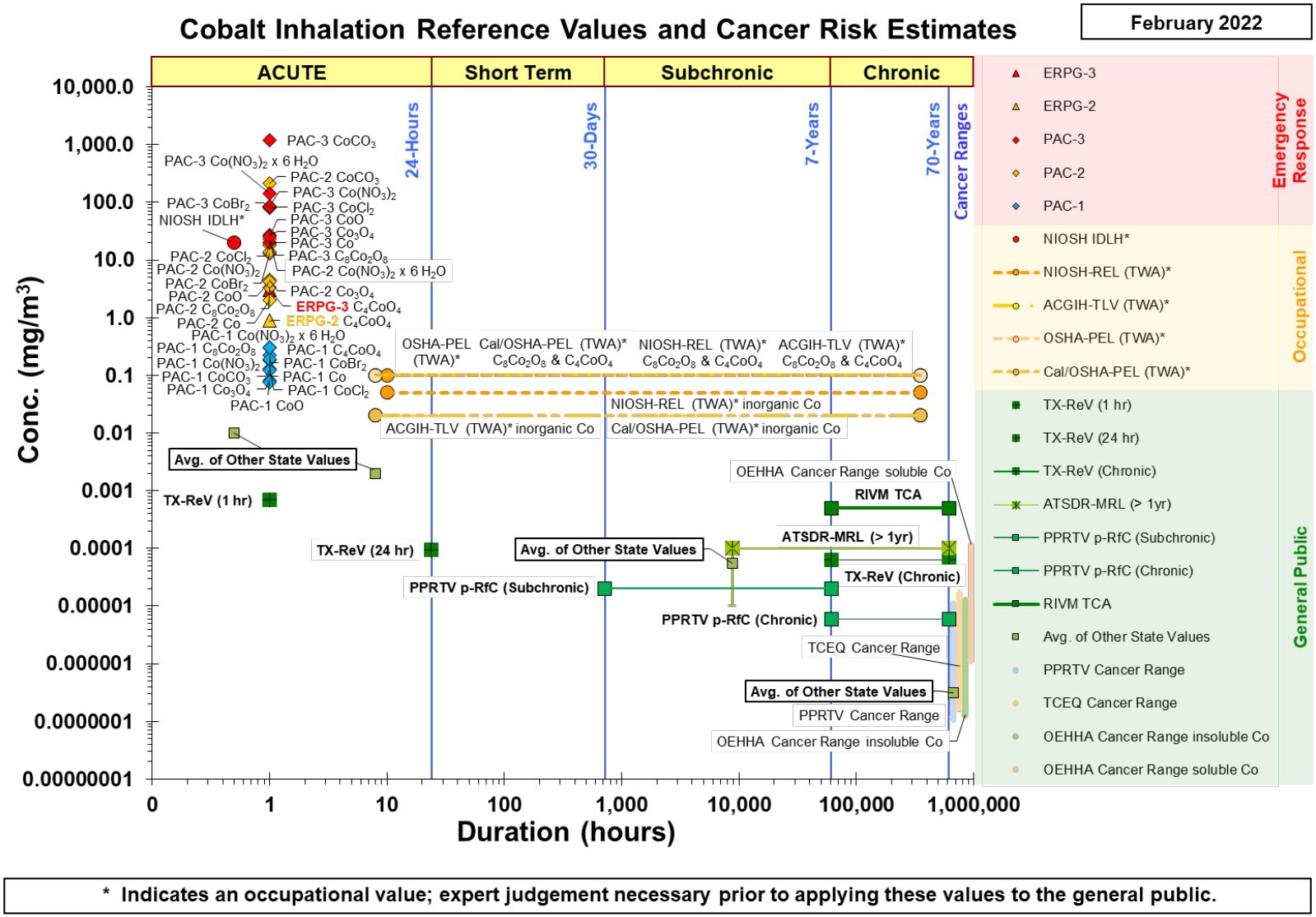

Figure B-1. Available noncancer and cancer toxicity values for inhalation exposure to cobalt.

Table B-2. Details on the derivation of existing inhalation cancer toxicity values for cobalt and cobalt compounds

Toxicity Value Name	Cobalt Form(s)	Toxicity Value	Health Effect	Point of Departure	Qualifier	Source	Notes on Derivation	Review Status
NDEP BCL	Cobalt	3.12×10^{-7} mg/m^3	Cancer	9 (mg/m^3)$^{-1}$	PPRTV IUR	U.S. EPA (2008)	Calculated[a]	Final NDEP (2017)
PPRTV IUR	Soluble cobalt sulfate hexahydrate, applied to additional compounds	9 (mg/m^3)$^{-1}$	Alveolar/bronchiolar adenomas and carcinomas in female rats exposed to cobalt sulfate hexahydrate	0.3 mg/m^3 0.012 mg Co/m^3 0.0095 mg Co/m^3 0.011 mg Co/m^3	NOAEL $NOAEL_{ADJ}$ $NOAEL_{HEC}$ BMDL	Bucher et al. (1999) and NTP (1998)	Duration adjusted, MW adjustment[b] HEC adjusted[c]	Provisional U.S. EPA (2008)
OEHHA IUR	Cobalt metal and water-insoluble compounds	7.7 (mg/m^3)$^{-1}$	Alveolar/bronchiolar adenomas and carcinomas in male mice exposed to cobalt metal	1.25 mg/m^3 0.23 mg/m^3 0.26 mg/kg-d 0.01122 mg/kg-d 4.46 (mg/kg-d)$^{-1}$ 27 (mg/kg-d)$^{-1}$	NOAEL $NOAEL_{ADJ}$ ADD $BMDL_{05}$ CSF_a CSF_h	NTP (2014)	Duration adjusted: (6.2-h/24-h) × (5-d/7-d) ADD adjusted[d] $CSF_a = 0.05 \div BMDL_{05}$ CSF_h calculated[e] IUR calculated[f]	Final OEHHA (2020)

Toxicity Value Name	Cobalt Form(s)	Toxicity Value	Health Effect	Point of Departure	Qualifier	Source	Notes on Derivation	Review Status
	Water-soluble cobalt compounds	0.86 $(mg/m^3)^{-1}$	Lung and adrenal tumors in female rats exposed to aerosolized cobalt sulfate	0.01504 mg/kg-d 3.32 $(mg/kg\text{-}d)^{-1}$ 13.41 $(mg/kg\text{-}d)^{-1}$ 3.0 $(mg\ Co/kg\text{-}d)^{-1}$	$BMDL_{05}$ CSF_a CSF_h MW-adjusted CSF	NTP (1998)	$CSF_a = 0.05 \div BMDL_{05}$ CSF_h calculated[g] MW adjusted[h] IUR calculated[i]	
TCEQ IUR	Cobalt compounds	6 $(mg/m^3)^{-1}$	Alveolar/bronchiolar adenomas and carcinomas in female rats exposed to cobalt sulfate hexahydrate	0.3 mg/m^3 0.012 $mg\ Co/m^3$ 0.0095 $mg\ Co/m^3$ 0.011 $mg\ Co/m^3$	NOAEL $NOAEL_{ADJ}$ $NOAEL_{HEC}$ $BMDL_{10}$	NTP (1998) and U.S. EPA (2008)	Duration adjusted), MW adjustment[j] HEC adjusted[k] Calculated[l]	Final TCEQ (2017)
			Alveolar/bronchiolar adenomas and carcinomas in female rats exposed to aerosolized cobalt metal	1.25 mg/m^3 0.223 mg/m^3 0.132 mg/m^3 0.108 mg/m^3	LOAEL $LOAEL_{ADJ}$ $LOAEL_{HEC}$ BMDL	NTP (2014) and Suh et al. (2016)		

Toxicity Value Name	Cobalt Form(s)	Toxicity Value	Health Effect	Point of Departure	Qualifier	Source	Notes on Derivation	Review Status

ADD = average daily dose; ADJ = adjusted; AT = averaging time; BCL = basic comparison level; BMDL = benchmark dose level; BW_a = animal body weight; BW_h = human body weight; Co = cobalt; $CoSO_4 \times 6\ H_2O$ = cobalt sulfate hexahydrate; CSF_a = animal cancer slope factor; CSF_h = human cancer slope factor; ED = exposure duration; EF = exposure frequency; EPA = Environmental Protection Agency; ET = exposure time; HEC = human equivalent concentration; IR = inhalation rate; IUR = inhalation unit risk; LOAEL = lowest-observed-adverse-effect level; MW = molecular weight; NDEP = Nevada Division of Environmental Protection; NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; OEHHA = California Office of Environmental Health Hazard Assessment; PPRTV = Provisional Peer-Reviewed Toxicity Value; RDDR = regional deposited dose ratio; TCEQ = Texas Commission on Environmental Quality; TR = target risk; URF = unit risk factor.

[a] $BCL = TR \times AT \div (ET \times EF \times ED \times URF) = (10^{-6} \times 70\ y \times 365\ d/y \times 24\ h/d) \div [24\ h/d \times 350\ d/y \times 26\ y \times 9\ (mg/m^3)^{-1}] = 3.12 \times 10^{-7}\ mg/m^3$.

[b] $NOAEL_{ADJ} = NOAEL \times (6\ h \div 24\ h) \times (5\ d \div 7\ d) \times [Co\ atomic\ mass \div (CoSO_4 \times 6\ H_2O)\ MW] = 0.3\ mg/m^3 \times (6\text{-}h \div 24\text{-}h) \times (5\text{-}d \div 7\text{-}d) \times (58.933\ g/mol \div 263.08\ g/mol) = 0.012\ mg\ Co/m^3$.

[c] $NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.012\ mg\ Co/m^3 \times 0.79 = 0.0095\ mg\ Co/m^3$.

[d] $ADD = 0.0345\ m^3/d \times (BW \div 0.025\ kg)^{2/3} \times NOAEL_{ADJ} \div BW = 0.0345\ m^3/d \times (0.0485\ kg \div 0.025\ kg)^{2/3} \times 0.23\ mg/m^3 \div 0.0485\ kg = 0.26\ mg/kg\text{-}d$.

[e] $CSF_h = CSF_a \times (BW_h \div BW_a)^{1/4} = 4.46\ (mg/kg\text{-}d)^{-1} \times (70\ kg \div 0.0485\ kg)^{1/4} = 27\ (mg/kg\text{-}d)^{-1}$.

[f] $IUR = CSF_h \times IR \div BW = 27\ (mg/kg\text{-}d)^{-1} \times 20\ m^3/d \div 70\ kg = 7.7\ (mg/m^3)^{-1}$.

[g] $CSF_h = CSF_a \times (BW_h \div BW_a)^{1/4} = 3.32\ (mg/kg\text{-}d)^{-1} \times (70\ kg \div 0.2633\ kg)^{1/4} = 13.41\ (mg/kg\text{-}d)^{-1}$.

[h] $MW\text{-}adjusted\ CSF = CSF_h \times [Co\ atomic\ mass \div (CoSO_4 \times 6\ H_2O)\ MW] = 13.41\ (mg/kg\text{-}d)^{-1} \times (58.9\ g/mol \div 263.1\ g/mol) = 3.0\ (mg\ Co/kg\text{-}d)^{-1}$.

[i] $IUR = CSF \times IR \div BW = 3.0\ (mg\ Co/kg\text{-}d)^{-1} \times 20\ m^3/d \div 70\ kg = 0.86\ (mg\ Co/m^3)^{-1}$.

[j] $NOAEL_{ADJ} = NOAEL \times (6\ h \div 24\ h) \times (5\ d \div 7\ d) \times [Co\ atomic\ mass \div (CoSO_4 \times 6\ H_2O)\ MW] = 0.3\ mg/m^3 \times (6\text{-}h \div 24\text{-}h) \times (5\text{-}d \div 7\text{-}d) \times (58.933\ g/mol \div 263.08\ g/mol) = 0.012\ mg\ Co/m^3$.

[k] $NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.012\ mg\ Co/m^3 \times 0.79 = 0.0095\ mg\ Co/m^3$.
$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR = 0.223\ mg\ Co/m^3 \times 0.592 = 0.132\ mg\ Co/m^3$.

[l] NTP 1998 $IUR = 0.1 \div BMDL_{10} = 0.1 \div 0.011\ mg/m^3 = 9.1\ (mg/m^3)^{-1}$.
NTP 2014 $IUR = 0.32 \div BMDL = 0.32 \div 0.108\ mg/m^3 = 3\ (mg/m^3)^{-1}$.
The two derived IURs were averaged to arrive at the final value: $[9.1\ (mg/m^3)^{-1} + 3\ (mg/m^3)^{-1}] \div 2 = 6\ mg/m^3$.

APPENDIX C. SYSTEMATIC EVIDENCE MAP

C.1. SYSTEMATIC EVIDENCE MAP (SEM) SPECIFIC AIMS

- Develop a systematic evidence map (SEM) to identify epidemiological (i.e., human) and toxicological (i.e., experimental animal) literature that report reporting effects of inhalation exposure to cobalt or cobalt compounds and cancer.
    - The SEM includes searches for studies published since the October 2020 inhalation 'unit risk estimates' (URE) or 'inhalation unit risk' (IUR) developed by California EPA OEHHA (2020). The SEM also includes a survey of prior assessments U.S. EPA (2008); OEHHA (2019); OEHHA (2020); TCEQ (2017); NTP (2016); ATSDR (2004) to ensure consideration of studies cited to develop cancer hazard conclusions or develop inhalation unit risk estimates. [8]

- Evaluate studies that meet SEM PECO criteria to identify studies most suitable for deriving an inhalation unit risk (IUR) for water-soluble and water-insoluble compounds of cobalt. Prioritized studies from this evaluation are those that appear at least as suitable for IUR derivation as the NTP rodent cancer bioassays NTP (2014, 1998) used in prior assessments U.S. EPA (2008);OEHHA (2019);OEHHA (2020);TCEQ (2017).

- Conduct study evaluation (evaluating risk of bias and sensitivity) and data extraction for prioritized epidemiological and toxicological studies.

- Identify supplemental material in the literature published since October 2020 or cited in the prior assessments listed above that may potentially inform dose-response analysis, clarify what is known currently about the cancer mode of action, inform conclusions on potential susceptibility, or help elucidate key science issues. Supplemental material content includes mechanistic *in vitro*, *in vivo*, *ex vivo*, or *in silico* studies; toxicokinetic and *absorption, distribution, metabolism, and excretion* (ADME) studies; pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) model studies; studies using non-inhalation route of exposure; non-mammalian model systems; exposure assessment studies with no health outcomes reported; mixture studies; human case studies and case reports; animal cancer studies using less than subchronic duration exposures; studies or reports with no original data; and conference/symposium abstracts or poster presentations, and studies assessing noncancer health outcomes. Studies considered PECO-relevant that also contain supplemental information are tagged as such.

[8] The full 2022 IARC Monograph on" Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy" was not publicly released at the time of preparing this SEM but will be surveyed for any missing citations when it becomes available.

C.2. POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO) CRITERIA AND SUPPLEMENTAL MATERIAL TAGGING

PECO criteria are used to focus the research question(s), search terms, and inclusion/exclusion criteria used in a SEM or systematic review. The SEM PECO criteria are presented in Table C-1. In addition, studies containing supplemental material are inventoried during the literature screening process using the categories presented in Table C-2.

Table C-1. Example Populations, Exposures, Comparators, and Outcomes (PECO) Criteria

Populations	**Human:** Any population and lifestage (occupational or general population, including in pregnant women, infants, children, adolescents and adults). **Animal:** Nonhuman mammalian animal species (whole organism) of any lifestage (including fetal, early postnatal, adolescents and adults). Studies of transgenic animals are tracked as mechanistic studies under "potentially relevant supplemental material". *Note: Studies meeting PECO criteria may also contain information on susceptible populations. When this occurs, these studies are also tagged as having information pertinent to susceptible populations. This typically happens during preparation of the literature inventory or full text extraction.*
Exposures	**Relevant forms for Clean Air Act:** cobalt aluminate (1345-16-0), cobalt bromide (7789-43-7), cobalt carbonate (513-79-1), cobalt carbonyl (10210-68-1), cobalt chloride (7646-79-9), cobalt (7440-48-4), cobalt hydrocarbonyl (16842-03-8), cobalt naphtha (61789-51-3), cobalt nitrate (10141-05-6), cobalt oxide (1307-96-6), cobalt oxide (II, III) (1308-06-1), and hexanoic acid, 2-ethyl-, cobalt(2+) salt (136-52-7). Many of these compounds do not have cancer toxicity information, thus other water-soluble and water-insoluble cobalt compounds that do have inhalation cancer evidence are included within the scope of this review, e.g., cobalt sulfate, cobalt hydroxide, and cobalt sulfide. *Radioactive isotopes (i.e., ^{60}Co) and vitamin B12 are considered out of scope.* **Human:** Any quantitative exposure to cobalt via the inhalation route, aside from acute or very short (days) duration. Studies of developmental exposure are also included. Studies will also be included if biomarkers of exposure are evaluated (e.g., measured compound or metabolite levels in tissues or bodily fluids) and the exposure route can be inferred as primarily inhalation. **Animal:** Any quantitative exposure to cobalt via the inhalation route for any subchronic and chronic exposure duration. Studies of developmental exposure are also included. Studies involving exposures to mixtures will be included only if they include exposure to a relevant form of cobalt alone. Non-inhalation routes, including oral, dermal or intravenous, are tracked as "potentially relevant supplemental information."
Comparators	**Human:** Referent populations exposed to lower (within the study) levels of cobalt. The results of the comparisons must be presented with sufficient detail of quantitative modeling (e.g., regression coefficients presented with statistical measure of variation). *Case reports describing findings in 1-3 people are tagged as "potentially relevant supplemental information."* **Animal:** A concurrent control group exposed to vehicle-only treatment and/or untreated control.
Outcomes	Any **cancer-related** effect on any system.

Table C-2. Categories of Potentially Relevant Supplemental Material

Category (Tag)	Description	Typical Assessment Use
Pharmacokinetics Data Potentially Informative to Assessment Analyses		
Classical pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) model studies	**Classical Pharmacokinetic or Dosimetry Model Studies**: Classical PK or dosimetry modeling usually divides the body into just one or two compartments, which are not specified by physiology, where movement of a chemical into, between, and out of the compartments is quantified empirically by fitting model parameters to ADME (absorption, distribution, metabolism, and excretion) data. This category is for papers that provide detailed descriptions of PK models but are not PBPK models. The data are typically the concentration time-course in blood or plasma after oral and or intravenous exposure, but other exposure routes can be described. **Physiologically Based Pharmacokinetic or Mechanistic Dosimetry Model Studies**: PBPK models represent the body as various compartments (e.g., liver, lung, slowly perfused tissue, richly perfused tissue) to quantify the movement of chemicals or particles into and out of the body (compartments) by defined routes of exposure, metabolism, and elimination, and thereby estimate concentrations in blood or target tissues. A defining characteristic is that key parameters are determined from a substance's physicochemical parameters (e.g., particle size and distribution, octanol-water partition coefficient) and physiological parameters (e.g., ventilation rate, tissue volumes).	PBPK and PK model studies are included in the assessment and evaluated for possible use in conducting quantitative extrapolations. PBPK/PK models are categorized as supplemental material with the expectation that each one will be evaluated for applicability to address assessment extrapolation needs and technical conduct. Specialized expertise is required for their evaluation. Standard operating procedures for PBPK/PK model evaluation and the identification, organization, and evaluation of ADME studies are outlined in *An umbrella Quality Assurance Project Plan (QAPP) for PBPK models* U.S. EPA (2018*).*
Pharmacokinetic (ADME)	Pharmacokinetic (ADME) studies are primarily controlled experiments, where defined exposures usually occur by intravenous, oral, inhalation, or dermal routes, and the concentration of particles, a chemical, or its metabolites in blood or serum, other body tissues, or excreta are then measured. These data are used to estimate the amount absorbed (A), distributed (D), metabolized (M), and/or excreted (E). ADME data can also be collected from human subjects who have had environmental or workplace exposures that are not quantified or fully defined. ADME data, especially metabolism and tissue partition coefficient information, can be generated using in vitro model systems. Although in vitro data may not be as definitive as in vivo data, these studies should also be tracked as ADME. For large evidence bases it may be appropriate to separately track the in vitro ADME studies.	ADME studies are inventoried and prioritized for possible inclusion in an ADME synthesis section on the chemical's PK properties and for conducting quantitative adjustments or extrapolations (e.g., animal-to-human). Specialized expertise in PK is necessary for inventory and prioritization. *Standard operating procedures for PBPK/PK model evaluation and the identification, organization, and evaluation of ADME studies are outlined in An umbrella Quality Assurance Project*

Category (Tag)	Description	Typical Assessment Use
	**Studies describing environmental fate and transport or metabolism in bacteria or model systems that are not applicable to humans or animals should not be tagged.*	*Plan (QAPP) for PBPK models U.S. EPA (2018).*
Supplemental Evidence Potentially Informative to Assessment Analyses		
Mechanistic endpoints	Studies that do not meet PECO criteria but report measurements that inform the biological or chemical events associated with phenotypic effects related to a health outcome. Experimental design may include in vitro, in vivo (by various routes of exposure; includes all transgenic models), ex vivo, and in silico studies in mammalian and nonmammalian model systems. Studies using New Approach Methodologies (NAMs, e.g., in vitro high throughput testing strategies, read across applications) are also categorized here. Studies where the chemical is used as a laboratory reagent (e.g., as a chemical probe used to measure antibody response) generally should not be tagged. Mechanistic evidence can also help identify factors contributing to susceptibility; these studies should also be tagged "susceptible populations." *[Notes: During screening, especially at the title and abstract (TIAB) level, it may not be readily apparent for studies that meet P, E, and C criteria if the endpoint(s) in a study are best classified as phenotypic or mechanistic with respect to the O criteria. In these cases, the study should be screened as "unclear" during TIAB screening, and a determination made based on full-text review (in consultation with a content expert as needed). Full-text retrieval is performed for studies of transgenic model systems that meet E and C criteria to determine if they include phenotypic information in wildtype animals that meet P and O criteria that is not reported in the abstract.]*	Prioritized studies of mechanistic endpoints are described in the mechanistic synthesis sections; subsets of the most informative studies may become part of the units of analysis. Mechanistic evidence can provide support for the relevance of animal effects to humans and biological plausibility for evidence integration judgments (including MOA analyses, e.g., using the MOA framework in the US EPA Cancer Guidelines 2005a)).
Non-PECO animal model	Studies that report outcomes in animal models that meet the outcome criteria but do not meet the population criteria in the PECO. Depending on the endpoints measured in these studies, they can also provide mechanistic information (in these cases studies should also be tagged "mechanistic endpoints"). *This categorization generally does not apply to studies that use species with limited human health relevance (e.g., ecotoxicity-focused studies are typically excluded).	Studies of non-PECO animals, exposures, or durations can be summarized to inform evaluations of consistency (e.g., across species or routes or durations), coherence, or adversity; subsets of the most informative studies may be included in the unit of analysis. These studies may also be used to inform evidence integration judgments of biological plausibility and/or MOA analyses and thus
Non-PECO route of exposure	Epidemiological or animal studies that use a non-PECO route of exposure, e.g., injection studies or dermal studies if the dermal route is not part of the exposure criteria.	

Category (Tag)	Description	Typical Assessment Use
	*This categorization generally does not apply to epidemiological studies where the exposure route is unclear; such studies are considered to meet PECO criteria if the relevant route(s) of exposure are plausible, with exposure being more thoroughly evaluated at later steps.	may be summarized as part of the mechanistic evidence synthesis.
Acute or short-term duration exposures	Given the focus on cancer, acute exposure durations (defined as animal studies of ≤1 d) or short-term (defined as animal studies of ≤90 d/13 weeks) are considered supplemental.	
Susceptible populations	Studies that help to identify potentially susceptible subgroups, including studies on the influence of intrinsic factors such as sex, lifestage, or genotype to toxicity, as well as some other factors (e.g., health status). These are often co-tagged with other supplemental material categories, such as mechanistic or ADME. Studies meeting PECO criteria that also address susceptibility should be co-tagged as supplemental. **Susceptibility based on most extrinsic factors, such as increased risk for exposure due to residential proximity to exposure sources, is not considered an indicator of susceptible populations for the purposes of IRIS assessments.*	Provides information on factors that might predispose sensitive populations or lifestages to a higher risk of adverse health effects following exposure to the chemical. This information is summarized during evidence integration for each health effect and is considered during dose-response, where it can directly impact modeling decisions.
Background Information Potentially Useful to Problem Formulation and Protocol Development (These studies fall outside the scope of IRIS assessment analyses)		
Human exposure and biomonitoring (no health outcome)	Information regarding exposure monitoring methods and reporting that are unrelated to health outcomes, but which provide information on the following: methods for measuring human exposure, biomonitoring (e.g., detection of chemical in blood, urine, hair), defining exposure sources, or modeled estimates of exposure (e.g., in occupational settings). Studies that compare exposure levels to a reference value, risk threshold or assessment points of departure are also included in this category. Studies related to environmental fate and transport are typically tagged as background materials unless otherwise described in the assessment-specific protocol. *Assessment teams may want to subtag studies that describe or predict exposure levels versus those that present exposure assessment methods.	This information may be useful for developing exposure criteria for study evaluation or refining problem formulation decisions. Notably, providing an assessment of typical human exposures (e.g., sources, levels) falls outside the scope of an IRIS assessment.
Mixture study	Mixture studies use methods that do not allow investigation of the health effects of exposure to the chemical of interest by itself (e.g., animal studies that lack exposure	Mixture studies are tracked to help inform cumulative risk analyses, which may provide useful context for risk

Category (Tag)	Description	Typical Assessment Use
	to chemical of interest alone or epidemiology studies that do not evaluate associations of the chemical of interest with relevant health outcome(s)). *Methods used to assess investigation of the exposure by itself may not be clear from the abstract, in particular for epidemiology studies. When unclear, the study is advanced to full-text review to determine eligibility.	assessment but fall outside the scope of an IRIS assessment.
Case reports or case series	Human studies that present an investigation of a single exposed individual or group of ≤ 3 subjects that describe health outcomes after exposure but lack a comparison group (i.e., do not meet the "C" in the PECO) and typically do not include reliable exposure estimates.	Tracking case studies can facilitate awareness of potential human health issues missed by other types of studies during problem formulation.
Noncancer health outcomes	Studies assessing noncancer health outcomes.	Out of scope for the assessment but tracked to facilitate any assessment work conducted by others in understanding potential non-cancer health publication trends.
Reference Materials		
Records with no original data	Records that do not contain original data, such as other agency assessments, informative scientific literature reviews, editorials, or commentaries.	Studies that are tracked for potential use in identifying missing studies, background information, or current scientific opinions (e.g., hypothesized MOAs).
Posters or conference abstracts	Records that do not contain sufficient documentation to support study evaluation and data extraction.	

C.3. METHODS: LITERATURE SEARCH STRATEGIES

C.3.1.Database Search Term Development

The literature search focused on the chemical name (and synonyms, trade names, and metabolites/degradants of interest) and was date limited to studies published after 2019 (Addendum 1). The literature search was completed on December 16, 2021. This date was selected to cover new studies published since the 2020 CalEPA cobalt assessment OEHHA (2020), which is the most recent US Federal or State assessment conducted. No language restrictions were applied. Chemical synonyms were identified by using the "Find Chemical Synonyms" feature in SWIFT (Sciome Workbench for Interactive computer-Facilitated Text-mining) Review Howard et al. (2016). In brief, this feature automatically creates a PubMed-formatted chemical search using (1) the common name for the chemical as presented in the Tox21 chemical inventory list U.S. EPA (2020d); (2) the Chemical Abstract Services Registry Number (CASRN); (3) synonyms from the ChemIDPlus database, which currently contains chemical names and synonyms for over 400,000 chemicals; and (4) removal of ambiguous or short alphanumeric terms that could lead to false positives. This search is manually reviewed to ensure that any synonyms listed in EPA's Dashboard U.S. EPA (2021) as "valid" or "good" are included. The PubMed search created from SWIFT Review, along with additional synonyms identified from EPA's Dashboard, is shared with EPA information specialists to develop search strategies tailored for each of the databases below, as each database has its own search architecture. Full details of the search strategy for each database are presented in the Addendum 1.

C.3.2.Database Searches

The databases listed below are searched by an EPA information specialist. Retrieved references are imported into the EPA's Health and Environmental Research Online (HERO) database and undergo a round of deduplication in HERO[9].

- Web of Science (Thomson Reuters)
- PubMed (National Library of Medicine)

The literature search is updated throughout SEM development. In addition to the databases listed below, a variety of other resources are subsequently searched using customized processes (see "Other Resources"). One process described in "Other Resources" is to review prior

[9] Deduplication in HERO involves first determining whether a matching unique ID exists (e.g., PMID, WoSID, or DOI). If one matches one that already exists in HERO, HERO will tag the existing reference instead of adding the reference again. Second, HERO checks if the same journal, volume, issue and page number are already in HERO. Third, HERO matches on the title, year, and first author. Title comparisons ignore punctuation and case

assessments of cobalt carcinogenicity to identify studies meeting the current SEM PECO criteria that would have been missed by the date limited database search described above.

The unique studies are imported into SWIFT Review software Howard et al. (2016) to identify those references most likely to be applicable to a human health risk assessment. In brief, SWIFT Review has pre-set literature search strategies ("filters") developed by information specialists that can be applied to identify studies that are more likely to be useful for identifying human health content from those that likely do not (e.g., environmental fate). The filters function like a typical search strategy where studies are tagged as belonging to a certain filter if the terms in the filter literature search strategy appear in title, abstract, keyword or Medical Subject Headings (*MeSH)* fields content. The details of the search strategies that underlie the filters are available online. For this SEM, filters for human, animal (human health models) and in vitro evidence were used. Studies not retrieved using the search strategies are not considered further. Studies that include one or more of the search terms in the title, abstract, keyword, or MeSH fields are exported as a Research information Systems (RIS) file for uploading into the screening software as described below in "Screening Process." Application of the SWIFT Review evidence stream filters to the initial search results (12/16/2021) reduced the number of studies for title and abstract screening from 29,833 to 4,589.

C.3.3.Searching Other Resources

The literature search strategies described above are designed to be broad, but like any search strategy, studies may be missed (e.g., cases where the specific chemical is not mentioned in title, abstract, or keyword content; ability to capture "gray" literature that is not indexed in the databases listed above). Thus, in addition to the database searches, the sources below are used to identify studies that may have been missed based on the database search. References that appear to meet the PECO criteria are uploaded into the screening software, annotated with respect to source of the record, and screened according to PECO as described below. Searching of these sources is summarized to include the source type or name, the search string (when applicable), the URL (when available and applicable), number of results, and number of unique references not otherwise identified from database searching (Addendum 2).

- For studies screened as 'included' based on full text review, manual review of the citation list of each study was then conducted at the title and abstract level.

- Review of the reference list from final or publicly available draft or finalized assessments (e.g., EPA IRIS [Integrated Risk Information System], EPA PPRTV [Provisional Peer Reviewed Toxicity], ATSDR [Agency for Toxic Substances and Disease Registry] Toxicological Profile, NTP [National Toxicology Program], California EPA, TCEQ [Texas Commission on Environmental Quality], IARC [International Agency for Research on Cancer]). Assessments are identified from the database search, the resources listed in Appendix B, or from the EPA CompTox Chemicals Dashboard ToxVal database U.S. EPA (2021). Citation review of these materials is focused on the most pertinent section, i.e.,

presentation of the human health literature, focusing on primary data studies pertinent to cancer.

- European Chemicals Agency (ECHA) registration dossiers to identify data submitted by registrants http://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation.

- EPA ChemView database U.S. EPA (2019) to identify unpublished studies, information submitted to EPA under Toxic Substances Control Act (TSCA) Section 4 (chemical testing results), Section 8(d) (health and safety studies), Section 8(e) (substantial risk of injury to health or the environment notices), and FYI (For Your Information, voluntary documents). Other databases accessible via ChemView include EPA's High Production Volume (HPV) Challenge database (https://iaspub.epa.gov/oppthpv/public_search.html_page) and the Toxic Release Inventory database.

- National Toxicology Program (NTP) Chemical Effects in Biological Systems (CEBS) database of study results and research projects.

- The Organisation for Economic Cooperation and Development (OECD) eChemPortal to retrieve results for OECD Screening Information DataSet (SIDS) and High Production Volume (HPV) Chemicals (https://www.echemportal.org/echemportal/).

- References identified by technical consultants, during peer-review, and during public comment periods (when applicable).

C.3.4.Non-Peer-Reviewed Data

IRIS assessments rely mainly on publicly accessible, peer-reviewed studies. However, it is possible that unpublished data directly relevant to the PECO may be identified during assessment development. In these instances, the EPA will try to get permission to make the data publicly available (e.g., in HERO); data that cannot be made publicly available are not used in IRIS assessments. In addition, on rare occasions where unpublished data would be used to support key assessment decisions (e.g., deriving a toxicity value), EPA may obtain external peer review if the owners of the data are willing to have the study details and results made publicly accessible, or if an unpublished report is publicly accessible (or submitted to EPA in a non-confidential manner) U.S. EPA (2015). This independent, contractor driven, peer review would include an evaluation of the study similar to that for peer review of a journal publication. The contractor would identify and select at least three scientists knowledgeable in scientific disciplines relevant to the topic as potential peer reviewers. Persons invited to serve as peer reviewers would be screened for conflict of interest. In most instances, the peer review would be conducted by letter review. The study and its related information, if used in the IRIS assessment, would become publicly available. In the assessment, EPA would acknowledge that the document underwent external peer review managed by the EPA, and the names of the peer reviewers would be identified. In certain cases, IRIS will assess the utility of a data analysis of accessible raw data (with descriptive methods) that has

undergone rigorous quality assurance/quality control review (e.g., ToxCast/Tox21 data, results of NTP studies not yet published) but that have not yet undergone external peer review.

Unpublished data from personal author communication can supplement a peer-reviewed study as long as the information is made publicly available. If such ancillary information is acquired, it will be documented in the Health Assessment Workspace Collaborative (HAWC, https://hawcprd.epa.gov/) or HERO project page (depending on the nature of the information received). HAWC is a web-based software application designed to manage and facilitate the process of conducting health assessments.

C.4. METHODS: LITERATURE SCREENING PROCESSES

C.4.1.Title/Abstract and Full Text Screening

The studies identified from the database searches and application of SWIFT Review filters are imported into SWIFT-Active Screener (https://www.sciome.com/swift-activescreener/) for title and abstract (TIAB) screening. SWIFT-Active Screener is a web-based collaborative software application that utilizes active machine learning approaches to reduce the screening effort Howard et al. (2020). TIAB screening is conducted by two independent reviewers and any screening conflicts are resolved by discussion between the primary screeners with consultation by a third reviewer, if needed. For citations with no abstract, articles are initially screened based on the following: title relevance (title should indicate clear relevance), and page length (articles two pages in length or less are assumed to be conference reports, editorials, or letters). Eligibility status of non-English studies is assessed using the same approach with online translation tools or engagement with a native speaker.

The machine learning screening process is designed to prioritize references that appear to meet PECO-criteria or supplemental material content for manual review (i.e., both types of references are screened as "include" for machine learning purposes). Screening continues until SWIFT-Active Screener indicates that it was likely at least 95% of the relevant studies are identified, a percent identification often used to evaluate the performance of machine learning applications and considered comparable to human error rates Bannach-Brown et al. (2018);Howard et al. (2016);Cohen et al. (2006). Any studies with "partially screened" status at the time of reaching the 95% threshold are then fully screened. Studies identified as meeting PECO criteria "unclear" or supplemental material during TIAB screening in SWIFT-Active Screener are then imported into DistillerSR software (https://www.evidencepartners.com/products/distillersr-systematic-review-software/). In DistillerSR, these studies underwent another round of TIAB screening to separate PECO-relevant studies from studies containing only supplemental material. The utility of studies classified as "unclear" was determined. Studies that met PECO or a specific type of supplemental content were tagged accordingly and added to the evidence stream.

In DistillerSR, both TIAB and full-text screening is conducted by two independent reviewers and any screening conflicts resolved by discussion between the primary screeners with

consultation by a third reviewer, if needed. Conflicts between screeners in applying the supplemental tags, which primarily occur at the TIAB level, are resolved by similarly, erring on the side of over-tagging based on TIAB content. Full-text references are sought through the EPA's HERO database for studies screened as meeting PECO criteria or "unclear" based on the TIAB screening. References that are not able to be procured within 45 days of attempt are determined to be unavailable.

The screening decisions are then imported into HAWC's Literature Review Module, where the screening and tagging results are visualized in interactive literature tag trees where additional tagging can be conducted, e.g., more details on the nature of mechanistic or ADME studies.

C.4.2.Supplemental Material Tagging

Supplemental material records (Table C-2) can be identified at either the TIAB or full-text levels. Conflicts between screeners in applying the supplemental material tags are resolved by discussion and consultation with a third reviewer (as needed), erring on the side of over-including at the TIAB level when the article content is relatively unclear.

It is important to emphasize that articles tagged as supplemental material are not necessarily excluded from consideration in an assessment. The tagging structure is designed to ensure that supplemental material studies are categorized for easy retrieval while conducting the assessment. Studies that meet the PECO criteria are those most likely to be used to derive toxicity values and thus will undergo subsequent individual study evaluation and data extraction. In contrast, the impact on the assessment conclusions of individual studies tagged as supplemental material is often difficult to assess during the screening phase of the assessment. These studies could emerge as being critically important to the assessment and need to be evaluated and summarized at the individual study level (e.g., cancer MOA or ADME studies). Supplemental materials might be helpful to provide context (e.g., summarize current levels of exposure, provide hazard evidence from routes or durations of exposure not pertinent to the PECO) or they might not be cited by the assessment (e.g., individual studies that contribute to a well-established scientific conclusion). The tagging inventory is intended to inform a systematic identification of key science issues and refine the assessment evaluation plan (i.e., approach for analysis of mechanistic and ADME/PK/PBPK content, or consideration of susceptible populations). When tagged during title and abstract screening, it may not be clear whether the chemical of interest is reported in the study (i.e., abstracts might not describe all chemicals investigated). In such cases, studies are still tagged with the expectation that additional screening would clarify if the studies are considered pertinent to address the specific aims of the assessment.

C.4.3.Multiple Publications of the Same Data

When there are multiple publications using the same or overlapping data, all publications will be included, with one selected for use as the primary study; the others will be considered as secondary publications with annotation in HAWC indicating their relationship to the primary record during data extraction. For epidemiology studies, the primary publication is most often the

one with the longest follow-up, the largest number of cases, or a factor relevant to study evaluation. For animal studies, the primary publication will typically be the one with the longest duration of exposure, or with the outcome(s) most informative to the PECO. For both epidemiology and animal studies, the assessments will include relevant data from all publications of the study, although if the same data are reported in more than one study, the data will only be extracted once. For corrections, retractions, and other companion documents to the included publications, a similar approach to annotation is taken and the most recently published data are incorporated in the assessments.

C.4.4.Literature Flow Diagrams

The results of the screening process are posted on the project page for the assessment in the HERO database (https://heronet.epa.gov/heronet/index.cfm/project/page/project_id/1478). Results are also summarized in a literature study flow diagram and interactive HAWC literature trees (where additional tagging can be documented and visualized, e.g., more details on the nature of mechanistic or ADME studies).

C.5. METHODS: LITERATURE INVENTORY PREPARATION

During title/abstract or full-text level screening in DistillerSR, studies that meet SEM PECO criteria or a category of supplemental information are categorized based on evidence type (human, animal, mechanistic, PBPK, etc.). Next, study design details for studies that meet SEM PECO criteria are summarized and a more granular tagging of supplemental material is conducted as described below. The results of this tagging are referred to as a literature inventory.

C.5.1.Studies That Meet SEM PECO Criteria

Human and animal studies that met SEM PECO criteria after full-text review are briefly summarized in tabular format. Summaries are done by one team member and quality checked by at least one other team member. For non-English studies online translation tools (e.g., Google translator) or engagement with a native speaker can be used to summarize studies at the level of the SEM literature inventory. Fee-based translation services for non-English studies are typically reserved for studies considered potentially informative for dose response, a consideration that typically occurs subsequent to the SEM during preparation of the draft assessment.

Assessing Suitability for Dose-Response Based on Study Design Considerations

The studies that meet SEM PECO criteria are evaluated with respect to the considerations below to identify studies that may be suitable for developing an IUR.

- Studies with chronic exposure durations or including exposure during reproduction or development, are prioritized over studies with shorter-term exposure durations.
- Animal studies using a species that is considered a relevant human surrogate.

- Studies with a broad exposure range and multiple exposure levels are preferred to the extent that they can provide information about the shape of the exposure-response relationship [see the EPA Benchmark Dose Technical Guidance, §2.1.1 U.S. EPA (2012b)] and facilitate extrapolation to more relevant (generally lower) exposures.

- For human studies, studies for which quantitative exposure measurements were available and exposure-response results are presented in sufficient detail (e.g., standardized mortality rate or relative risks, numbers of cases/controls, etc) are prioritized. Studies based exclusively on duration of exposure analyses (i.e., longer versus shorter exposure duration) are typically not considered suitable for dose response unless additional information on exposure can be incorporated.

- For epidemiological studies, studies that used biomarker measurements in tissues or bodily fluids as the metric for exposure were only considered suitable for dose-response analysis if data or PBPK models are available to extrapolate between the reported biomarker measurement and the level of exposure.

- For both animal and human studies, whether the nature of the outcomes/endpoints assessed were interpretable with respect to potential adversity, was considered. Typically, apical or clinical measures ("phenotypic") are preferred over other endpoints for dose response. However, "mechanistic" endpoints can be useful in dose-response analyses when they can be reasonably established as predictive of, or strongly associated with, phenotypic outcomes interpreted as adverse.

- High or medium confidence studies are highly preferred over low confidence studies (see "Study Evaluation" below).

In addition to the broad criteria presented above, attributes of animal studies that met the SEM PECO criteria are compared to the NTP inhalation cancer bioassays for soluble and insoluble cobalt compounds NTP (2014, 1998) used by prior assessments to develop cancer inhalation unit risk values OEHHA (2020, 2019; TCEQ (2017; U.S. EPA (2008). Only studies considered to be comparable to (or an improvement over) the NTP studies will be considered for dose-response. Key study attributes of the NTP studies are presented in (Table C-3).

Table C-3. Preferred design features of animal dose-response studies of inhalation exposures to cobalt compounds.

Attribute	Preferred design feature	Rationale
Exposure duration	At least 2 years	Tumors in NTP (2014, 1998) were late-onset. Prefer chronic exposures to observe tumors.
Exposure design	Cyclical daily or workweek exposure	Prefer studies to inform chronic continuous exposure. NTP (2014, 1998) exposed animals for 6 hours/day, 5 days/week.
Measurement of exposure	Measures of particle size (i.e., MMAD). Analytical validation of chamber air concentration	Particle size information is necessary for inhalation dosimetry, dose-response modeling, and human extrapolation. Analytical validations should be comparable to NTP protocols.
Number of exposure groups	At least 3 (excluding controls)	NTP (2014, 1998) utilized 3 groups.

Attribute	Preferred design feature	Rationale
Animal sex	Both male and female	NTP (2014, 1998) utilized both sexes.
Animal species/strain	A species that is a relevant or reliable human surrogate	NTP (2014, 1998) utilized F344 rats and B6C3F$_1$ mice.
Number of animals/groups	At least 50	NTP (2014, 1998) utilized 50 animals per group.
Dose range	At least two concentration groups below 5 mg Co/m^3	5 mg/m^3 is the highest concentration group in the NTP (2014) study of insoluble cobalt metal. Tumor incidences were high at this concentration. Data at lower levels (which are more environmentally relevant and near the modeled benchmark response rate) are preferred.
Measurement of health outcome	Tumor incidence per group, with adenomas/carcinomas listed separately.	NTP (2014, 1998) reports tumor incidence per group, with adenoma and carcinomas presented separately.
Individual-level data	Individual-level animal tumor and survival data.	NTP (2014, 1998) provides individual-level data and poly-3 survival statistic. Individual-level data are needed for time-to-tumor modeling. NTP also reported changes in survival rate as a function of concentration and time.
Study evaluation	Tumor data considered *medium* or *high* confidence	Both NTP reports NTP (1998); NTP (2014) were considered *high confidence* (https://hawc.epa.gov/summary/visual/assessment/100500295/NTP-Cancer-Bioassays/)

Study Evaluation

Epidemiological or animal studies that are prioritized from the analysis of suitability for dose response will undergo study evaluation. When available, study evaluations from prior assessments (e.g., RoC Monograph) were used to identify major limitations that would preclude the study from being considered suitable for dose-response in this assessment. Studies considered suitable for dose-response - such as the NTP rodent cancer bioassays NTP (1998); NTP (2014) - undergo full study evaluation using IRIS methodology - a domain-based approach to evaluate studies. The detailed approaches are described in the Office of Research and Development (ORD) Staff Standard Operating Procedures for Developing Integrated Risk Information System (IRIS) Assessments (Version 1.0, October 2020, referred to as the "IRIS Handbook") U.S. EPA (2020c).

The key concerns for the review of studies are potential bias (factors that affect the magnitude or direction of an effect in either direction) and insensitivity (factors that limit the ability of a study to detect a true effect; low sensitivity is a bias towards the null when an effect exists). Each outcome or grouping of related outcomes within a study is judged independently by two or more ORD staff reviewers using the HAWC Study Evaluation module. Reviewers reach a consensus judgment (with conflict resolution by an additional reviewer, as needed) for each evaluation domain and overall confidence determination. Judgments could differ from one outcome to another within the same study, and with the overall study confidence determination. During review, for each evaluation, domain reviewers reach a consensus judgment of *good*, *adequate*, *deficient*, *not reported*, or *critically deficient*. It is important to emphasize that evaluations are performed in the context of the study's utility for identifying individual hazards. Limitations

specific to the usability of the study for dose-response analysis are useful to note, but they do not contribute to the study confidence classifications. Once the evaluation domains have been rated, the identified strengths and limitations are considered collectively to reach a study confidence classification of *high*, *medium*, or *low* confidence, or *uninformative* for a specific health outcome. This classification is based on the reviewer judgments across the evaluation domains and considers the likely impact that inadequate reporting or the noted deficiencies in bias and sensitivity have on the outcome-specific results. The specific limitations identified during study evaluation are carried forward to help inform the synthesis within each body of evidence for a given health effect. Health outcomes evaluated as *uninformative* are considered unusable for hazard and dose-response given that the findings of interest are considered to be uninterpretable based on the identified flaws. These studies have no impact on evidence synthesis or integration conclusions but may be used to highlight research gaps.

(a) Individual evaluation domains

Epidemiology	Animal	In vitro
• Exposure measurement • Outcome ascertainment • Participant selection • Confounding • Analysis • Selective reporting • Sensitivity	• Allocation • Observational bias/blinding • Confounding • Attrition • Chemical administration and characterization • Endpoint measurement • Results presentation • Selective reporting • Sensitivity	• Observational bias/blinding • Variable control • Selective reporting • Chemical administration and characterization • Endpoint measurement • Results presentation • Sensitivity

(b) Domain level judgments and overall study rating

Domain judgments

Judgment	Interpretation
Good	Appropriate study conduct relating to the domain and minor deficiencies not expected to influence results.
Adequate	A study that may have some limitations relating to the domain, but they are not likely to be severe or to have a notable impact on results.
Deficient	Identified biases or deficiencies interpreted as likely to have had a notable impact on the results or prevent reliable interpretation of study findings.
Critically Deficient	A serious flaw identified that makes the observed effect(s) uninterpretable. Studies with a critical deficiency are considered "uninformative" overall.

Overall study rating for an outcome

Rating	Interpretation
High	No notable deficiencies or concerns identified; potential for bias unlikely or minimal; sensitive methodology.
Medium	Possible deficiencies or concerns noted but they are unlikely to have a significant impact on results.
Low	Deficiencies or concerns were noted, and the potential for substantive bias or inadequate sensitivity could have a significant impact on the study results or their interpretation.
Uninformative	Serious flaw(s) makes study results uninterpretable but may be used to highlight possible research gaps.

Figure C-1. Overview of Integrated Risk Information System (IRIS) study evaluation process. (a) individual evaluation domains organized by evidence type, and (b) individual evaluation domains judgments and definitions for overall ratings (i.e., domain and overall judgments are performed on an outcome-specific basis).

Data Extraction of Study Methods and Results

Data will be extracted from prioritized studies into EPA's version of Health Assessment Workspace Collaborative (HAWC, https://hawcprd.epa.gov/), a web-based software application designed to manage and facilitate the process of conducting health assessments. Because the focus of the current assessment is to develop a cancer IUR for inclusion in the IRIS database, tumor data

(along with any other data relevant to dose-response, such as animal survival rates and individual-level data) are prioritized for data extraction. Data are also be stored in other formats (i.e., Excel, BMDS, Word). See Section 4.2.1 "Selecting Endpoints for Dose-Response Assessment."

For quality control, data extraction is be performed by one member of the evaluation team and independently verified by at least one other member. Discrepancies in data extraction are resolved by discussion or consultation with a third member of the evaluation team.

C.5.2.Supplemental Material

The results of the supplemental material tagging (Table C-2) conducted in DistillerSR are imported into the Literature Inventory module in HAWC, where more granular sub-tagging within a type of supplemental material content category is conducted during assessment development (including after preparation of the SEM). A single study can have multiple tags. Tagging judgements in HAWC are made by one assessment member and confirmed during preparation of draft assessment by another member of the assessment team.

C.6. RESULTS: LITERATURE SCREENING RESULTS

The database searches yielded 29,833 references in HERO after duplicate removal (Figure C-1). Application of the SWIFT Review literature search filters (available online from Sciome Company) for "human", "animal (human health models)", and "*in vitro"* evidence reduced the number of studies for consideration to 4,588 after duplicate removal. The studies were screened in SwiftActive Screener using predictive relevance, resulting in 2095 studies being manually screened to identify 742 studies that were considered potentially PECO relevant or supplemental ("included" for the purposes of machine learning) and 1353 references that were manually excluded. After manually reviewing these 2095 references, screening was stopped because SWIFT ActiveScreener indicated at least 95% of the relevant studies are identified, a percent identification often used to evaluate the performance of machine learning applications and considered comparable to human error rates Bannach-Brown et al. (2018);Howard et al. (2016);Cohen et al. (2006). More specifically, in this project screening stopped when a predicted 96% of relevant studies were identified.

Separately, over 1600 unique records were identified from the other sources searched and compared to the 4588 that were initially uploaded into SWIFTActive Screener, yielding 502 unique records. These 502 studies, as well as the 742 studies previously identified as potentially PECO relevant or supplemental, were imported into DistillerSR for a total of 1244 studies screened at TIAB level. During TIAB screening in DistillerSR, 62 were included for full-text review, 826 were tagged as supplemental material, and 399 were excluded as not relevant to PECO.

During full-text review, 19 studies were considered PECO relevant (11 animal studies and 8 human studies), 22 studies were excluded, and 22 studies were tagged as supplemental material. The PECO relevant human and animal studies were then assessed for suitability for dose response

(Table C-4, Table C-5). Literature search results are summarized graphically in Figure C-1 and in an interactive version in Figure C-2.

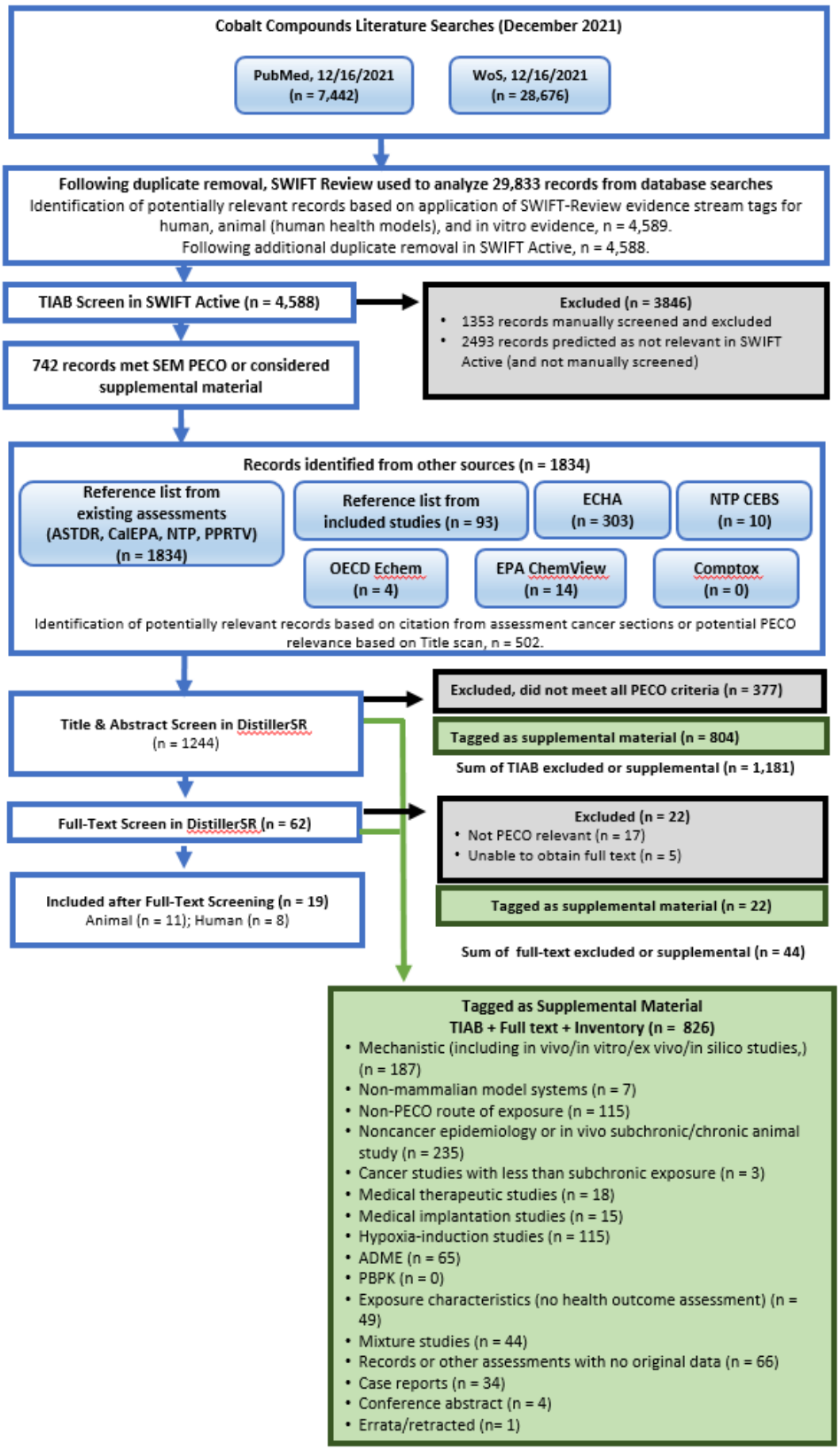

Figure C-2. Study Flow Diagram

Studies can be tagged to multiple supplemental tags, therefore, total number of supplemental subtags is greater than the total number of supplemental references.

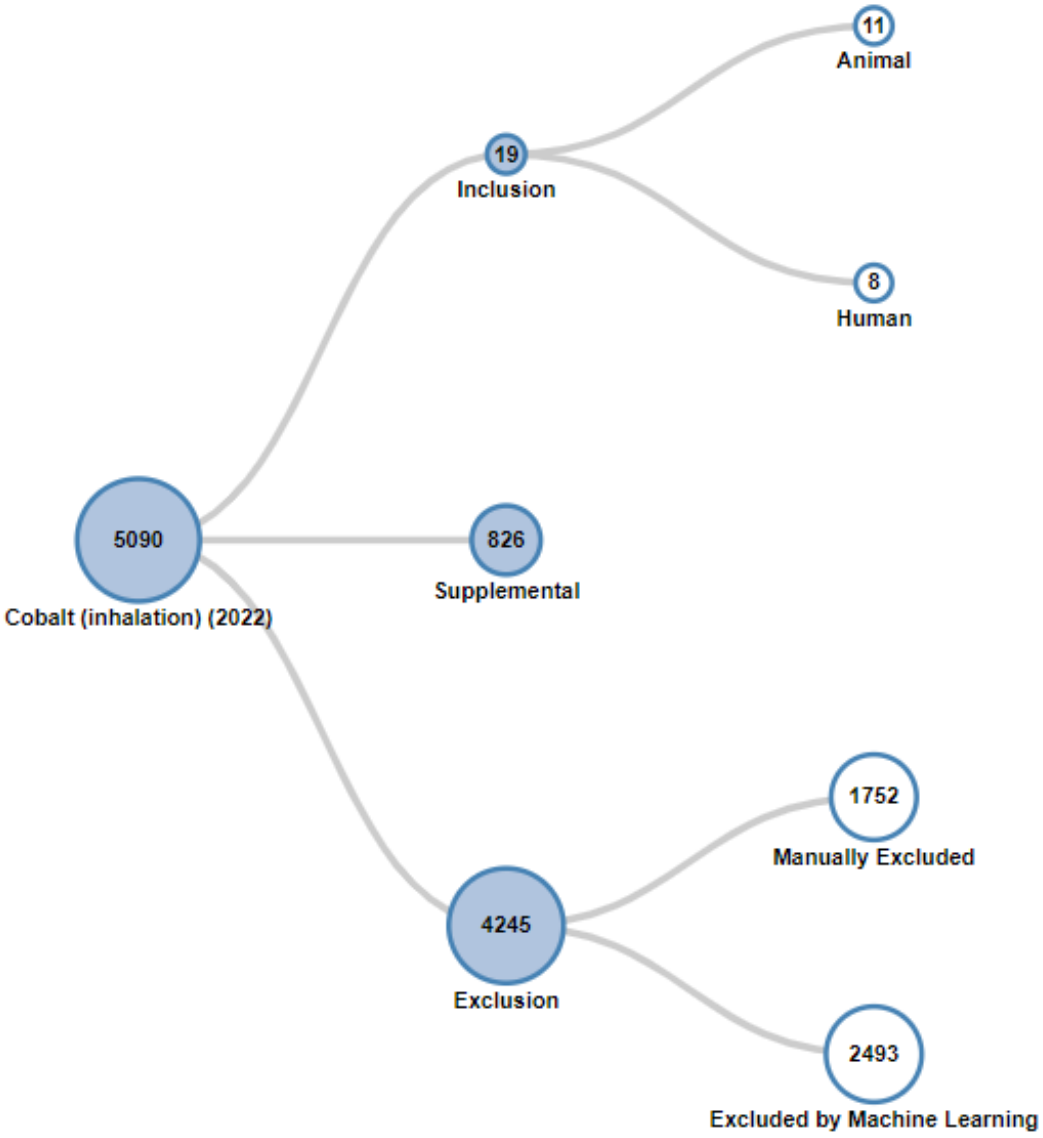

Figure C-3. Literature tree. Click here for interactive version.

C.7.LITERATURE INVENTORY

C.7.1.Characterizing Epidemiological Studies for Dose-Response Analysis

Six epidemiological studies were identified that met the SEM PECO criteria, which were developed to identify studies of cancer in relation to quantitative estimates of exposure Mur et al. (1987); Moulin et al. (1998); Tuchsen et al. (1996); Sauni et al. (2017); White et al. (2019); Kresovich et al. (2019) (Table C-5). Four of the epidemiological studies involved workers, and included evaluations of: malignant tumor (ICD-8 140-209) mortality in an electrochemical plant workers Mur et al. (1987); lung cancer in a case-control study nested in a cohort study of workers in the French hard-metal industry Moulin et al. (1998); lung cancer in women exposed to cobalt-aluminum spinel in a retrospective cohort study Tuchsen et al. (1996); and multiple cancer types (including lung) in Finnish cobalt production workers Sauni et al. (2017). The remaining two studies assessed breast cancer in relation to environmental exposure to air pollutants including cobalt (participants of the U.S.-wide Sister Study White et al. (2019), and participants of the Cancer Care in Chicago study Kresovich et al. (2019)).

Among the epidemiological studies, 3 had been included in the *NTP RoC Monograph Cobalt and Cobalt Compounds that Release Cobalt Ions In Vivo* NTP (2016); the summary of study strengths and limitations presented in the RoC Monograph Mur et al. (1987); Moulin et al. (1998); Tuchsen et al. (1996); Kresovich et al. (2019) were used to evaluate this set of studies for suitability for dose-response analysis. For the 3 studies published after the RoC Monograph Sauni et al. (2017); White et al. (2019); Kresovich et al. (2019), a targeted evaluation based on the considerations outlined in the IRIS Handbook U.S. EPA (2020c).and summarized in section 8.5 was performed. This targeted evaluation revealed concerns in all 3 studies that precluded their use for dose-response, namely the lack of individual-level exposure information, and the potential for confounding by co-exposures to other carcinogens. These limitations are summarized in Table C-4. As the 3 earlier studies evaluated in the RoC Monograph also had limitations, none of the human studies were deemed to be more suitable for dose-response compared to the NTP animal cancer bioassay studies.

C.7.2.Characterizing Animal Studies for Dose-Response Analysis

Eleven animal studies were identified that met SEM PECO criteria, including three NTP Toxicity Reports NTP (1991); NTP (1998); NTP (2014) and six associated publications Bucher et al. (1990); Bucher et al. (1999); Ozaki et al. (2002); Behl et al. (2015); Hong et al. (2015); Ton et al. (2021). The two remaining publications had been considered in prior assessments Kerfoot (1973); Palmes et al. (1959) and no new cancer bioassays were identified. The NTP rodent cancer bioassays NTP (1998);NTP (2014) were both considered *high confidence* (Figure C-3), and the six associated publications Bucher et al. (1990);Bucher et al. (1999);Ozaki et al. (2002);Behl et al. (2015);Hong et al. (2015);Ton et al. (2021) weNational Toxicology Program (NTP) (670835); NTP (2014) based on comparisons outlined in Table C-3. All other studies were determined to be inadequate for dose-response for multiple reasons, with short exposure durations being the most

common rationale (see Table C-5). The three subchronic studies (NTP (1991), Kerfoot (1973), and Palmes et al. (1959)) contained no tumor dose-response data. In addition, Kerfoot (1973), and Palmes et al. (1959) had insufficient study designs and data reporting.

Table C-4. Analysis of Human Studies Meeting PECO Criteria for Suitability for Dose-Response.

Study	Study design and population	Exposure	Endpoints	Study evaluation observation	Suitability for dose-response
Mur et al. (1987)	Cohort of electrochemical plant workers producing cobalt and sodium (1950-1980)	Occupational categories (whole cohort, general services, maintenance, sodium production, cobalt production)	Malignant tumor mortality, lung cancer mortality	"Exposure duration: 60% worked greater than 10 years; 75% hired before 1975. Confounding: Likely inadequate control for smoking; however, likely co-exposure to nickel and arsenic with no control for coexposures. Strengths: Cobalt production workers exposed primarily to cobalt compounds. Limitations: Small number of exposed cases; high loss to follow-up (20%); potential for selection bias due to left truncation" (page 49 from RoC Monograph, NTP (2016). Study quality concerns identified in the confounding and sensitivity domains (page 47 from RoC Monograph, NTP (2016).	*Not suitable for dose-response* Main limitations related to confounding, sensitivity and selection bias
Moulin et al. (1998)	Nested case control study of French hard-metal industry workers (10 facilities, 1968-1991). 5777 males, 1682 females	Job-exposure matrix, 320 job periods and semi-quantitative estimation of exposure to cobalt and to tungsten carbide	All cancer mortality, lung cancer	"No information on actual exposure level or average exposure duration for the cohort. Confounding: Potential concern for exposure to other lung carcinogens, which were not controlled in the cobalt alone analyses. Strengths: Exposure-response analyses with multiple exposure metrics; JEM validated for atmospheric concentrations of cobalt; incident cohort reducing the potential for left truncation; internal analysis reducing the impact of the reported HWE; and lagged analysis. Limitations: Potential confounding by coexposures classified only as "ever/never" in the JEM" (page 51 from RoC Monograph, NTP (2016) Study quality concerns identified in the confounding domain (page 47 from RoC Monograph, NTP (2016)	*Not suitable for dose-response* Main limitations related to confounding from exposure to other carcinogens.
Tuchsen et al. (1996)	Retrospective cohort of two Danish porcelain factories, 874 women	Dust and airborne concentrations (only for certain years)	All-cause mortality, organ- specific	"Employment in factories/departments with or without cobalt. Confounding: No control for smoking; however, smoking data on subset of	*Not suitable for dose-response*

Study	Study design and population	Exposure	Endpoints	Study evaluation observation	Suitability for dose-response
	occupationally exposed to cobalt (and 520 women not exposed)		cancer incidence (including lung and breast cancer)	workers suggests that smoking was not associated with exposure. Strengths: Population exposed primarily to cobalt compounds alone; only female population with data on cobalt. Limitations: Small number of exposed cases. Differential selection out of the cohort could have occurred as the authors mentioned that records of ill persons may have been removed potentially resulting in an underestimate of the true incidence of cancer." (Page 47 from RoC Monograph, NTP (2016) "This study had low sensitivity to detect an effect because of (1) small numbers of exposed cases in this relatively small cohort and (2) potentially combining workers with high and low exposures together, which could dilute any effect and bias the results towards the null. In addition, no lagged analyses were reported. A concern about differential selection also exists in this study. The authors suggested that removal of records of ill persons was known to take place in Danish manufacturing. The possibility of differential selection out of the cohort could have resulted in an underestimation of the true incidence of lung cancer in this study." Study quality concerns identified in the sensitivity domain (page 47 from RoC Monograph, NTP (2016)	Main limitations related to low sensitivity
Sauni et al. (2017)	Cohort study of male cobalt production workers (Finland, 1969-2013). 995 men with 26083 person-years.	Occupational categories	Cancer incidence (including lung, tongue, other cancer types)	Male worker cohort stratified by age and exposure level. Strengths: routine stationary measurements and personal sampling with worker history verified. Smoking data available. Limitation: potential confounding by other carcinogens, namely nickel. No information on alcohol consumption. Study quality concerns: confounding and sensitivity	*Not suitable for dose-response* Main limitations related to potential confounding and limited generalizability.

Study	Study design and population	Exposure	Endpoints	Study evaluation observation	Suitability for dose-response
White et al. (2019)	The Sister Study (US-wide prospective cohort) of 50,884 women.	U.S. EPA National Air Toxics Assessment	Breast cancer	General population study with estimated exposure to ambient toxic pollutants. Strengths: Large study population. Limitations: Exposure to cobalt estimated based on national air pollutant data. No measurement of actual cobalt exposure levels. Potential confounding by other air pollutants. Study quality concerns: specificity of exposure and confounding	*Not suitable for dose-response* Main limitations related to potential confounding due to exposure to other carcinogens.
Kresovich et al. (2019)	Breast Cancer Care in Chicago (population-based cohort study) study of 696 women.	U.S. EPA National Air Toxics Assessment	Breast cancer	General population study with estimated exposure to ambient toxic pollutants. Strengths: Health outcome (breast cancer) medically verified. Limitations: Exposure to cobalt estimated based on national air pollutant data. No measurement of actual cobalt exposure levels. Potential confounding by other air pollutants. Study quality concerns: specificity of exposure and confounding	*Not suitable for dose-response* Main limitations related to potential confounding due to exposure to other carcinogens.

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Table C-5. Analysis of Animal Studies Meeting PECO Criteria for Suitability for Dose-Response.

Study	Species, strain, sex	Dur.	Design	Air measurements	Sample size/group	Conc (mg/m^3)	Outcome measure	Suitability for dose-response
NTP (1998)*	F344 rats, $B6C3F_1$ mice M, F	2 yr	6h/day, 5d/week	Particle size and mg/m^3 validation	50	0 0.114 0.38 1.14	Tissue pathology (quantitative)	Suitable for dose-response. Chronic study. Tumors observed. Individual animal data available. Large sample size.
NTP (2014)*	F344 rats, $B6C3F_1$ mice M, F	2 yr	6h/day, 5d/week	Particle size and mg/m^3 validation	50	0 1.25 2.5 5.0	Tissue pathology (quantitative)	Suitable for dose-response. Chronic study. Tumors observed. Individual animal data available. Large sample size.
NTP (1991)	F344 rats, $B6C3F_1$ mice M, F	90 d	6h/day, 5d/week	Particle size and mg/m^3 validation	10	0 0.114 0.38 1.14 3.8	Tissue pathology (quantitative). No tumors observed.	Not suitable for dose-response. Subchronic study. No tumors observed. Small sample size limits power to observe rare effects.

						11.4		
Kerfoot (1973)	Mini. swine (sex not specified)	90 d	6h/day, 5d/week	No particle or air validation presented	5	0 0.1 1	Tissue pathology (qualitative). No tumors observed.	Not suitable for dose-response. Insufficient data (animal specification, air and outcome quantitation). Subchronic study. No tumors observed. Small sample size and few exposure groups. No individual animal data available.
Palmes et al. (1959)	Albino rats (M), guinea pigs, dogs	90 d	6h/day, 5d/week	Gaseous cobalt hydrocarbonyl. Air mg/m^3 validation	41 control, 75 exposed (rats)	0 9	Tissue pathology (qualitative), hematology, pharmacokinetics	Not suitable for dose-response. Insufficient data (outcome quantitation). Subchronic study. No tumors observed. Single high exposure group (above 5 mg/m^3). No individual animal data available.

*Related studies include Bucher et al. (1990), Bucher et al. (1999), Ozaki et al. (2002), Behl et al. (2015), Hong et al. (2015), and Ton et al. (2021).

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ADDENDUM 1. LITERATURE SEARCH STRATEGY (DATE LIMITED TO 2019- 2021)

Search	Search Strategy	Results and Date
WOS	(TS=("cobalt" OR "7440-48-4" OR "10124-43-3" OR "Cobaltsulfat" OR "7646-79-9" OR "Cobaltous chloride" OR "Dichlorocobalt" OR "1317-42-6" OR "71-48-7" OR "6147-53-1" OR "917-69-1" OR "513-79-1" OR "10210-68-1" OR "21041-93-0" OR "21158-51-0" OR "61789-51-3" OR "10141-05-6" OR "10026-22-9" OR "1308-04-9" OR "1307-96-6" OR "1308-06-1" OR "10026-24-1" OR "Cobaltic acetate" OR "Dicobalt octacarbonyl" OR "Cobalt(II) hydroxide" OR "Cobaltous hydroxide" OR "Cobalt(II) acetate" OR "Cobalt(II) acetate tetrahydrate" OR "Cobalt(III) acetate" OR "Cobalt(II) carbonate" OR "Cobalt(II) chloride" OR "Cobalt(II) hydroxide" OR "Cobalt(II) mesoporphyrin" OR "Cobalt(II) naphthenate" OR "Cobalt(II) nitrate" OR "Cobalt(II) nitrate hexahydrate" OR "Cobalt(II) oxide" OR "Cobalt(III) oxide" OR "Cobalt(II) sulfate" OR "Cobalt(II) sulfate heptahydrate" OR "Naftolite" OR "Cobaltdinitrat" OR "Cobaltous nitrate" OR "Cobaltous oxide" OR "C.I. Pigment Black 13" OR "Cobaltoxid" OR "Cobaltic oxide" OR "Dicobalt oxide" OR "Cobaltosic oxide" OR "Cobaltic-cobaltous oxide" OR "Cobalto-cobaltic oxide" OR "Tetraoxyde de tricobalt" OR "Tricobalttetraoxid" OR "tricobalt tetraoxide" OR "Tricobalt tetraoxide" OR "Tricobalt tetroxide" OR "Cobaltous sulfate heptahydrate" OR "cobalt element" OR "cobalto") AND (PY=2019-2021))	28,676 12/16/2021
PubMed	"cobalt"[tw] OR "7440-48-4"[rn] OR "10124-43-3"[tw] OR "Cobaltsulfat"[tw] OR "7646-79-9"[tw] OR "Cobaltous chloride"[tw] OR "Dichlorocobalt"[tw] OR "1317-42-6"[tw] OR "71-48-7"[tw] OR "6147-53-1"[tw] OR "917-69-1"[tw] OR "513-79-1"[tw] OR "10210-68-1"[tw] OR "21041-93-0"[tw] OR "21158-51-0"[tw] OR "61789-51-3"[tw] OR "10141-05-6"[tw] OR "10026-22-9"[tw] OR "1308-04-9"[tw] OR "1307-96-6"[tw] OR "1308-06-1"[tw] OR "10026-24-1"[tw] OR "Cobaltic acetate"[tw] OR "Dicobalt octacarbonyl"[tw] OR "Cobalt(II) hydroxide"[tw] OR "Cobaltous hydroxide"[tw] OR "Cobalt(II) acetate"[tw] OR "Cobalt(II) acetate tetrahydrate"[tw] OR "Cobalt(III) acetate"[tw] OR "Cobalt(II) carbonate"[tw] OR "Cobalt(II) chloride"[tw] OR "Cobalt(II) hydroxide"[tw] OR "Cobalt(II) mesoporphyrin"[tw] OR "Cobalt(II) naphthenate"[tw] OR "Cobalt(II) nitrate"[tw] OR "Cobalt(II) nitrate hexahydrate"[tw] OR "Cobalt(II) oxide"[tw] OR "Cobalt(III) oxide"[tw] OR "Cobalt(II) sulfate"[tw] OR "Cobalt(II) sulfate heptahydrate"[tw] OR "Naftolite"[tw] OR "Cobaltdinitrat"[tw] OR "Cobaltous nitrate"[tw] OR "Cobaltous oxide"[tw] OR "C.I. Pigment Black 13"[tw] OR "Cobaltoxid"[tw] OR "Cobaltic oxide"[tw] OR "Dicobalt oxide"[tw] OR "Cobaltosic oxide"[tw] OR "Cobaltic-cobaltous oxide"[tw] OR "Cobalto-cobaltic oxide"[tw] OR "Tetraoxyde de tricobalt"[tw] OR "Tricobalttetraoxid"[tw] OR "tricobalt tetraoxide"[tw] OR "Tricobalt tetraoxide"[tw] OR "Tricobalt tetroxide"[tw] OR "Cobaltous sulfate heptahydrate"[tw] OR "cobalt element"[tw] OR "cobalto"[tw]) AND (2019/01/01:3000[dp])	7,442 12/16/2021
	Unique items were discovered using the search strategy above.	29,833
	Number of records after application of SWIFT Review tags for human, animal (human health models), and in vitro evidence	4,589
TOTAL	Number of records after an addition round of de-duplication SWIFT Active	4,588

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ADDENDUM 2. PROCESS AND RESULTS FOR SEARCHING AND COLLECTING EVIDENCE FROM OTHER RESOURCES

Process

Review of reference lists from existing assessments (final or publicly available draft) and journal studies considered relevant to PECO based on full-text screening

Citations from cancer sections of prior assessments were compiled and reviewed manually by scanning the titles for those that appear to meet the PECO criteria. Any unique records identified from these sources are formatted in an RIS file format, imported into DistillerSR, annotated with respect to source, and screened as outlined previously in "Literature Screening Processes".

Reference lists from journal articles are also reviewed manually by scanning the titles for those that appear to meet the PECO criteria. This is only done for journal articles that meet PECO criteria based on full-text review and not for journal articles tagged as supplemental material.

European Chemicals Agency

A search of the ECHA-registered substances database is conducted using the CASRN. The registration dossier associated with the CASRN number is retrieved. The general information page and all subpages included under the Toxicological Information tab are downloaded in PDF format, including all nested reports that have unique URLs.

At this stage, each study summary is reviewed for inclusion on the basis of the PECO criteria. When a study summary considers relevant reported data from a study or lab report, a citation for the full study is generated in HERO, and it is verified that the study is not already identified from the database search (or searches of "other sources consulted") prior to moving forward to screening.

EPA ChemView

A search of the EPA ChemView database U.S. EPA (2019) using the chemical CASRN is conducted. The prepopulated CASRN match and the "Information Submitted to EPA" output option filter is selected before generating results. If results are available, the square-shaped icon under the "Data Submitted to EPA" column is selected, and the following records are considered:

- High Production Volume Challenge Database (HPVIS)

- Human Health studies (Substantial Risk Reports)
- Monitoring (Includes environmental, occupational and general entries)
- TSCA Section 4 (Chemical testing results)
- TSCA Section 8(d) (Health and safety studies)
- TSCA Section 8(e) (Substantial Risk)
- FYI (Voluntary documents)

All records for ecotoxicology and physical & chemical property entries are excluded. When results are available, extractors navigate into each record until a substantial risk report link is identified and saved as a PDF file. If the report cannot be saved, due to file corruption or broken links, the record is excluded during full-text review as "unable to obtain record." Most substantial risk reports contain multiple document IDs; thus, citations are derived by concatenating the unique report numbers (OTS, 8EHD Num, DCN, TSCATS RefID, CIS) associated with each document along with the typical author organization, year, and title. Once a citation is generated, the study is moved forward to DistillerSR, where it is screened according to PECO criteria.

NTP Chemical Effects in Biological Systems

This CEBS database is searched using the chemical CASRN (https://manticore.niehs.nih.gov/cebssearch). All non-NTP data are excluded using the "NTP Data Only" filter. Data tables for reports undergoing peer review are also searched for studies that have not been finalized (https://ntp.niehs.nih.gov/data/tables/index.html) on the basis of a manual review of chemical names.

OECD Echem Portal

The OECD Echem Portal (https://hpvchemicals.oecd.org/UI/Search.aspx) is searched using the chemical CASRN to retrieve results for OECD Screening Information DataSet (SIDS) and High Production Volume (HPV) Chemicals (https://www.echemportal.org/echemportal/). Only database entries from those resources are included, and entries from all other databases are excluded in the search. Final assessment reports and other relevant SIDS reports embedded in the links are captured and saved as PDF files.

Results of Searching Other Resources

Source	Source address	Search terms	Search date	Total unique number of results retrieved	Records not otherwise identified that were screened in DistillerSR
Review of reference lists of studies considered relevant to PECO based on full-text screening.	NA	NA	7/15/2022	93	34
Review of reference lists from existing assessments (final or publicly available draft)	NA	NA	3/24/22	1,834	465
EPA CompTox Chemicals Dashboard version to retrieve a summary of any ToxCast or Tox21 high throughput screening information	https://comptox.epa.gov/dashboard	7440-48-4; 1345-16-0 7789-43-7; 513-79-1; 10210-68-1; 16842-03-8; 7646-79-9; 61789-51-3; 1307-96-6; 1308-06-1; 136-52-7; 10141-05-6; 10026-22-9; 10124-43-3	3/16/2022	0	0
ECHA	https://echa.europa.eu/da/information-on-chemicals/registered-substances	7440-48-4; 1345-16-0; 7789-43-7; 513-79-1; 10210-68-1; 16842-03-8; 7646-79-9; 61789-51-3; 1307-96-6; 1308-06-1; 136-52-7; 10141-05-6; 10026-22-9; 10124-43-3	3/17/2022	303	0
EPA ChemView	https://chemview.epa.gov/chemview	7440-48-4; 1345-16-0; 7789-43-7; 513-79-1; 10210-68-1; 16842-03-8; 7646-79-9; 61789-51-3; 1307-96-6; 1308-06-1; 136-52-7; 10141-05-6; 10026-22-9; 10124-43-3	3/15/2022	14	0

Source	Source address	Search terms	Search date	Total unique number of results retrieved	Records not otherwise identified that were screened in DistillerSR
NTP CEBS	https://manticore.niehs.nih.gov/cebssearch/	7440-48-4; 1345-16-0; 7789-43-7; 513-79-1; 10210-68-1; 16842-03-8; 7646-79-9; 61789-51-3; 1307-96-6; 1308-06-1; 136-52-7; 10141-05-6; 10026-22-9; 10124-43-3	3/16/2022	10	0
OECD Echem Portal	https://hpvchemicals.oecd.org/UI/Search.aspx	7440-48-4; 1345-16-0; 7789-43-7; 513-79-1; 10210-68-1; 16842-03-8; 7646-79-9; 61789-51-3; 1307-96-6; 1308-06-1; 136-52-7; 10141-05-6; 10026-22-9; 10124-43-3	3/17/2022	4	4

PECO = Populations, Exposures, Comparators, and Outcomes; NA = not applicable; POD = point of departure; ECHA = European Chemicals Agency; NTP CEBS = National Toxicology Program Chemical Effects in Biological Systems; OECD = Organisation for Economic Co-operation and Development.