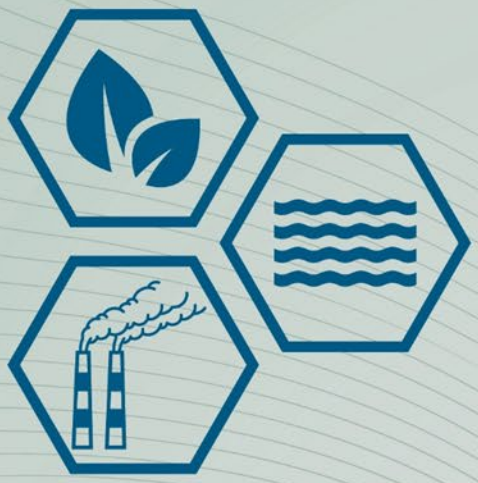

Toxicological Profile for Cobalt

Draft for Public Comment

January 2023

ATSDR
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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VERSION HISTORY

Date	Description
January 2023	Draft for public comment released
April 2004	Final toxicological profile released
July 1992	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1. OVERVIEW AND U.S. EXPOSURES

Cobalt and cobalt compounds are naturally occurring and have similar physicochemical properties to those of iron and nickel. The largest use of metallic cobalt is in rechargeable batteries, followed by uses as super alloys in gas turbine aircraft engines. Cobalt forms compounds with several other elements including chloride, sulfur, and oxygen. These compounds are used as pigments, catalysts in the petroleum and other industries, paint driers, animal feed additives, and are part of Vitamin B_{12}; they are also used as trace element additives in agricultural soil-amendments and medicinal products.

Cobalt can be released to the environment by human activities, as well through the weathering of rocks and soil. The primary anthropogenic sources of cobalt in the environment are from the burning of fossil fuels, application of cobalt-containing sludge or phosphate fertilizers, mining and smelting of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds. Cobalt released to the atmosphere is deposited onto soil or water surfaces by wet and dry deposition. In soils, cobalt generally has low mobility and strong adsorption. However, its mobility increases in moist, acidic soils. In water, cobalt largely partitions to sediment and to suspended solids in the water column; however, the amount that is adsorbed to suspended solids is highly variable. Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, intake from food sources is much greater than from drinking water and air. The cobalt intake in food has been estimated to be (geometric mean) 5–40 µg/day for the general population and urinary cobalt (geometric mean) detected in humans ranged from 0.32 to 0.42 µg/L and blood cobalt (geometric mean) was 0.151 µg/L based on measurements taken in 2013. The biochemically relevant form of cobalt is vitamin B_{12}, also known as cyanocobalamin, which plays a crucial role in maintaining optimal health in humans and animals.

The general population can be exposed to low levels of cobalt by breathing air, eating food, or drinking water with food being the largest source of exposure. Some exposure is also possible from medical devices and prosthetics. Occupational exposure to cobalt occurs in the hard metal industry (tool production, grinding, etc.) and in industries such as coal mining, metal mining, smelting, and refining, cobalt dye painting, and cobalt chemical production. Radioactive cobalt decays or changes into a stable non-radioactive substance. Half of ^{60}Co decays in 5.27 years and half of ^{57}Co decays in 272 days. While the general population is rarely exposed to radioactive cobalt, radiation therapy patients may be exposed to radiation from cobalt located inside a therapy machine or during radiosurgery using a gamma knife that

uses ^{60}Co. Workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be exposed to small amounts of radioactive cobalt and its radiation from these sources. Additional details of exposure to radioactive cobalt and related health effects are discussed in the Toxicological Profile for Ionizing Radiation (ATSDR 1999).

1.2. SUMMARY OF HEALTH EFFECTS

Exposure data in this section are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days). Studies regarding the health effects of cobalt come primarily from oral and inhalation studies in humans and laboratory animals. As an essential trace element in Vitamin B_{12}, cobalt can be beneficial for human health. Inhalation exposure is predominantly seen with occupational exposure of humans to cobalt metal and targets the respiratory tract. The health effects observed include decreased pulmonary function, asthma, interstitial lung disease, wheezing, and dyspnea. Animal studies corroborate these effects and have identified respiratory tract hyperplasia, pulmonary fibrosis, and emphysema as sensitive effects of inhaled cobalt on the pulmonary system. Cobalt inhalation also affects cardiac function and causes allergic dermatitis manifesting as eczema and erythema. These dermal effects could potentially be due to concurrent dermal exposure and the development of immunosensitization to cobalt. Oral toxicity studies have evaluated several endpoints, with the most sensitive endpoint in humans being an increase in erythrocyte numbers, hematocrit, and hemoglobin that some articles characterized as polycythemia (Davis and Fields 1958; Taylor et al. 1977). When addressed in this toxicological profile (profile), polycythemia refers to absolute polycythemia (an increase in red cell mass regardless of cause) specifically from exposure to a substance, such as cobalt. When absolute polycythemia is discussed in this profile, it is in reference to polycythemia caused by cobalt toxicity. Animal studies that examined the hematological endpoint after oral exposure also showed an increase in erythrocyte numbers and changes in other parameters such as blood cell count (Awoyemi et al. 2017; Domingo et al. 1984; Gluhcheva et al. 2020; Shrivastava et al. 2008). Adequate chronic-duration studies of the oral toxicity of cobalt or cobalt compounds in humans and animals have not been identified. Dermal exposure in humans most frequently results in dermatitis (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No studies were identified that examine carcinogenic effects in humans after inhalation exposure; however, animal studies reported carcinogenicity in rats and mice of both sexes after inhalation exposure. Oral data on the carcinogenic effects of cobalt and cobalt compounds are not available. Cobalt ions in the body give rise to inhibition of DNA repair, genotoxicity, and generation of reactive oxygen species (ROS) resulting in oxidative damage. The Environmental Protection Agency (EPA) has not classified cobalt for carcinogenicity. The International Agency for Research on Cancer (IARC) has classified cobalt as *Group*

2B- possibly carcinogenic to humans. National Toxicology Program (NTP) under U.S. Department of Health and Human Services (DHHS) has classified cobalt and cobalt compounds that release ions inside the body as reasonably anticipated to be a human carcinogen based on evidence from human and animal studies.

Figure 1-1 and Figure 1-2 summarize the health effects observed in human and animal inhalation and oral studies. Based on the current body of literature, the respiratory and hematological endpoints are the most evaluated in human toxicity studies and appear to be among the most sensitive endpoints of cobalt toxicity as presented in Figure 1-1 (inhalation) and Figure 1-2 (oral). A systematic review was conducted on these endpoints. The weight-of-evidence conclusions are defined in Appendix C. The review resulted in the following hazard identification conclusions:

- Respiratory effects are a known health effect of inhalation exposure to cobalt.
- Hematological effects are a presumed health effect of oral exposure to cobalt.
- Bodyweight effects also appear to be among the most sensitive endpoints after exposure to cobalt.

Respiratory Effects. Human and laboratory animal studies support respiratory toxicity as a sensitive endpoint following inhalation exposure to cobalt. Inhaled cobalt dust in humans is absorbed in the lungs and is associated with increases in chronic phlegm and decreases in spirometric parameters (Hamzah et al. 2014; Linna et al. 2003; Sauni et al. 2010; Walters et al. 2012). Chronic-duration inhaled cobalt exposure leads to decreased lung function in exposed workers, as well as increased cough, sputum, and dyspnea (Gennart and Lauwerys 1990; Kusaka et al. 1986a). Evidence from animal studies indicates that acute-duration cobalt inhalation exposure causes pulmonary irritation, dose-dependent edema, and damage in the lungs (Palmes et al. 1959). Intermediate-duration cobalt inhalation resulted in lesions and degeneration in the respiratory tract (Bucher et al. 1990; NTP 1991), inflammation in lungs, changes in lung weights, and alterations of pulmonary tissues (Johansson et al. 1987; Johansson et al. 1992). Chronic-duration exposure in animals caused inflammation in the nose, larynx, and lung along with emphysema and lesions in the respiratory tract (NTP 1998, 2014; Wehner et al. 1977). These findings are consistent with decreased lung function and inflammation observed in animals and humans which are associated with respiratory toxicity caused by cobalt inhalation exposure.

Hematological Effects. Laboratory animal studies and a few human studies lend support to hematological effects being a sensitive endpoint following cobalt inhalation and oral exposures. Occupational exposure to inhaled cobalt did not alter hematological parameters in a human study (Lantin et al. 2011). However, studies in laboratory animal that examined higher concentrations of inhaled cobalt identified changes in

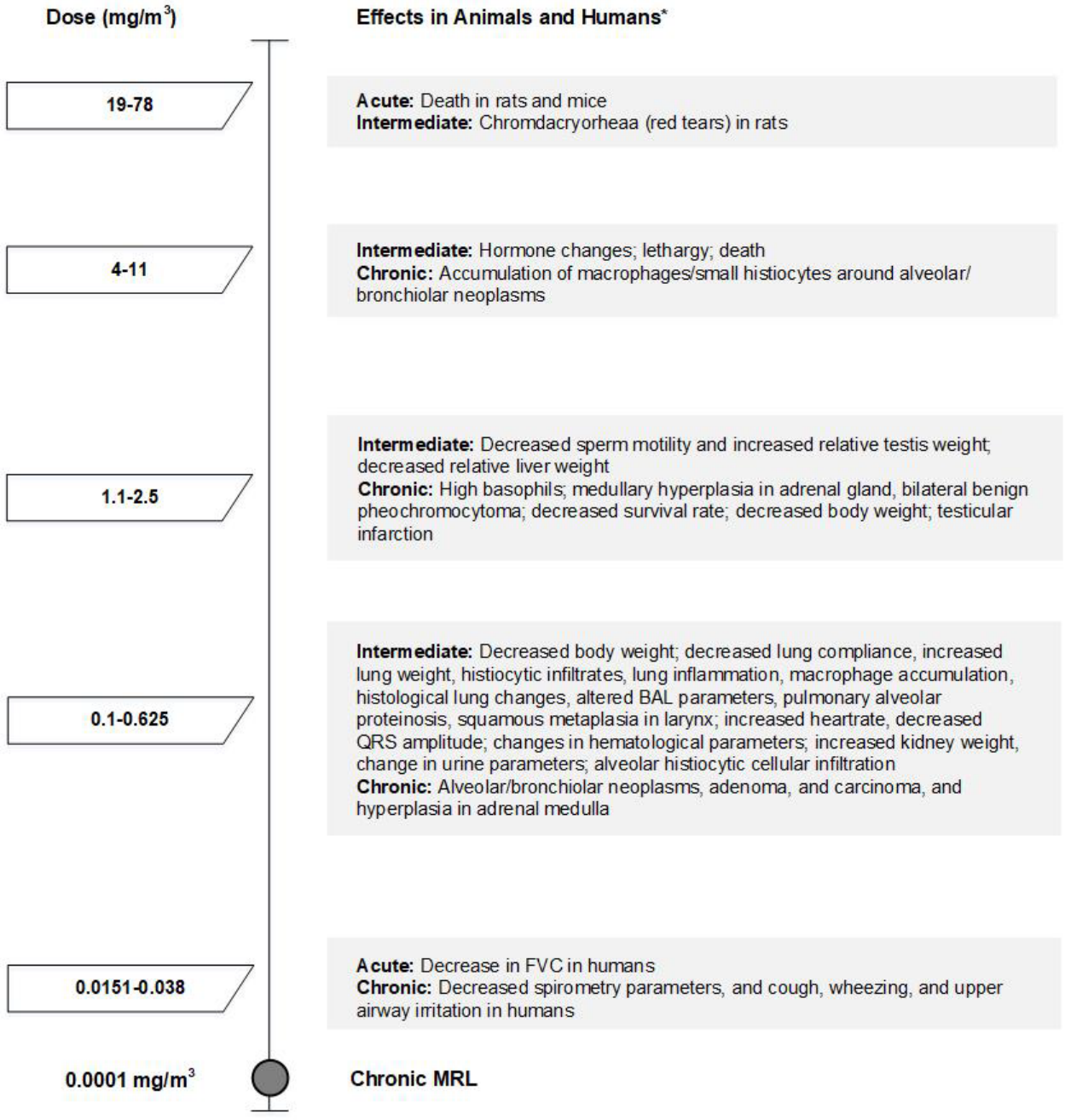
the levels of hemoglobin, basophils, and monocytes (NTP 1991, 2014; Palmes et al. 1959). Oral exposure to cobalt and cobalt compounds in humans and animals caused an increase in levels of erythrocytes, hemoglobin, and hematocrit in blood, which some authors in this profile characterized as polycythemia. When addressed in this profile, polycythemia refers to absolute polycythemia, which is an increase in red cell mass from exposure to a substance, such as cobalt, i.e., cobalt toxicity. This profile does not address other forms or causes of polycythemia. Davis and Fields (1958) reported an increase in erythrocyte levels following exposure that returned to normal upon cessation of cobalt exposure. Tvermoes et al. (2014) found no significant changes in hematological parameters following a 90-day exposure to cobalt in 10 volunteers. The animal studies corroborated the effects seen in human studies. Acute-duration oral exposure to cobalt increased erythrocytes, hematocrit, and hemoglobin (Awoyemi et al. 2017; Domingo and Llobet 1984; Shrivastava et al. 2010). Intermediate-duration oral exposure to cobalt also had similar effect in animals (Brewer 1940; Bryan and Bright 1973; Chetty et al. 1979; Corrier et al. 1985; Krasovskii and Fridlyand 1971). Pregnant dams exposed to cobalt orally had altered levels of hemoglobin and hematopoiesis (Gluhcheva et al. 2014). These findings are consistent with increased erythrocyte counts observed in animals and humans and are associated with hematological toxicity caused by oral exposure to cobalt.

Bodyweight Effects. The evidence of bodyweight being a sensitive point is based on results from laboratory animal studies. No studies in humans examined changes in body weight following inhalation, oral, or dermal exposure to cobalt for any duration. Several studies in animals indicate that inhalation exposure to cobalt and cobalt compounds results in decreased body weight (Bucher et al. 1990; Kerfoot 1974; NTP 1991; NTP 2014). There were no acute-duration inhalation studies examining bodyweight effects in animals. Intermediate-duration inhalation exposure to cobalt compounds (cobalt sulfate heptahydrate and cobalt metal) resulted in decreased body weight in rats and mice of both sexes compared to control rats (NTP 1991; NTP 2014). A separate study of cobalt sulfate heptahydrate showed reduced mean body weights in male rats (Bucher et al. 1990). Decreased body weight was also seen in pigs (strain not specified) exposed to cobalt metal by inhalation for intermediate duration (Kerfoot 1974). However, no weight loss was seen in albino rats or guinea pigs (strain not specified) after an intermediate-duration inhalation exposure to cobalt hydrocarbonyl (Palmes et al. 1959). Continuous chronic-duration inhalation exposure decreased body weight in rats and mice of both sexes (NTP 2014). Lifetime continuous inhalation exposure to cobalt oxide did not result in decreased body weight gain in hamsters (ENG:ELA strain) (Wehner et al. 1977).

In an acute-duration oral study, no effects on body weight were seen in Sprague-Dawley rats exposed to cobalt (Saker et al. 1998). Several intermediate-duration oral exposure studies in animals report that

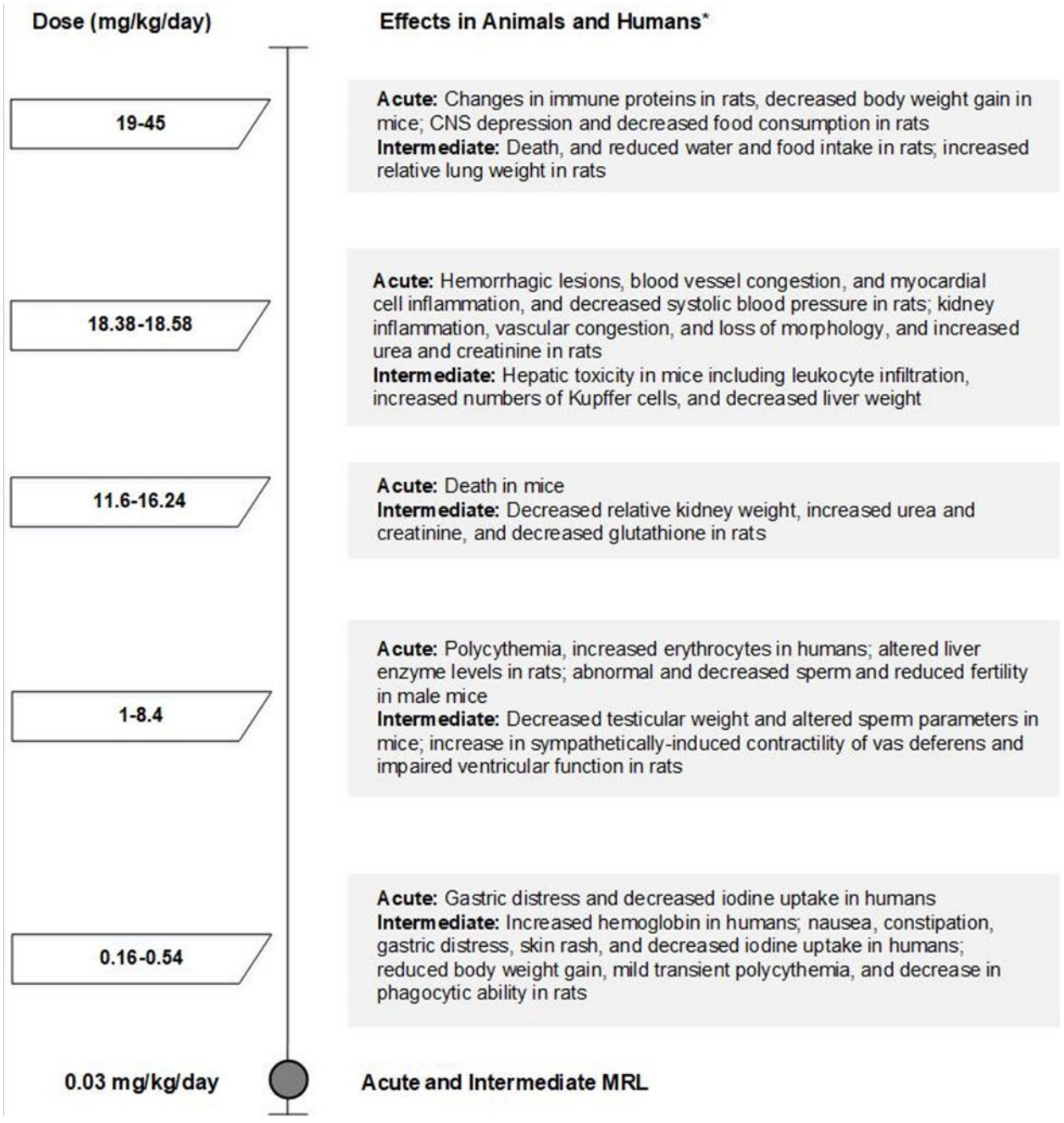
decreased body weight is commonly observed from exposure to cobalt and its compounds. Intermediate-duration exposure to cobalt chloride decreased body weight gain in male Sprague-Dawley rats (Chetty et al. 1979; Clyne et al. 1988). Rats also showed a decrease in body weight after an intermediate-duration oral exposure to cobalt sulfate (Haga et al. 1996; Pehrsson et al. 1991). Intermediate-duration oral exposure to cobalt chloride decreased bodyweight in mice (Elbetieha et al. 2008; Gluhcheva et al. 2020; Zaksas et al. 2013). Danzeisen et al. (2020) demonstrated that intermediate-duration oral exposure to $CoCl_2$ decreased body weight in rats of both sexes whereas there were marginal effects on rats of both sexes after oral exposure to Co_3O_4. There were no chronic-duration oral studies examining bodyweight effects in animals. There is no weight-of-evidence conclusions as this health effect was not included in the systematic review detailed in Appendix C.

Figure 1-1. Health Effects Found in Humans and Animals Following Inhalation Exposure to Cobalt



*All effects listed were observed in animals, unless otherwise specified. Acute-duration ≤ 14 days; Intermediate-duration = 15-364 days; Chronic-duration ≥365 days; BAL = Bronchoalveolar lavage; FVC = Forced vital capacity; QRS complex is the combination of three of the graphical deflections seen on a typical electrocardiogram

Figure 1-2. Health Effects Found in Humans and Animals Following Oral Exposure to Cobalt



*All effects listed were observed in animals, unless otherwise specified. CNS = Central Nervous System

1.3. MINIMAL RISK LEVELS (MRLs)

Minimal risk levels (MRLs) for inhalation and oral exposures to cobalt were derived. As presented in Figure 1-3, following inhalation exposure, the respiratory and hematological systems are sensitive targets

of cobalt toxicity. The inhalation database was considered inadequate for the derivation of inhalation MRLs for acute- or intermediate-duration inhalation exposure to cobalt; however, an MRL was derived for chronic-duration inhalation exposure. The endocrine, gastrointestinal and hematological systems appear to be sensitive targets of oral cobalt toxicity, as shown in Figure 1-4. The oral database was considered adequate for the derivation of acute- and intermediate-duration oral MRLs for cobalt. There were no studies that examined chronic-duration oral exposure to cobalt, and therefore the derivation of an oral chronic MRL was not possible. MRLs derived for both the inhalation and oral exposure routes for cobalt are summarized in Table 1-1 and are discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Cobalt–Inhalation

The respiratory hematological, renal and cancer endpoints are the most sensitive targets of cobalt following inhalation exposure.

Number in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively

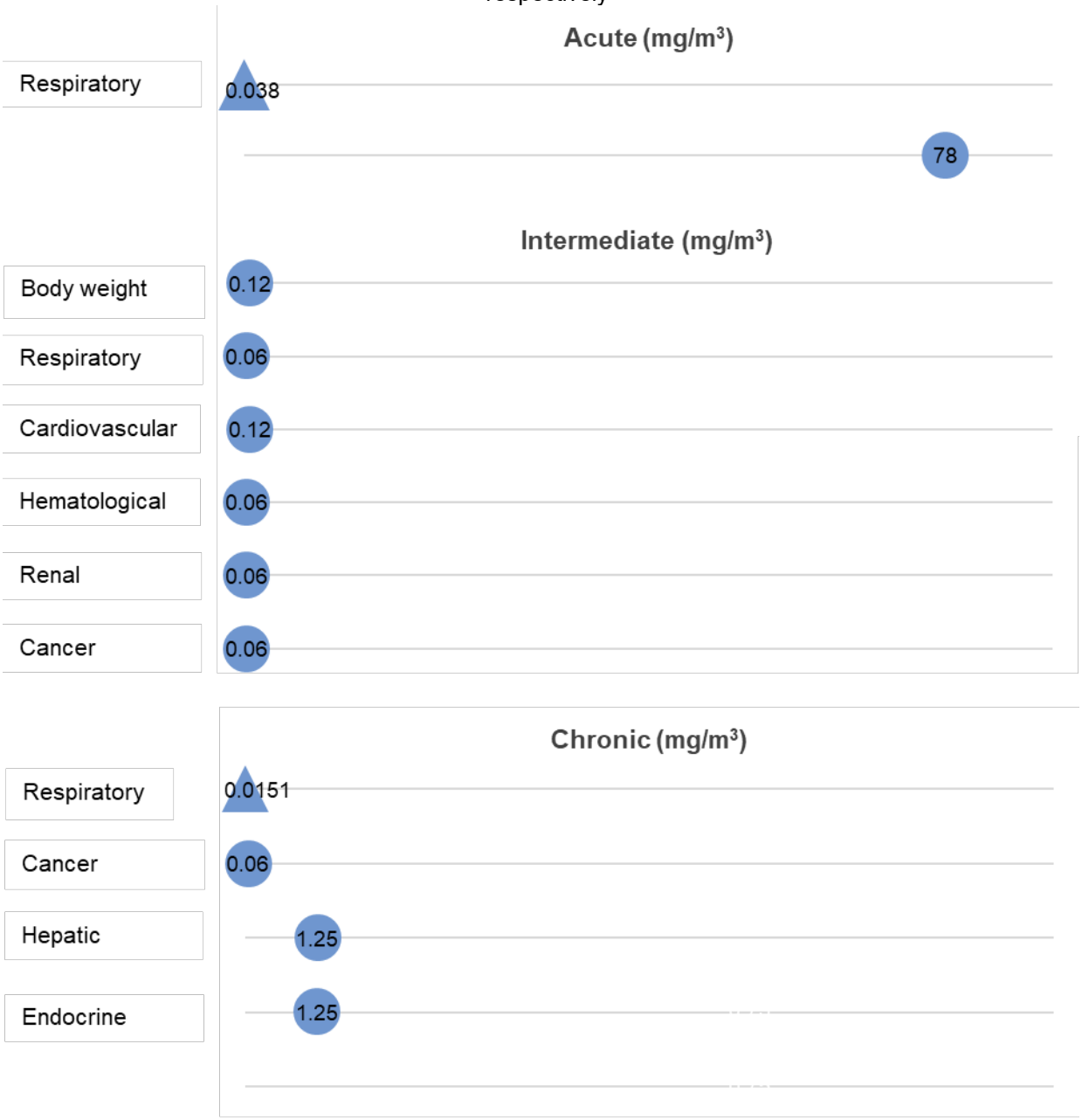


Figure 1-4. Summary of Sensitive Targets of Cobalt–Oral

The gastrointestinal, endocrine, and hematological endpoints are the most sensitive targets of cobalt following oral exposure.

Number in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.

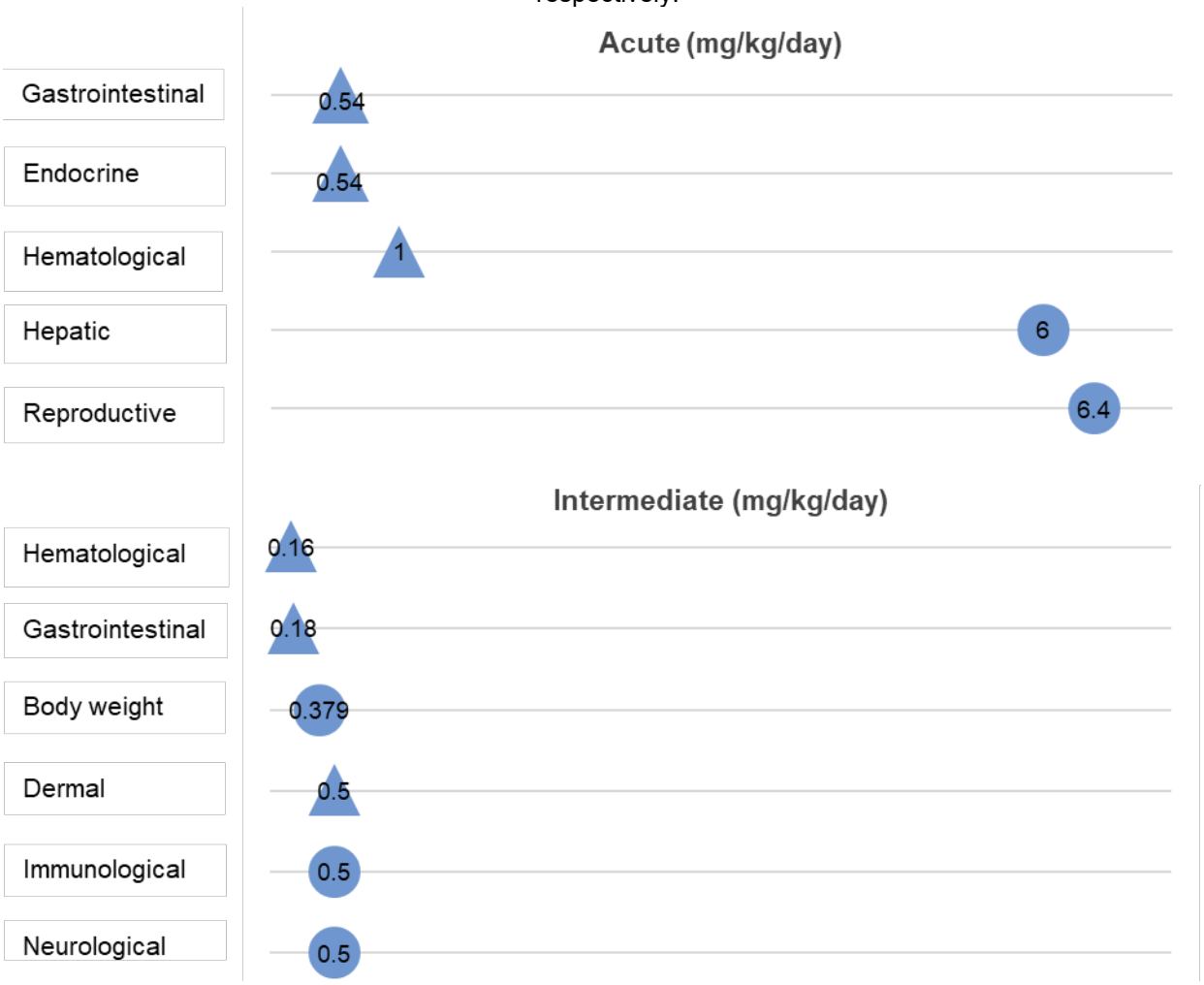


Table 1-1. Minimal Risk Levels (MRLs) for Cobalt[a]

Exposure duration	Provisional MRL	Critical effect(s)	Point of departure	Uncertainty factor	Reference
Inhalation exposure (mg Cobalt/m^3)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	**0.0001** (0.1 µg/m^3)	Reduced spirometry parameter values	NOAEL: 0.0053 (NOAEL$_{ADJ}$: 0.0013)	10	(Nemery et al. 1992)
Oral exposure (mg Cobalt/kg/day)					
Acute	**0.03**	Production of polycythemia	LOAEL: 1.0	30	(Davis and Fields 1958)
Intermediate	**0.03**	Production of polycythemia	NOAEL: 0.8	30	(Davis and Fields 1958)
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NOAEL$_{ADJ}$= adjusted from occupational to continuous exposure; polycythemia = the classification term used in cited articles, meaning absolute polycythemia only (increased hemoglobin, erythrocyte count, or hematocrit that can result from exposure to a substance)

CHAPTER 2. HEALTH EFFECTS

2.1. INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of cobalt. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to cobalt, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to cobalt was also conducted; the results of this review are presented in Appendix C.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2, and human and animal oral studies are presented in Table 2-2 and Figure 2-3; limited dermal data were identified for cobalt and are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be

classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

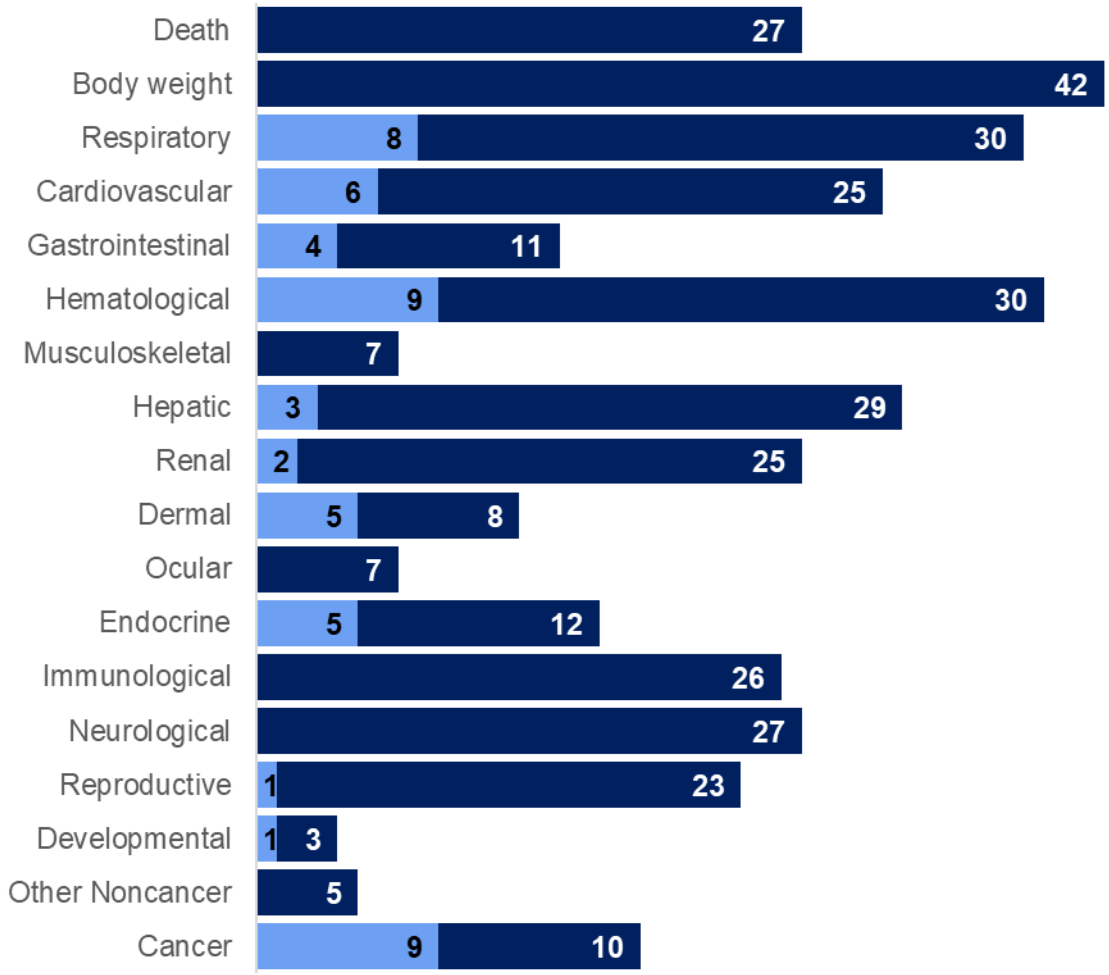
A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

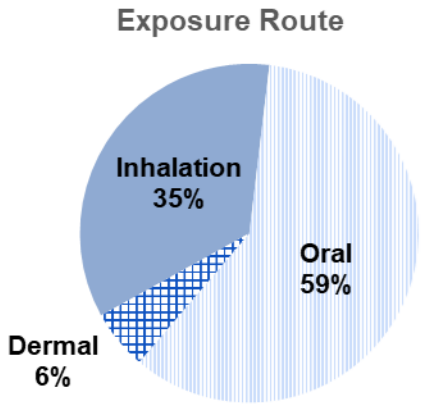
The health effects of cobalt were evaluated in laboratory animals and a few human occupational and controlled-exposure studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation and oral studies in animals. Animal data are available for each exposure route and exposure duration category except for chronic-duration oral and chronic-duration dermal exposure. The effects on body weight are those that were examined most frequently in the literature followed by respiratory and hematological effects. There are few human studies that include control groups and occupational studies that examine health effects of exposure to cobalt. In those studies, both respiratory and hematological endpoints were identified as health effects following cobalt exposure. The cobalt database includes studies of its genotoxicity.

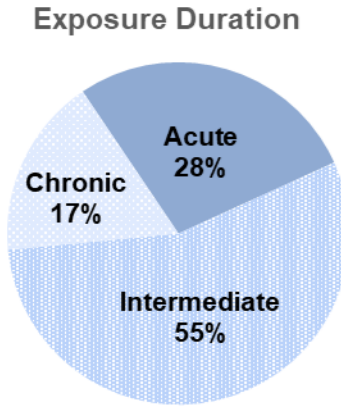
Figure 2-1. Overview of the Number of Studies Examining Cobalt Health Effects

***Most studies examined the potential body weight, hematological, and respiratory effects of cobalt.**

Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint).







*Includes studies discussed in Chapter 2. A total of 100 studies (including those finding no effect) have examined toxicity. Studies may have examined more than one endpoint for health effects.

As outlined in Chapter 1, the most sensitive effects from inhaled cobalt exposure appear to be respiratory, hematological, renal, and cancer. Meanwhile those from ingested cobalt exposure appear to be gastrointestinal, endocrine, and hematological. Overall, respiratory and hematological effects are considered the most significant from a health perspective and are detailed below. The available human toxicity studies were primarily evaluated for the respiratory and hematological endpoints including in controlled-exposure studies. Observational and controlled-exposure cohort studies and population level studies have primarily examined respiratory, cardiovascular, gastrointestinal, and hematological endpoints. Animal studies have examined all endpoints following oral and inhalation exposure to cobalt. The respiratory and hematological endpoints were the most examined in animal studies. Animal studies have also examined body weight, renal, hepatic, and reproductive effects in oral animal studies. A very limited number of animal studies examined toxicity following dermal exposure. Respiratory and hematological effects were considered the most sensitive outcomes of cobalt exposure due to the frequency at which they were reported and the relatively low doses at which these health effects were observed (0.0151 and 0.8 mg Co/m^3, respectively), as health effects were observed even at low doses, and are commonly reported in case studies. Therefore, a systematic review (Appendix C) was conducted on these endpoints. The information in those human and animal studies indicate the following regarding potential targets of cobalt toxicity:

- ***Respiratory Effects***. Human and laboratory animal studies support respiratory toxicity as a sensitive endpoint following inhalation exposure to cobalt. Inhaled cobalt in humans was absorbed in the lungs and was associated with increases in chronic phlegm and decreases in spirometric parameters (Hamzah et al. 2014; Linna et al. 2003; Sauni et al. 2010; Walters et al. 2012). Chronic inhaled cobalt exposure is associated with decreased lung function in exposed workers, as well as increased cough sputum and dyspnea (Gennart and Lauwerys 1990; Kusaka et al. 1986a). Evidence from animal studies indicates that acute-duration cobalt inhalation particulate exposure causes pulmonary irritation, dose-dependent edema, and damage in the lungs (Palmes et al. 1959). Intermediate-duration inhalation of cobalt resulted in lesions and degeneration in respiratory tract tissues (Bucher et al. 1990; NTP 1991), including a 25% increase in lung weights, tissue inflammation with infiltrates of mainly neutrophils, lymphocytes, and eosinophils (Johansson et al. 1987; Johansson et al. 1992). Chronic-duration animal exposures caused inflammation in the nose, larynx, and lung combined with emphysema and lesions in the

respiratory tract (NTP 1998, 2014; Wehner et al. 1977). These findings in animal and human studies indicate inhalation exposure to cobalt can cause respiratory toxicity.

- ***Hematological Effects***. Several studies in animals and a few human studies lend support to hematological effects being a sensitive endpoint following both inhalation and oral exposures to cobalt. Some studies have called the effects polycythemia. When addressed in this profile, polycythemia refers to absolute polycythemia, which is an increase in red cell mass from exposure to a substance, such as cobalt. This profile does not address other forms or causes of polycythemia. Absolute polycythemia, when mentioned in this profile refers to polycythemia caused by cobalt toxicity. Other causes of erythrocytosis and polycythemia that will not directly be discussed in this profile include primary polycythemia (such as polycythemia vera or familial polycythemia), secondary polycythemia (elevated serum erythropoietin [EPO] as might be seen from a deficient oxygen supply), or relative polycythemia (plasma volume contraction as associated with dehydration).
  In the study by Lantin et al. (2011), the integrated exposure index (IEI) was significantly ($P< 0.001$) correlated with mean corpuscular hemoglobin concentration (MCHC) in both univariate and multivariate regression analyses, but there was no significant relationship between the IEI and the red cell count (red cell count was not affected), even after occupational exposure to inhaled cobalt (Lantin et al. 2011). Studies in laboratory animals examined higher concentrations of inhaled cobalt and identified changes in the levels of hemoglobin, basophils, and monocytes (NTP 1991, 2014; Palmes et al. 1959). Oral exposure to cobalt and cobalt compounds in humans and animals caused an increase in levels of erythrocytes (Davis and Fields 1958; Awoyemi et al. 2017). Davis and Fields (1958) reported an increase in erythrocyte levels that returned to normal upon cessation of cobalt exposure. The animal studies corroborated the effects seen in human studies. Acute-duration oral exposure to cobalt increased red blood cells, hematocrit, and hemoglobin (Awoyemi et al. 2017; Domingo and Llobet 1984; Shrivastava et al. 2010). Intermediate-duration oral exposure to cobalt also had effects in animals (Brewer 1940; Bryan and Bright 1973; Chetty et al. 1979; Corrier et al. 1985; Krasovskii and Fridlyand 1971) that were similar to those seen in the acute-duration studies. Pregnant dams exposed to cobalt orally showed unspecified changes in levels of hemoglobin and hematopoiesis (Gluhcheva et al. 2014). These findings in animal and human studies indicate oral exposure to cobalt can cause hematological toxicity.

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
ACUTE EXPOSURE									
Kusaka et al. 1986									**Cobalt Metal**
1	HUMAN 15M	6 hours	0, 0.038	CS OF	Resp		0.038		Non-dose related decrease in FVC
Palmes et al. 1959									**Cobalt Hydrocarbonyl**
2	RAT (Albino) 5M	30 minutes/day, Once	0, 7, 26, 47, 68, 78, 118, 191, 215, 222, 408	CS LE	Death			78	3/5 dead
					Resp	7	26	90	LOAEL: Edema (not otherwise described) observed at 26 mg/m^3 SLOAEL: Severe Edema (not otherwise described) observed at 90 mg/m^3
INTERMEDIATE EXPOSURE									
NTP 1991									**Cobalt Sulfate Heptahydrate**
3	RAT (F344/N) 10M, 10F	13 weeks, 5 days/week, 7 hours/day	0, 0.06, 0.21, 0.61, 2.09, 6.29	BC BI BW CS GN HE HP IX LE NX OF OW	Bd wt	6.29 F			
						2.09 M	6.29 M		17% decrease in body weight
					Resp	0.06 F	0.21 F		14% increase in lung weight in females
							0.06 M		7% increase in relative lung weight in males
					Cardio	6.29			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Hemato	0.61 F	2.09 F		Polycythemia seen in female rats; the platelet count decreased in females (not otherwise described)
						0.21 M	0.61 M		Increases in erythrocytes, mean hemoglobin concentration, and hematocrit in male rats
					Renal	6.29 F			
							0.06 M		6% increase in kidney weight; increase in epithelial cells in urine (not otherwise described)
					Ocular	6.29			
					Endocr	0.61 F	2.09 F		Low T3 (not otherwise described)
						2.09 M	6.29 M		Low TSH (not otherwise described)
					Immuno	6.29			
					Neuro	6.29			
					Repro	6.29			
					Cancer			0.06 F	7/10 rats showed chronic inflammation of larynx and squamous metaplasia in the larynx (respiratory system)
								0.06 M	9/10 rats showed chronic inflammation of larynx and squamous metaplasia in the larynx (respiratory system)

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
NTP 1991									**Cobalt Sulfate Heptahydrate**
4	RAT (F344/N) 5M,5F	16 days, 5 days/week, 6 hour/day	0, 0.02, 0.1, 0.99, 10.5, 41.72	BC BI BW CS GN HE HP IX LE NX OF OW	Death			41.72 F	5/5 died
								10.5 M	2/5 died
					Bd wt	0.99 F		10.5 F	22% decrease in bodyweight
						0.99 M		10.5 M	47% decrease in bodyweight
					Resp	0.99	10.5		Degeneration of olfactory epithelium, hyperplasia and squamous metaplasia in the epithelium of respiratory turbinates; inflammation in the nose and lungs (not otherwise described)
					Cardio	10.5			
					Hepatic		41.72		Congestion and necrosis of liver (not otherwise described)
					Ocular	0.99	10.5		Chromodacryorrhea (not otherwise described)
					Immuno	0.99	10.5		Necrosis of thymus and decrease in weights for both males and females (not otherwise described)
					Neuro	0.99	10.5		Congestion of vessels in brain and hypoactivity (not otherwise described)
					Repro	10.5 F			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
						0.99 M	10.5 M		Atrophy in testes- decrease in number of cells in the seminiferous tubules and atypical germinal epithelial cells in the epididymal ducts (not otherwise described)
NTP 2014									**Cobalt Metal**
5	RAT (F344/N) 5M, 5F	16 days, 5 days/week, 6 hours + T90 (12 minutes)/day	0, 2.5, 5, 10, 20, 40	BC BW CS GN HP LE OW UR	Death			20	5/5 males and 3/5 females died
					Bd wt	5 F	10 F	20 F	LOAEL: 12% less body weight than controls SLOAEL: 45% less body weight than controls
						5 M		20 M	20% less body weight than controls
					Resp		2.5 F	20 F	LOAEL: Significantly increased incidence of cytoplasmic vacuolization of bronchiole epithelium, and atrophy and necrosis of olfactory epithelium SLOAEL: respiratory epithelium necrosis

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
							2.5 M	20 M	LOAEL: Significantly increased incidence of cytoplasmic vacuolization of bronchiole epithelium, and atrophy of olfactory epithelium SLOAEL: abnormal breathing; increased incidence of lung hemorrhage and acute inflammation
					Cardio	20 F			
						10 M			
					Hepatic	10 F	20 F		Significant 15.9% increase in relative liver weight (in 2/5 rats) compared to controls
							2.5 M		Significant 12.8% decrease in relative liver weight compared to controls
					Renal	10 F	20 F		Significant 291% increase in urinary creatinine levels and 23.5% increase in relative kidney weight, compared to controls
						5 M	10 M		Significant 7.5% decrease of relative left kidney weight and 80% increase in urinary creatinine, compared to controls
					Endocr	20 F			
						10 M			
					Immuno	10 F	20 F		64% decrease in relative thymus weight
						10 M			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Neuro	20 F	40 F		Lethargy
						10 M	20 M		Lethargy
					Repro	10 M			
NTP 2014									**Cobalt Metal**
6	RAT (F344/N) 10M, 10F	14 weeks, 5 days/week, 6 hours + T90 (12 minutes)/day	0, 0.625, 1.25, 2.5, 5	BW CS GN HP OW RX	Bd wt	5			
					Resp			0.63	Increased incidence of chronic active inflammation in lung, pulmonary alveolar proteinosis, and increased relative lung weight (16-22%), all compared to controls
					Cardio	5			
					Gastro	5			
					Hemato	0.63 F	1.25 F		9% increase in hematocrit, hemoglobin, and erythrocyte levels, compared to controls
							0.63 M		4.5% increase in hemoglobin levels and 5.2% increase in erythrocytes, compared to controls
					Musc/skel	5			
					Hepatic	5			
					Renal	2.5 F	5 F		Significant 12.7% increase in relative right kidney weight, compared to controls

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
						2.5 M	5 M		23.5% increase in urinary creatinine by week 14 compared to controls
					Dermal	5			
					Ocular	5			
					Endocr	5			
					Immuno	5			
					Neuro	5			
					Repro	5 F			
						1.25 M		2.5 M	Significant decrease in % sperm motility by 5.6% and 10.1% increase in relative weight of right testis, all compared to controls
Palmes et al. 1959									**Cobalt Hydrocarbonyl**
7	RAT (Albino) 34-57 M	3 months, 5 days/week, 6 hours/day	0, 9	BW CS GN HE HP UR	Bd wt	9			
					Resp		9		Lung inflammation (not otherwise described)
					Hemato		9		10% increase in hemoglobin
NTP 1991									**Cobalt Sulfate Heptahydrate**
8	MOUSE (B6C3F1) 5M, 5F	16 days, 5 days/week, 6 hour/day	0, 0.02, 0.1, 0.99, 10.5, 41.72	BC BI BW CS GN HE HP IX LE NX OF OW	Death			10.5	4/5 male and 1/5 female mice died
					Bd wt	0.99		10.5	33% and 20% decrease in body weight in males and females, respectively

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Resp	0.1			
								0.99 F	Gray discoloration of lungs and fluid in larynx and trachea; 25% increase in relative lung weight; degeneration of olfactory epithelium
								0.99 M	Gray discoloration of lungs and fluid in larynx and trachea; 22% increase in relative lung weight; degeneration of olfactory epithelium
					Cardio	41.72			
					Gastro	41.72			
					Musc/skel	41.72			
					Hepatic	10.5 F			
						0.99 M	10.5 M		Necrosis of hepatocytes (not otherwise described)
					Renal	10.5			
					Dermal	10.5			
					Ocular	10.5	10.5		Chromodacryorrhea was observed (not otherwise described)
					Endocr	10.5			
					Immuno		10.5 M		Decrease in relative thymus weight (not otherwise described)
					Neuro	0.99	10.5		Hypoactivity and congestion of vessels in brain (not otherwise described)
					Repro	10.5			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Cancer			10.5	Hyperplasia of the squamous epithelium in the larynx (not otherwise described)
NTP 1991									**Cobalt Sulfate Heptahydrate**
9	MOUSE (B6C3F1) 10M, 10F	13 weeks, 5 days/week, 7 hours/day	0, 0.06, 0.21, 0.61, 2.09, 6.29	BC BI BW CS GN HE HP IX LE NX OF OW	Death			6.29 M	2/10 died
					Bd wt	2.09			
								6.29 F	22% decrease in body weight
							6.29 M		14% decrease in body weight
					Resp	0.06 F		0.21 F	9/10 showed histiocytic infiltrates
								0.06 M	10/10 showed histiocytic infiltrates
					Gastro	6.29			
					Hemato		0.06 F		5% decrease in hemoglobin and 3% decrease in hematocrit
						0.06 M	0.21 M		4% decrease in platelet count
					Musc/skel	6.29			
					Hepatic	6.29			
					Renal	6.29			
					Dermal	6.29			
					Immuno	2.09	6.29		Lymph node hyperplasia (not otherwise described)
					Repro	2.09 F		6.29 F	Increased length estrous cycle in females by 19%
								0.61 M	Decreased sperm motility by 79%

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Cancer			0.06	Larynx metaplasia in 7/10 male and 8/10 female mice
NTP 2014									**Cobalt Metal**
10	MOUSE (B6C3F1) 5M, 5F	17 days, 5 days/week, 6 hours + T90 (12 minutes)/day	0, 2.5, 5, 10, 20, 40	BW GN HP LE OW	Death			40	4/10 died
					Bd wt	10 F	20 F	40 F	LOAEL: 16.3% less body weight compared to controls SLOAEL: 37.5% less body weight than controls
						20 M		40 M	26.5% less body weight than controls
					Resp			2.5	Increased incidence of cytoplasmic vacuolization of bronchiole and respiratory epithelium, and atrophy of olfactory epithelium
					Cardio	20 F	40 F		Significant 39% increase of relative heart weight compared to controls
						40 M			
					Hepatic		2.5		Significant 10%-11% decrease in relative liver weight
					Renal	20			
					Endocr	40			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Immuno	2.5	5		Significantly increased incidence of minimal to moderate alveolar histiocytic cellular infiltration (accumulation of macrophages within the alveolar spaces and septa)
					Neuro	5 F	10 F		Lethargy
						10 M	20 M		Lethargy
					Repro	40 M			
NTP 2014									**Cobalt Metal**
11	MOUSE (B6C3F1) 10M, 9-10F	14 weeks, 5 days/week, 6 hours + T90 (12 minutes)/day	0, 0.625, 1.25, 2.5, 5, 10	BW CS GN HP OW RX	Bd wt	5	10		13%-14% decrease in body weight compared to controls
					Resp			0.63	Cytoplasmic vacuolization of bronchiole epithelium and squamous metaplasia of larynx in all mice
					Cardio	10			
					Gastro	10			
					Hemato	5 F	10 F		Significant 4.7% increase in erythrocytes compared to controls
						5 M	10 M		Significant 3% increase in hemoglobin and erythrocyte levels compared to controls
					Musc/skel	10			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Hepatic	1.25 F	2.5 F		Significant 8.4% decrease of relative liver weight
						5 M	10 M		Significant 14.2% decrease of relative liver weight
					Renal	2.5	5		Significant 7.7%-12.4% decrease in relative kidney weight compared to controls
					Dermal	10			
					Ocular	10			
					Endocr	10			
					Immuno		0.63		Alveolar histiocytic cellular infiltration characterized by the presence of low to moderate numbers of histiocytes (macrophages)
					Neuro	10			
					Repro	5 F	10 F		Significantly longer estrous cycle
						1.25 M	2.5 M		Significant 4.7% decrease in % sperm motility compared to controls
Camner et al. 1993									**Cobalt Chloride**
12	GN PIG (Hartley) 6 F	6 hours/day, 7 days/week, 2 weeks	0, 2.4	BI CS OF	Resp			2.4	20% increase in lung weight, 53% increased retention of lavage fluid
Palmes et al. 1959									**Cobalt Hydrocarbonyl**
13	GN PIG 6-32M	3 months, 5 days/week, 6 hours/day	0, 9	CS GN HE HP LE UR	Hemato		9		5% increase in hemoglobin

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
Johansson et al. 1987									**Cobalt Metal**
14	RABBIT (NS) 8M	17 weeks, 5 days/week, 6 hours/day	0, 0.4, 2.0	CS HP OF OW	Resp		0.4	2	LOAEL: Moderate inflammation observed in lungs; accumulation of macrophages in lungs (not otherwise described) SLOAEL: Severe lung inflammation and accumulation of macrophages (not otherwise described); increase in weight of lower lung lobe by 25%
Johansson et al. 1991									**Cobalt Chloride**
15	RABBIT (NS) 8 M	4 months, 5 days/week, 6 hours/day	0, 0.5	BI CS GN HP	Resp	0.5			
Johansson et al. 1992									**Cobalt Chloride**
16	RABBIT (NS) 8 M	4 months, 5 days/week, 6 hours/day	0, 0.6	BI CS GN HP	Resp		0.6		Histologic alterations in pulmonary tissue; altered BAL parameters; 22% decrease in macrophages
Kerfoot 1975									**Cobalt Metal**
17	PIG 5NS	3 months, 5 days/week, 6 hour/day	0, 0.115, 0.991	GN HP CS UR	Bd wt		0.12		16% decrease in body weight
					Resp		0.12		29% decrease in specific compliance (a metric of mechanical ventilation)
					Cardio		0.12		14% increase in heartrate, 38% decrease in QRS amplitude

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Hemato	0.99			
					Hepatic	0.99			
					Renal	0.99			
					Immuno	0.99			
CHRONIC EXPOSURE									
Deng et al. 1991									**Cobalt Metal**
18	HUMAN 362	Occupational (occupational)	0, 0.0175	CS	Resp	0.02			
Kusaka et al. 1986									**Cobalt Metal**
19	HUMAN	3 years (occupational)	0, 0.85, 0.126	CS OF	Resp	0.09	0.13		2.7% decrease in FEV1% in exposed workers, suggestive of bronchial obstruction
Nemery et al. 1992									**Cobalt Metal**
20	HUMAN 212 M 41 F	Occupational (occupational)	0, 0.0053, 0.0151	CS OF UR	Resp	0.0053[b]	0.0151		Decreased FEV1(5%) and FVC (5%); increased cough (11/91), wheezing (4/91), and upper airway irritation (40/91) observed in the subjects
NTP 1998									**Cobalt Sulfate Heptahydrate**
21	RAT (Fischer-344) 50M, 50F	105 weeks, 5 days/week, 6 hours/day	0, 0.06, 0.21, 0.63	BW CS GN HP LE OW	Bd wt	0.63			
					Resp	0.06	0.21		Alveolar inflammation and lung lesions; metaplasia in the nose and epiglottis observed in 50/50 female and 49/50 male rats (not otherwise described)

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Cancer			0.06 F	Alveolar/bronchiolar neoplasms; hyperplasia in the adrenal medulla in 23/50 rats
								0.06 M	Alveolar/bronchiolar neoplasms
NTP 2014									**Cobalt Metal**
22	RAT (F344/N) 50M, 50F	105 weeks, 5 days/week, 6 hours + T90 (12 minutes)/day	0, 1.25, 2.5, 5	BW GN HP	Death			2.5 F	Decreased survivability compared to controls
					Bd wt	1.25 F	2.5 F	5 F	LOAEL: 11.6% less mean body weight than controls by exposure weeks 53-103 SLOAEL: 21.5% less mean body weight compared to controls by exposure weeks 53-103
						2.5 M		5 M	22.7% less mean body weight compared to controls by exposure weeks 53-103
					Resp			1.25	Significantly increased incidence of lung neoplasms and nonneoplastic lesions of lungs and nose; including hyperplasia of alveolar and bronchiole epithelium, chronic active inflammation (lung and nose), metaplasia and atrophy of olfactory epithelium
					Cardio	5			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Gastro	5			
					Musc/skel	5			
					Hepatic	2.5 F	5 F		Increased incidence of basophilic focus (33/50 rats) compared to controls (16/50)
							1.25 M		Increased incidence of basophilic focus (17/50 rats) compared to controls (5/50 rats)
					Renal	5			
					Dermal	5			
					Ocular	5			
					Endocr		1.25 F	2.5 F	LOAEL: Increased incidence (27/50) of medullary hyperplasia in the adrenal gland compared to controls (12/50) SLOAEL: Increased incidence (8/50 rats) of bilateral benign pheochromocytoma compared to controls (2/50 rats)
								1.25 M	Significantly increased incidence (13/50) of bilateral benign pheochromocytoma, compared to controls (4/50)
					Immuno	2.5 F	5 F		Accumulation of macrophages around the alveolar/bronchiolar neoplasms
						5 M			
					Neuro	5			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Repro	5 F			
						1.25 M		2.5 M	Increased incidence of testicular infarction (12/50 rats) compared to controls (1/50); unilateral with complete effacement of the parenchyma due to necrosis
					Cancer			1.25 F	Significantly increased incidence of mononuclear cell leukemia compared to controls (adjusted incidence rate: 62.4% in exposed, 35.7% in controls)
NTP 1998									**Cobalt Sulfate Heptahydrate**
23	MOUSE (B6C3F1) 50 M 50 F	105 weeks, 5 days/week, 6 hours/day	0, 0.06, 0.21, 0.63	BW CS GN HP LE OW	Bd wt	0.63			
					Resp		0.06		Non-neoplastic lesions on nose and larynx in 37 males and 45 females
					Hepatic	0.63			
					Endocr	0.63			
					Cancer			0.06 F	Combined alveolar/bronchiolar adenoma/carcinoma in 14/50 mice
								0.06 M	Combined alveolar/bronchiolar adenoma/carcinoma in 7/50

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
NTP 2014									**Cobalt Metal**
24	MOUSE (B6C3F1) 50M, 50F	105 weeks, 5 days/week, 6 hours + T90 (12 minutes)/day	0, 1.25, 2.5, 5		Death			2.5 M	Significantly less survival probability compared to controls
					Bd wt	2.5 F		5 F	25% less mean bodyweight than controls by weeks 53-103
							5 M		11.3% less mean body weight than controls by weeks 53-103
					Resp			1.25	Increased incidence of lung neoplasms and neoplastic lesions in the lung, nose, larynx and trachea, compared to controls. This includes hyperplasia and cytoplasmic vacuolization of alveolar/bronchiolar epithelium, alveolar/bronchiolar carcinoma, atrophy and hyperplasia of olfactory epithelium, and turbinate atrophy
					Cardio	5			
					Gastro	5			
					Musc/skel	5			
					Hepatic	5			
					Renal	5			
					Dermal	5			
					Ocular	5			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects
					Endocr	5			
					Immuno	2.5	5		Accumulations of small histiocyte/macrophage infiltrates aggregated adjacent to alveolar/bronchiolar neoplasms
					Neuro	5			
					Repro	5 F			
						2.5 M		5 M	Increased incidence (21/50 mice) of minimal to mild germinal epithelium degradation compared to controls (9/50 mice)
					Cancer			1.25	Increased rate of alveolar/bronchiolar carcinoma, multiple in exposed mice compared to controls (Adjusted rated in exposed: 79.4% in males, 53.8% in females; adjusted rates in controls: 22.8% in males, 11.3% in females)
Wehner et al. 1977									**Cobalt Oxide**
25	HAMSTER (ENG:ELA) 51M	Lifetime, 5 days/week, 7 hours/day	0,7.9	BW CS LE OF	Bd wt	7.9			
					Resp			7.9	Lung Inflammation and emphysema observed (not otherwise described)
					Other noncancer	7.9			

Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Effects

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a chronic inhalation minimal risk level (MRL) of 0.0001 mg/m^3; concentration adjusted for intermittent exposure and divided by an uncertainty factor of 10 (for human variability).

Studies listed in the table could potentially have examined more than one endpoint.

BC = serum (blood) chemistry; BI = biochemical changes; BW or bd wt = body weight; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FVC = Forced vital capacity; Gastro = gastrointestinal; GN = gross necropsy; HE = hematological; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = Musculo/skeletal; Neuro = neurological; NOAEL = no-observed-effect-level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; Resp = respiratory; T3 = Triiodothyronine; TSH = Thyroid-stimulating hormone; UR = urinalysis; polycythemia = author reported term associated with increased hemoglobin or erythrocyte count; RX = reproductive function; UR = urinalysis; (W) = water; WI = water intake

Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Acute (≤14 days)

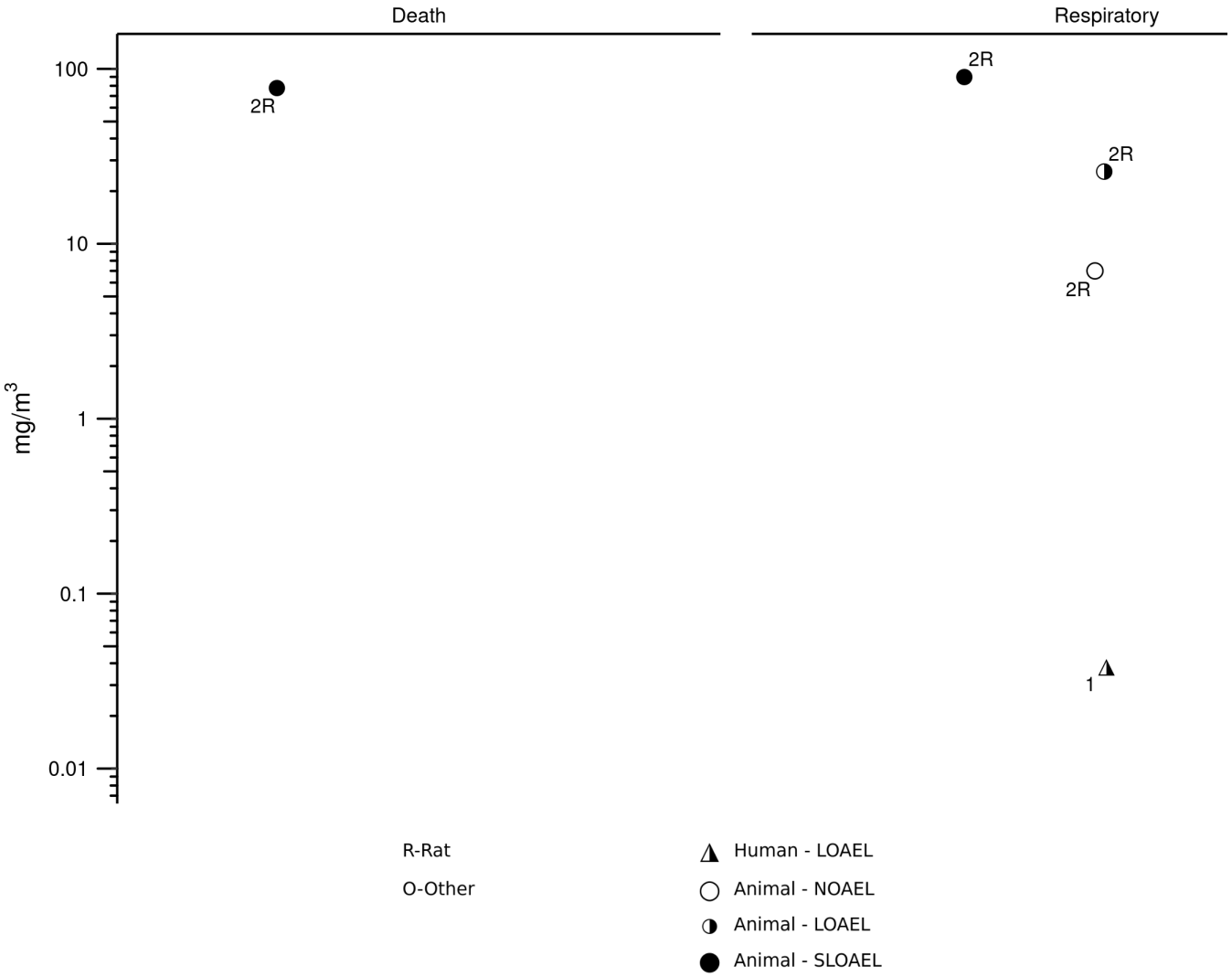


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Intermediate (15-364 days)

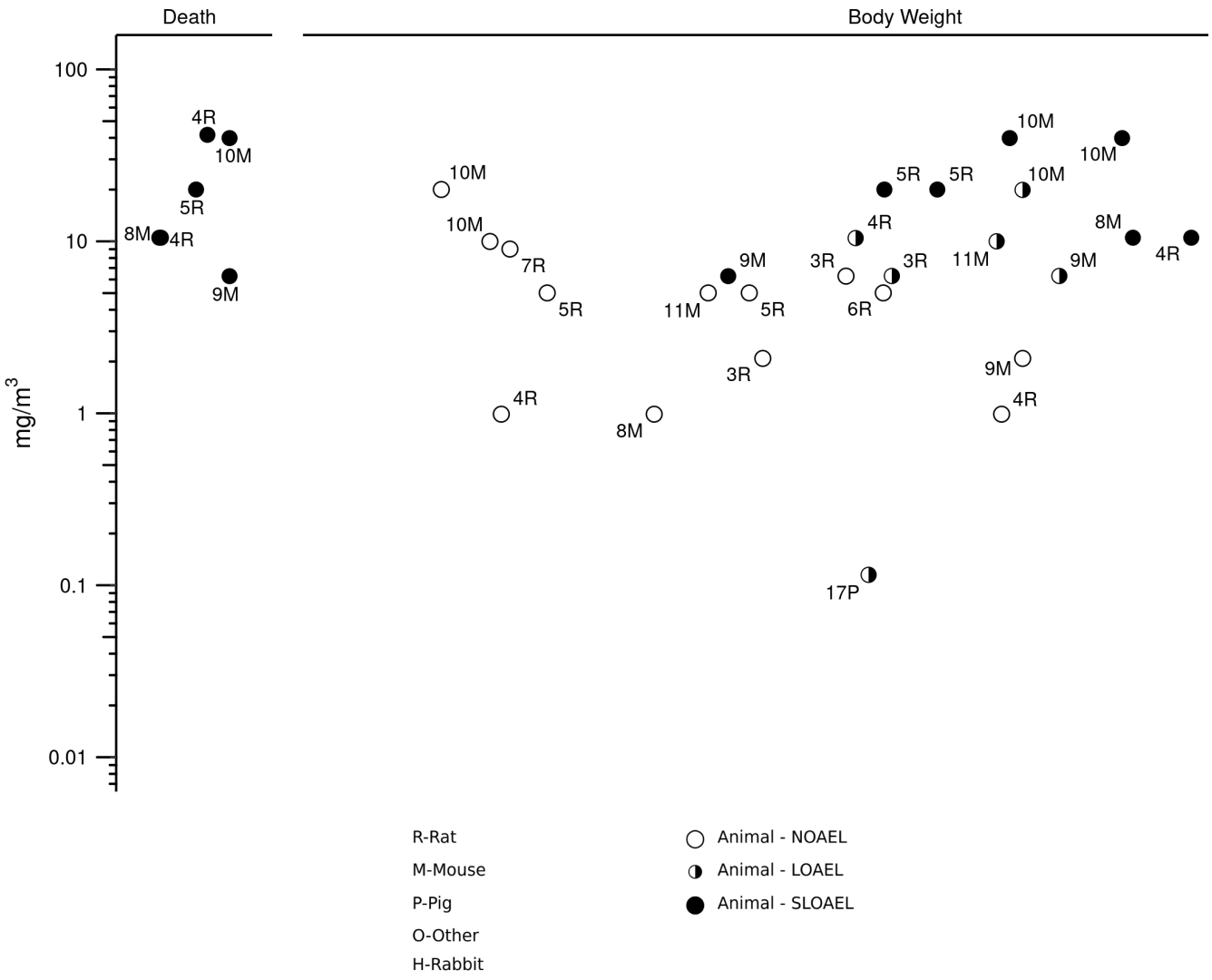


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Intermediate (15-364 days)

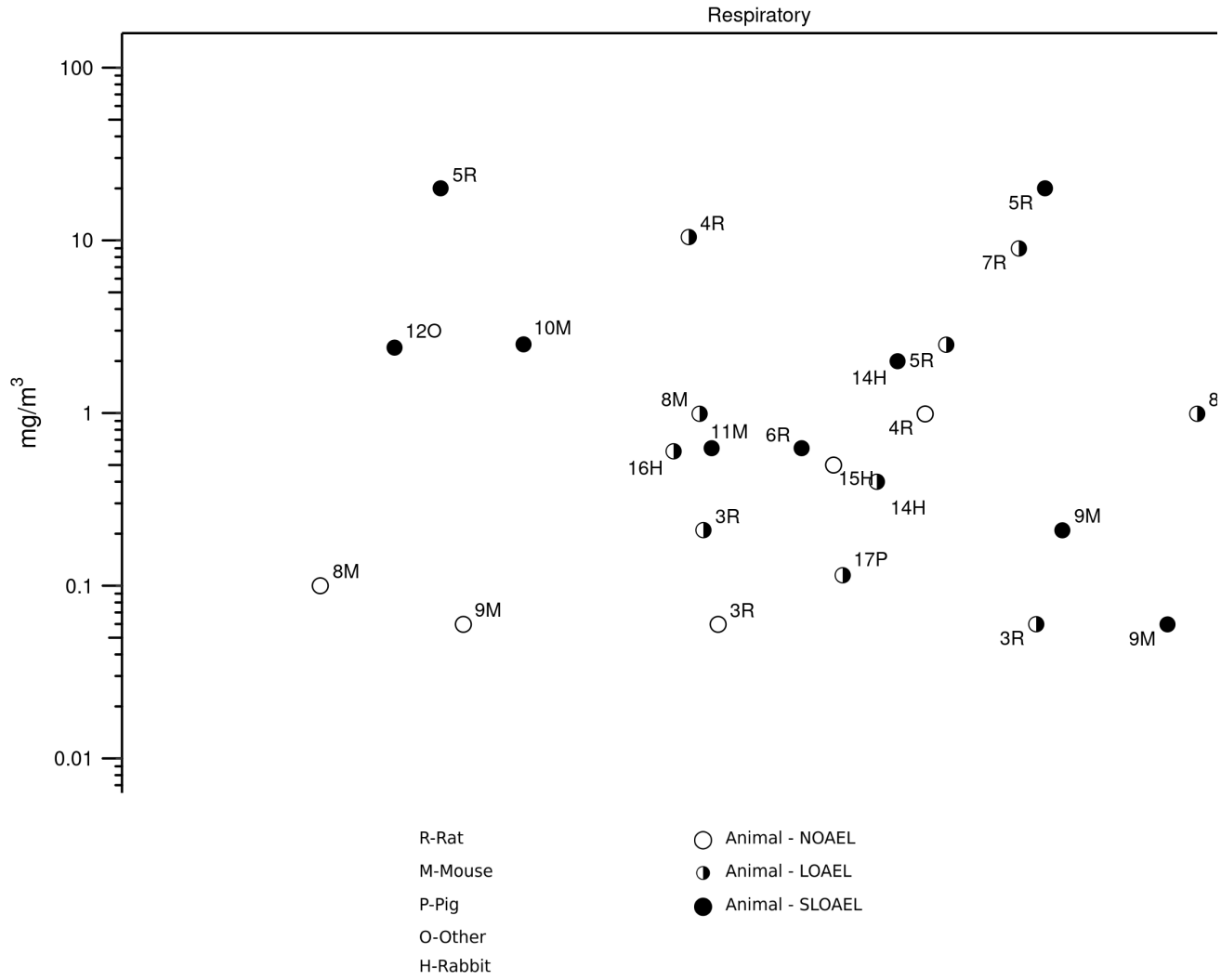


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Intermediate (15-364 days)

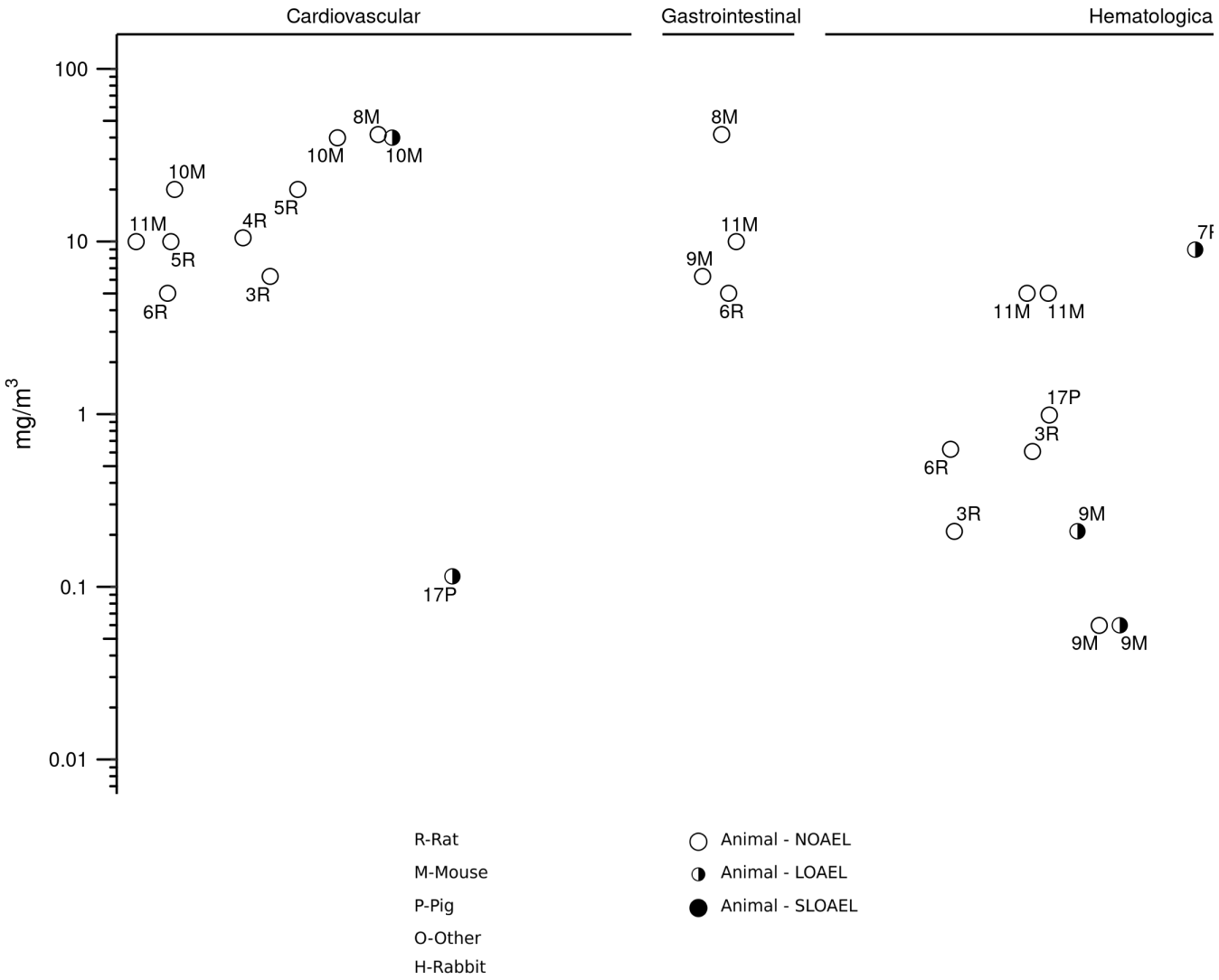


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Intermediate (15-364 days)

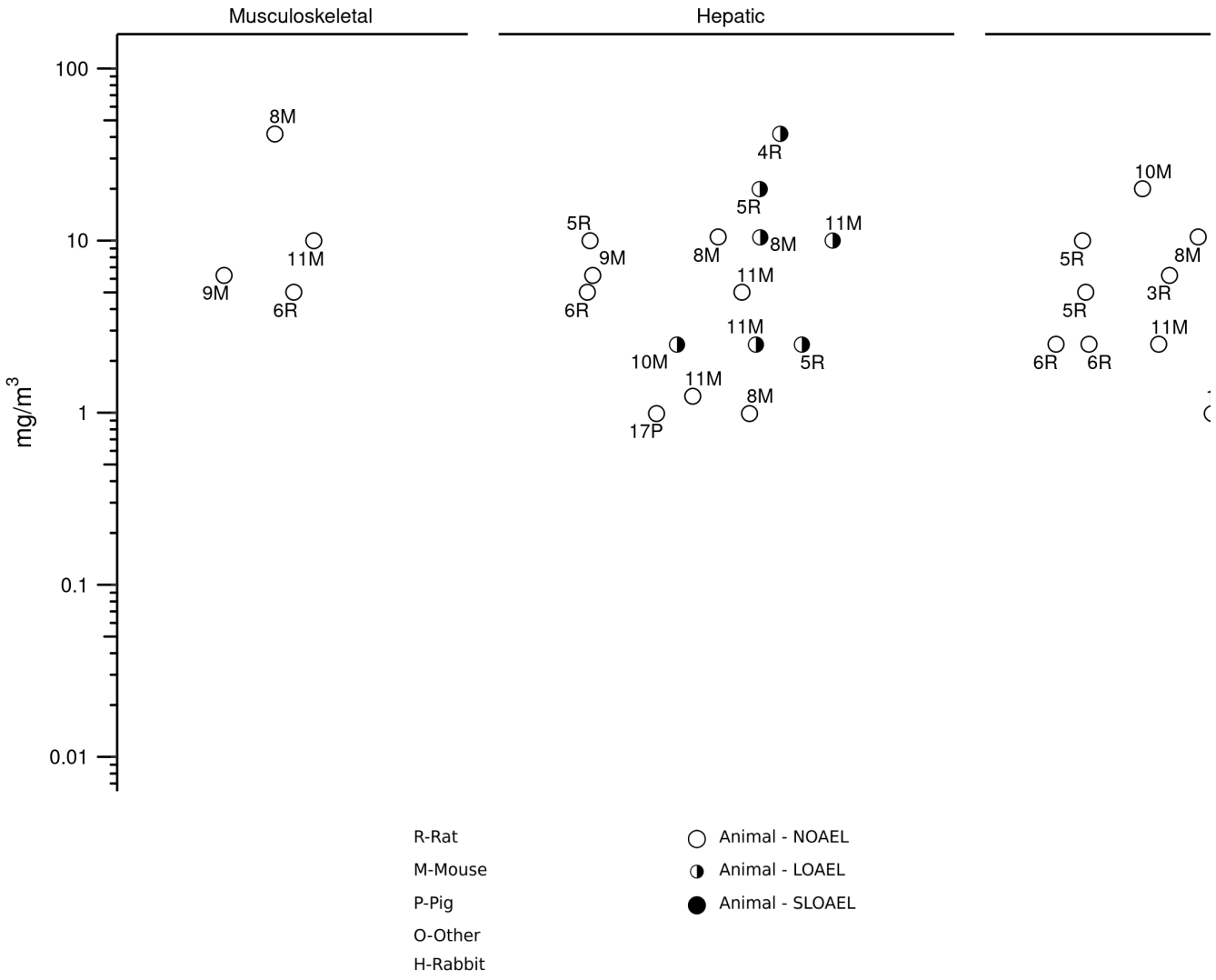


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Intermediate (15-364 days)

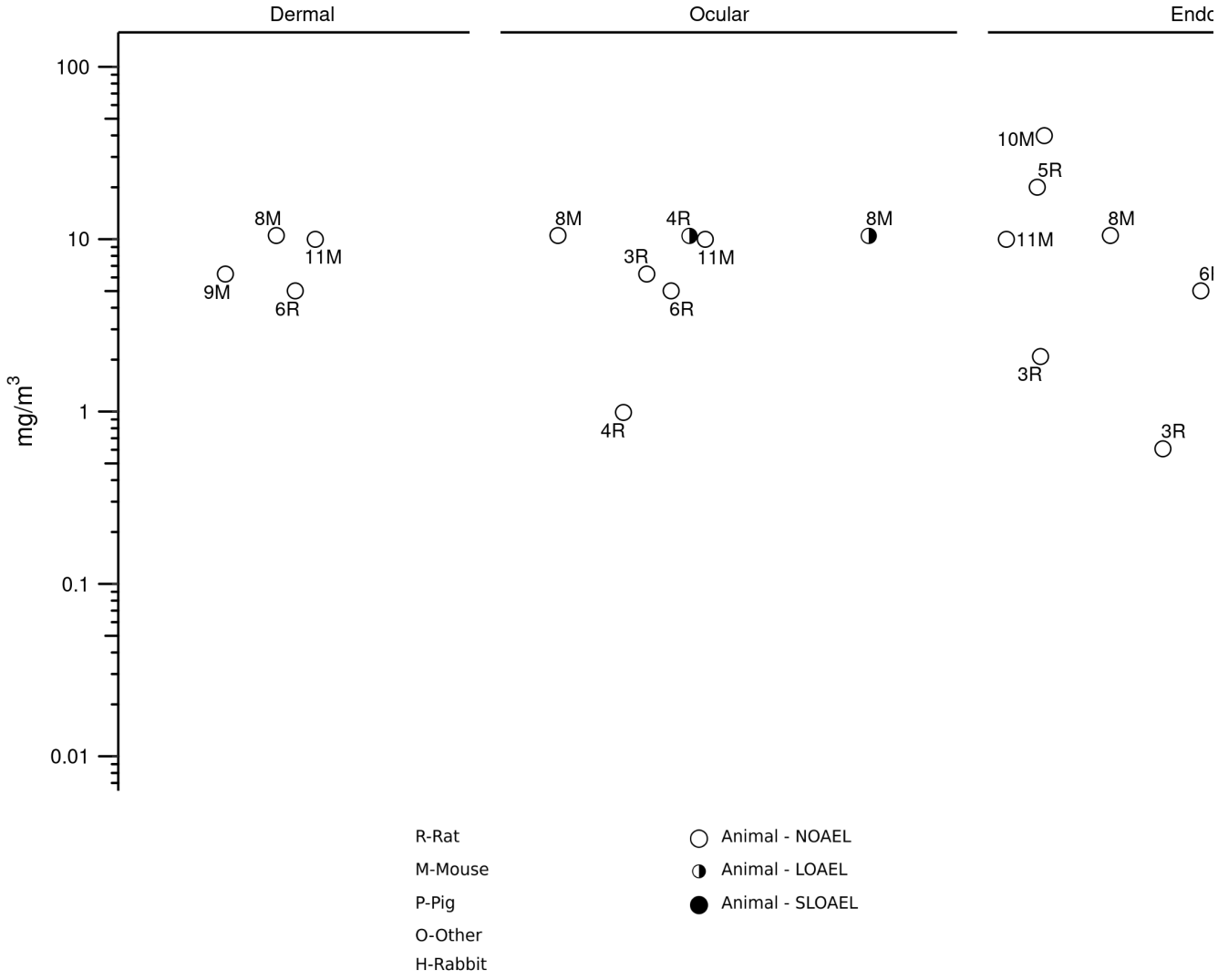


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Intermediate (15-364 days)

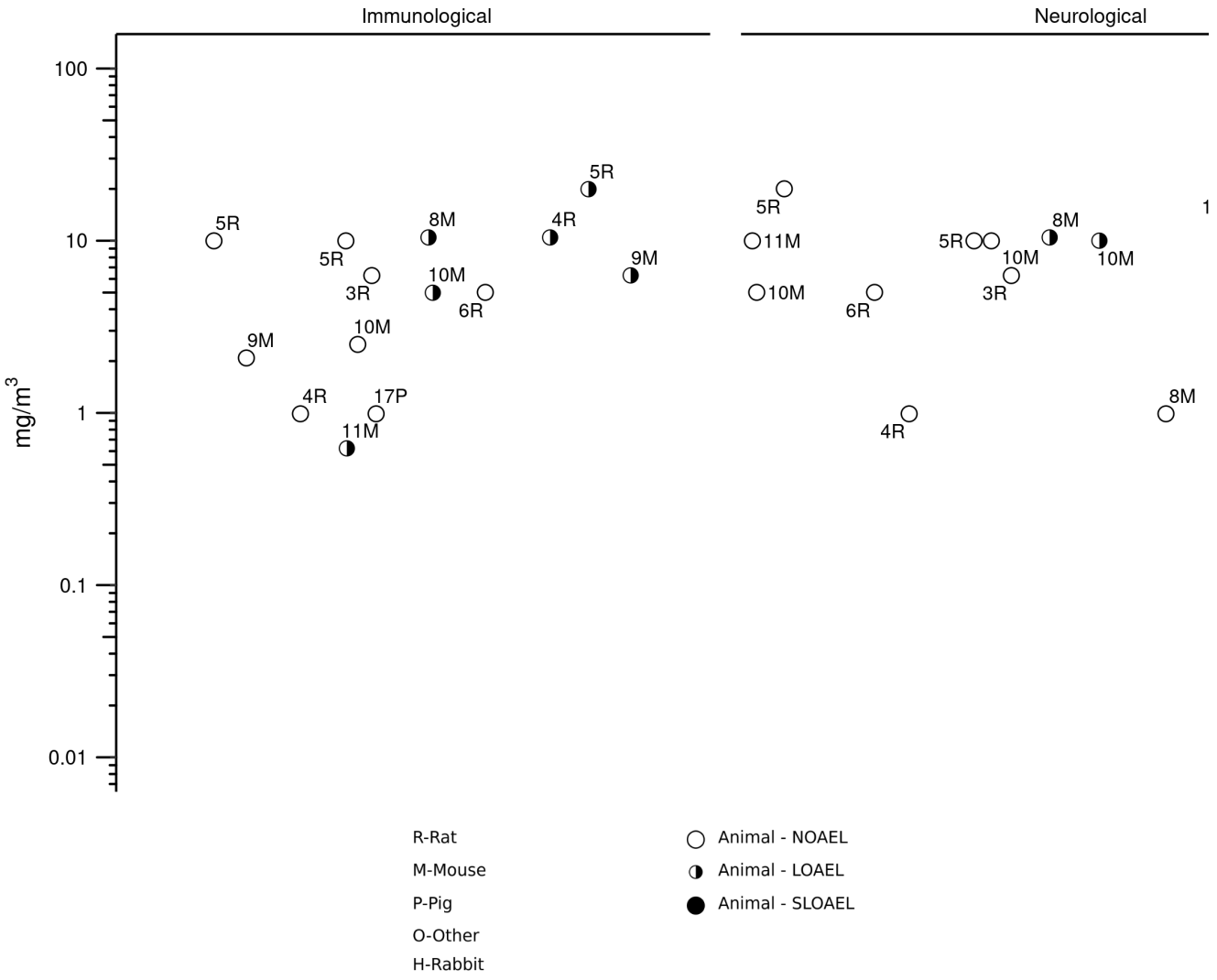


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Intermediate (15-364 days)

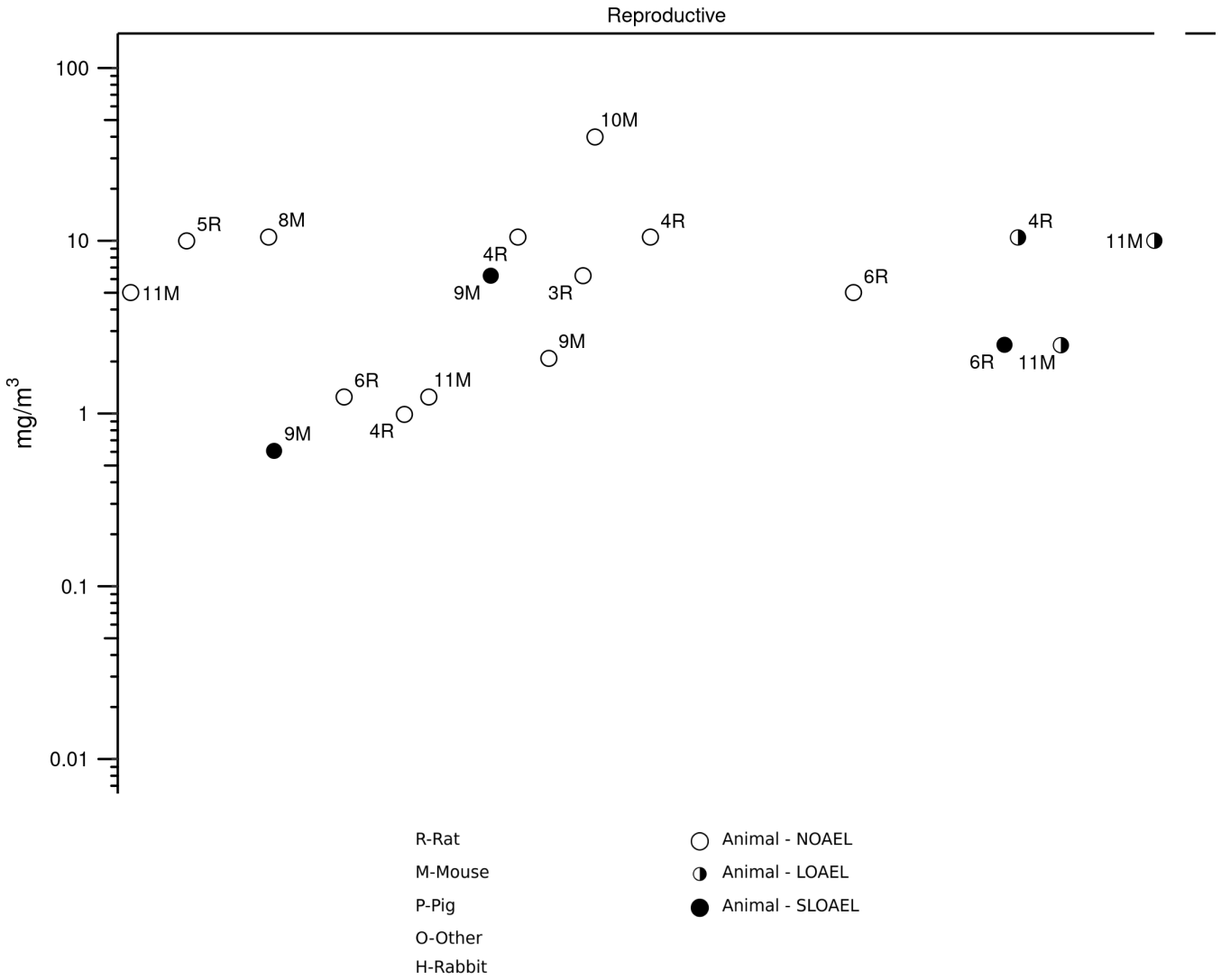


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Chronic (≥365 days)

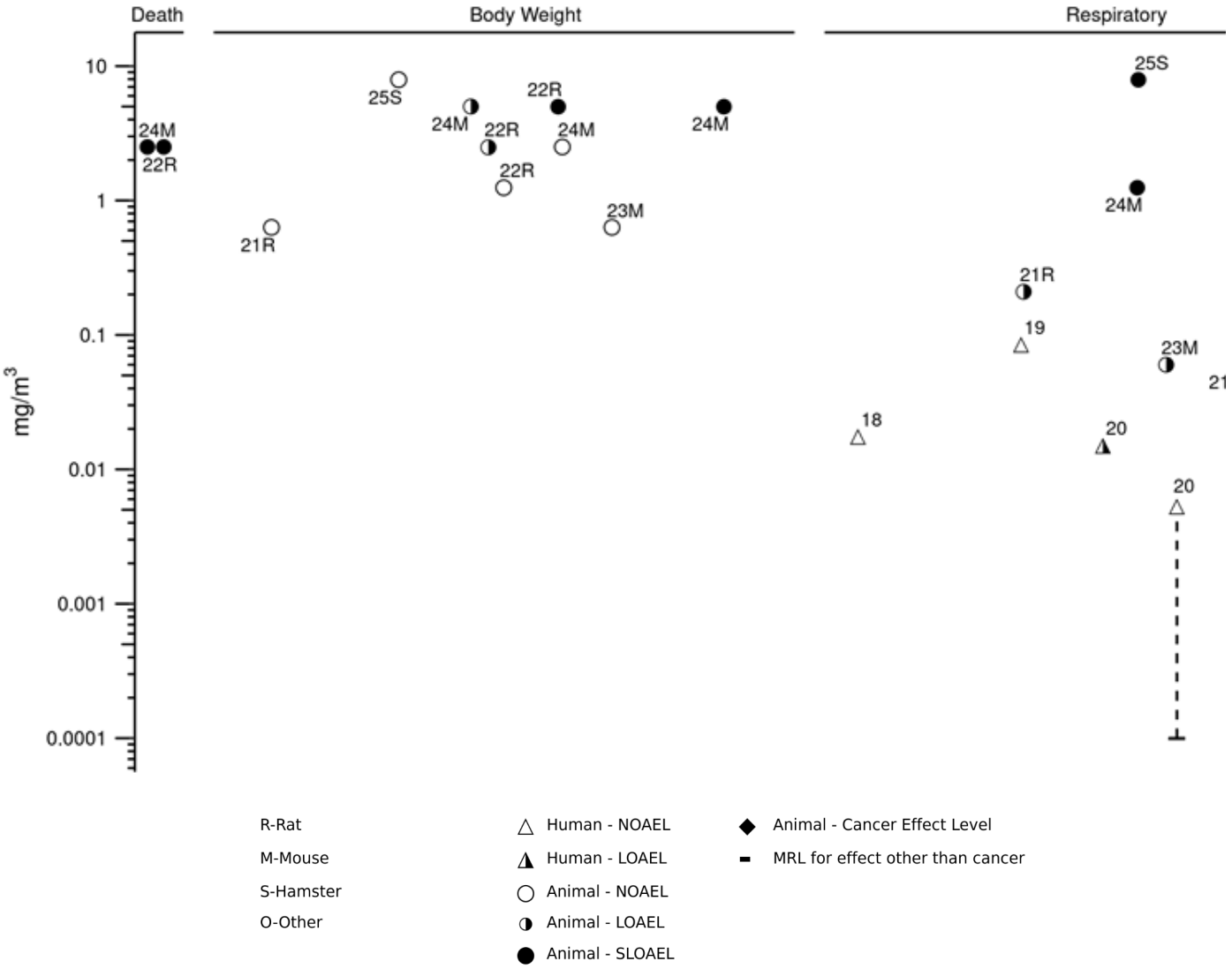


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Chronic (≥365 days)

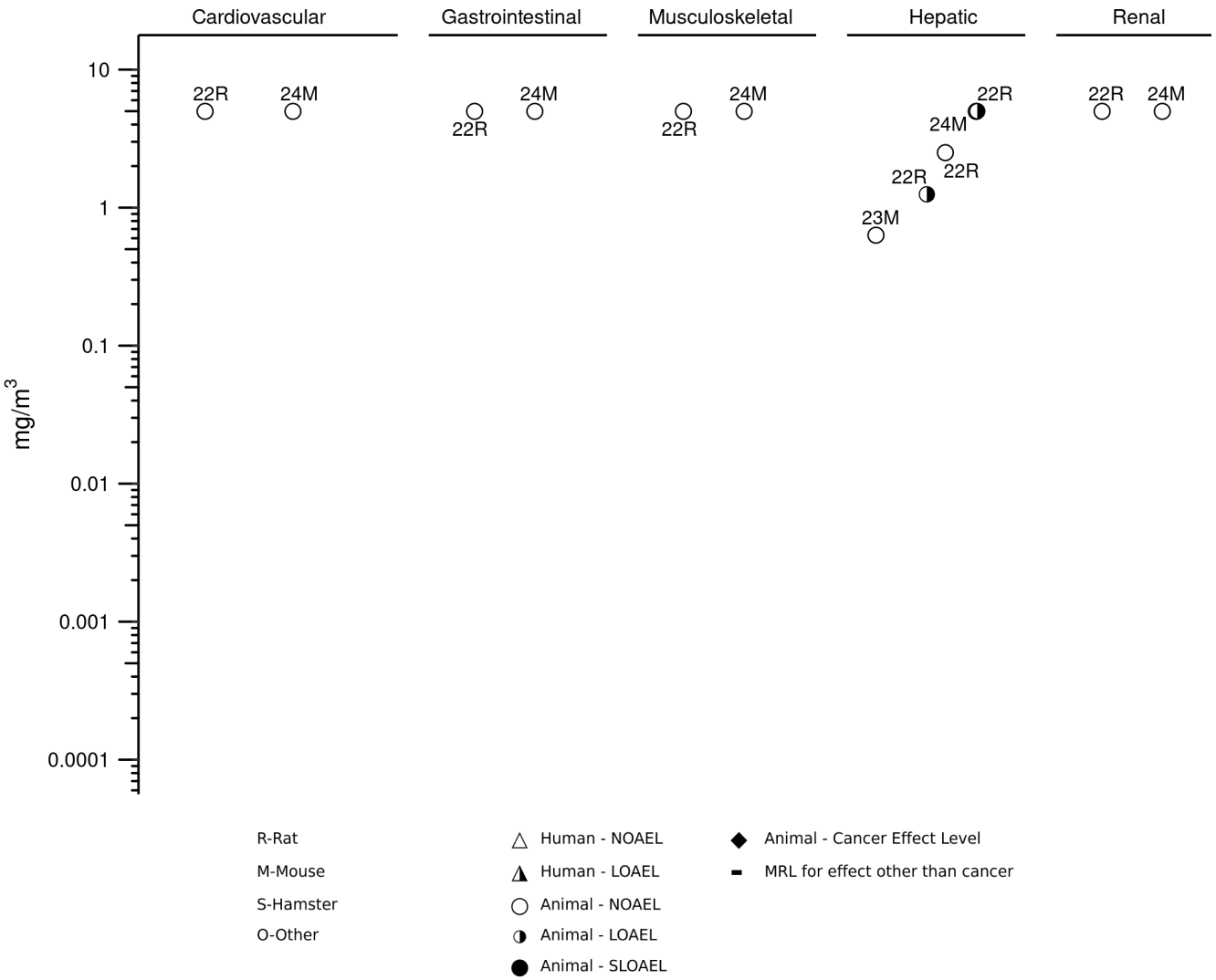


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Chronic (≥365 days)

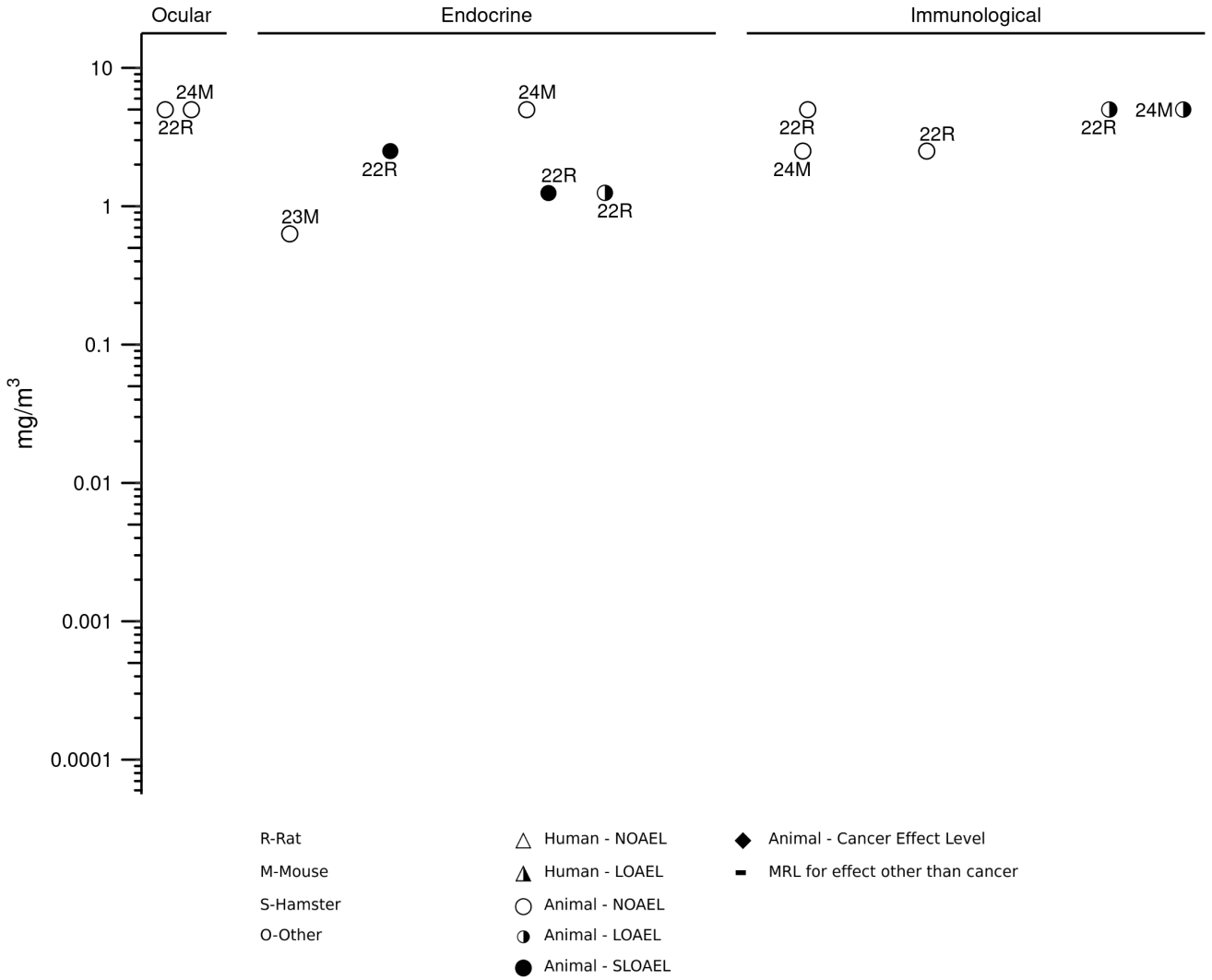


Figure 2-2. Levels of Significant Exposure to Cobalt–Inhalation
Chronic (≥365 days)

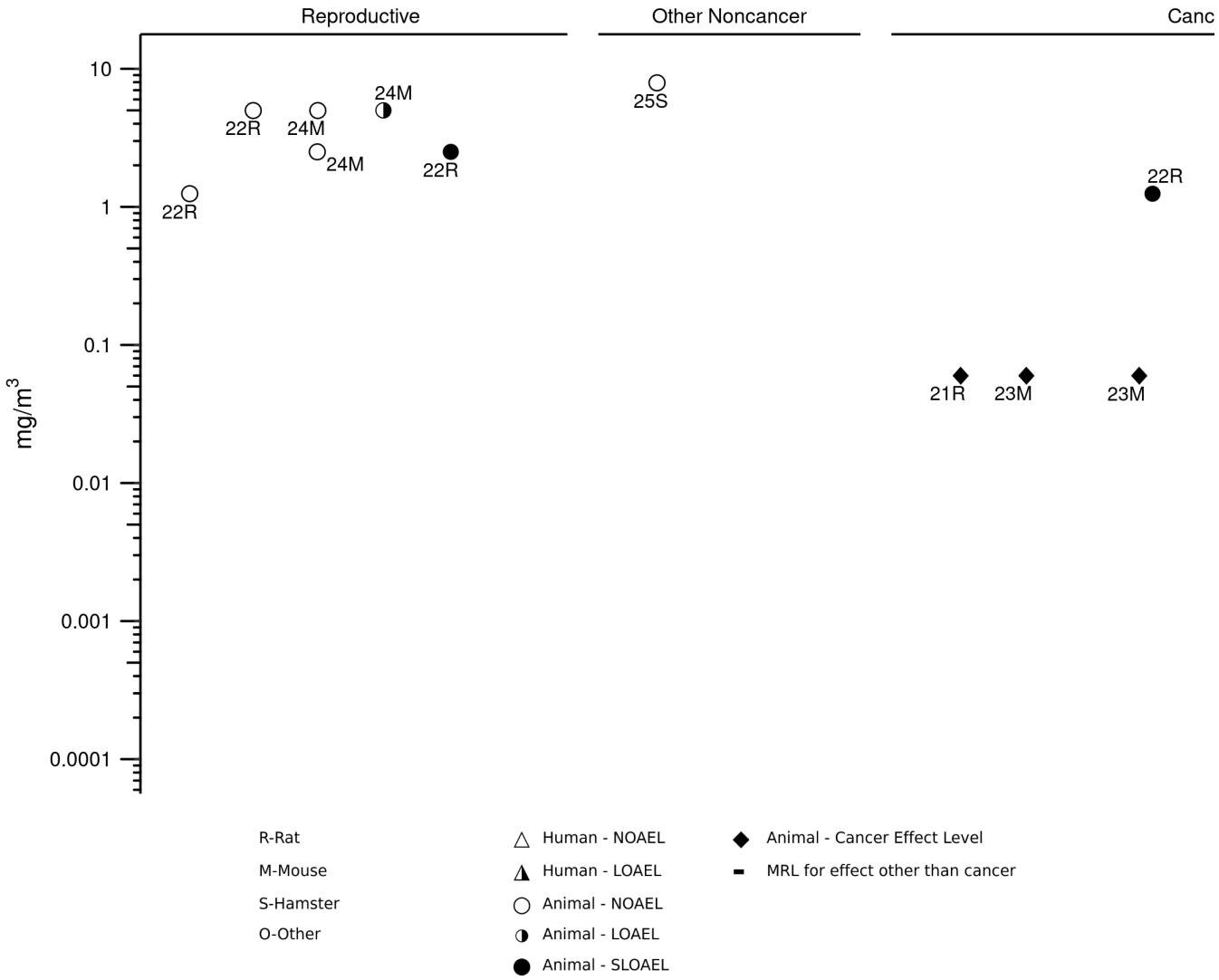


Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
Davis and Fields 1958									**Cobalt Chloride**
1	HUMAN 3M	6- 14 days, Daily (C)	0, 1	BC CS HE	Hemato		1[b]		Polycythemia, 8.7% increase in erythrocyte numbers
Paley et al. 1958									**Cobalt Chloride**
2	HUMAN 3M	10-14 days, Daily (C)	0, 0.54	BC CS OF	Gastro		0.54		Mild gastric distress
					Endocr		0.54		Decreased iodine uptake by thyroid in euthyroid subjects; ranged from 3.1/5.2=40% to 2.2/5.2=58% at 15 min in 3/3 subjects, and by 35/57=39% at 24 hr in 1/3 subjects
Ajibade et al. 2017									**Cobalt Chloride**
3	RAT (Wistar) 6M	2 weeks, Daily, 7days/week (GW)	0, 33.7	BI OF	Cardio		33.7		Cellular infiltration and cardiac cell swelling observed in the heart along with 67% increase in the NF-kB
					Renal		33.7		Histopathological study showed increased inflammation; 300% increase in NF-kB in the kidneys

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Akinrinde et al 2016b									**Cobalt(II) Chloride Hexahydrate**
4	RAT (Wistar) 7M	1 week, Daily, 7 days/week (W)	0, 19	BI HP OF	Cardio		19		Inflammation of the myocardium and areas of myocardial infarction; decreases of systolic blood pressure by 17%, diastolic blood pressure by 24%, and mean arterial pressure by 21%
					Renal		19		Inflammation in the peri- tubular and peri-vascular areas of kidney along with focal tubular necrosis
Akinrinde et al. 2016a									**Cobalt(II) Chloride Hexahydrate**
5	RAT (Wistar) 8M	2 weeks, Daily, 7days/week (W)	0, 18.4	BI GN HP OF	Cardio		18.38		Hemorrhagic lesions with congestion in the blood vessels along with inflammation in the myocardial cells; 12% decrease in systolic blood pressure and 150% increase in LDH compared to controls
					Renal		18.38		Loss of normal morphology, increased inflammation and vascular congestion in kidneys; increase in urea and creatinine by 33% and 19%
Akinrinde et al. 2016c									**Cobalt Chloride**
6	RAT (Wistar) 7M	7 days, Daily (W)	0, 19	BI HP IX OF	Gastro		19		Histopathology showed significant intestinal injury with depletion of absorptive epithelial cells; decrease in relative small intestine weight by 16%; decrease in GPx by 17%

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic		19		Histology showed necrosis in the liver along with cytotoxicity in hepatocytes and other abnormal morphology; decrease in relative liver weight by 14%
					Immuno		19		Increase in TNF α by 60% and decrease in IL1β by 25%
Akinrinde et al. 2019									**Cobalt(II) Chloride Hexahydrate**
7	RAT (Wistar) 12M	1 week, Daily, 7days/week (GW)	0, 67.5	BC BI CS NX	Immuno			67.5	300% increase in IL-1β and 100% increase in TNF α
					Neuro			67.5	Battery of neurobehavioral tests showed poor performance in exposed rats and a 60% increase in AChE activity compared to controls
Awoyemi et al. 2017									**Cobalt(II) Chloride Hexahydrate**
8	RAT (Albino) 10M	1 week, Daily, 7 days/week, (W)	0, 6, 11, 22	BI BW CS HE OF	Hemato	6	11		~400% increase in the frequency of micronucleated polychromatic erythrocytes
					Hepatic		6	11	LOAEL: Alteration in liver enzyme levels (16% increase of ALT) SLOAEL: Hepatocytes with focal areas of moderate congestion of vessels, mild infiltration by inflammatory cells, focal area of necrosis and congestion of vessels

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Domingo and Llobet 1984									**Cobalt Chloride**
9	RAT (Sprague-Dawley) 20M	Once (GW)	0, 161	BC CS HE LE OF	Death			161	5/20 died
					Hemato		161		8% increase in hematocrit levels
					Hepatic	161			
					Renal			161	68% increase in urea and 57% decrease in uric acid
Domingo et al. 1985									**Cobalt(II) Chloride Hexahydrate**
10	RAT (Sprague-Dawley) 20M	Once (G)	0, 31, 67	LE	Death			37	10/20 died
Richardson et al. 2018									**Cobalt Chloride**
11	RAT (Sprague-Dawley) 5NS	5 days, Daily (W)	0, 12, 21, 37	OF	Gastro	21	37		Changes in gut microbiota composition (not otherwise described)
Shrivastava et al. 2009									**Cobalt(II) Chloride Hexahydrate**
12	RAT (Sprague-Dawley) 8M	1 week, Daily (G)	0, 12.5	BC BI BW HE HP OP OW	Bd wt	12.5			
					Resp	12.5			
					Cardio		12.5		

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hemato		12.5		60%, 10%, and 8% increase in RBC, hematocrit, and hemoglobin, respectively
					Hepatic	12.5			
					Renal	12.5			
					Immuno	12.5			
					Neuro	12.5			
Singh and Junnarkar 1991									**Cobalt Chloride**
13	RAT (Wistar) 5M, 5F	Once (GW)	0, 4.24	CS NX	Neuro		4.24		CNS depressant indicated by mild hypothermic effect and increased sleeping time by 31%
Singh and Junnarkar 1991									**Cobalt Sulfate**
14	RAT (Wistar) 5M, 5F	Once (GW)	0, 19.4	CS NX	Neuro		19.4		CNS depressant indicated by mild hypothermic effect and increased sleeping time by 19%
Wellman et al. 1984									**Cobalt Chloride**
15	RAT (Long-Evans) 7M	3 days, Daily (F)	0, 9, 45, 90	BW CS FI NX WI	Bd wt	90			
					Neuro	9	45		Taste aversion demonstrated by reduced saccharin consumption
					Other noncancer	9	45		~20% decrease in food consumption

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Bryan and Bright, 1973									**Cobalt(II) Chloride Hexahydrate**
16	MOUSE (Swiss-Webster) 3M	2 days, Once/day (W)	0, 763	BC BW HE	Hemato		763		Unspecified alterations in electrophoretic profile of serum proteins
Elbetieha et al. 2008									**Cobalt(II) Chloride Hexahydrate**
17	MOUSE (Swiss) 10M	12 days, Daily (W)	0, 6.4, 11.6, 23	BW CS HP OW RX WI	Death			11.6	1/10 mice died during the 10th week of exposure
					Bd wt		23		Significant 7.1% decrease in body weight gain compared to controls
					Repro			6.4	Significant 16.8% increase of relative preputial gland weight, 13.3% decrease in sperm count, and decreased male fertility compared to controls
Hassan et al. 2006									**Cobalt Chloride**
18	MOUSE (NS) 3M	5 days, Once/day (W)	0, 7, 14, 28	RX	Repro			7	126% increase in abnormal sperm
Seidenberg 1986									**Cobalt Chloride**
19	MOUSE 28F	5 days, Daily (Gd 8-12) (GW)	0, 81	CS FX MX DX	Bd wt			81	32% decrease in maternal weight gain
					Develop	81			

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Singh and Junnarkar 1991									**Cobalt Sulfate**
20	MOUSE (Swiss-Webster) 5M	Once (GW)	0, 12.3	CS NX	Neuro		12.3		CNS depression observed in mice (not otherwise described)
Singh and Junnarkar 1991									**Cobalt Chloride**
21	MOUSE (Swiss-Webster) 5M	Once (GW)	0, 8.9	CS NX	Neuro		8.9		CNS depression observed in mice (not otherwise described)
INTERMEDIATE EXPOSURE									
Davis and Fields 1958									**Cobalt Chloride**
22	HUMAN 2M	15-22 days, Daily (C)	0, 0.8, 1	BC CS HE	Hemato	0.8	1[c]		Polycythemia, 9.7% increase in erythrocyte numbers
Duckham and Lee 1976									**Cobalt Chloride**
23	HUMAN 6M 6F	12 weeks, 7days/week Twice/day (C)	0, 0.18	BC CS OF	Gastro		0.18 F		Nausea and constipation
					Hemato		0.18 F		Increased hemoglobin in anephric, hemoglobin deficient patients by 26-70%

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Holly 1955									**Cobalt Chloride**
24	HUMAN 20F	13 weeks, 7 days/week, Once/day (C)	0, 0.5-0.6	BC BI DX HE OF UR	Gastro		0.5		Gastric intolerance
					Hemato	0.6			
					Hepatic	0.6			
					Dermal		0.5		Skin rash in 1/20 disappeared when Co exposure was discontinued
					Endocr	0.5			
					Develop	0.5			
Paley et al. 1958									**Cobalt Chloride**
25	HUMAN 2F	21-25 days, Daily (C)	0, 0.54	CS OF	Gastro		0.54		Gastric distress
					Endocr		0.54		Decreases in Iodine uptake in hyperthyroid subjects of 24/28=14% and 2.3/12.5=92% at 15 min in 2/2 subjects
Taylor et al. 1977									**Cobalt Chloride**
26	HUMAN 8 NS	12-32 weeks, 7days/week (C)	0, 0.16, 0.32	BI CS HE	Hemato		0.16		Unspecified increase in hemoglobin

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Abdel-Rehman et al. 2019									**Cobalt Chloride**
27	RAT (Wistar) 10M	60 days, Daily (W)	0, 27		Death			27	4/10 rats died
					Neuro			27	Decrease in neurotransmitters levels- 23% decrease in serotonin, 26% decrease in norepinephrine, 48% decrease in dopamine, and 39% decrease in GABA; increases in encephalopathy were observed in cerebral cortex (not otherwise described); upregulation of microglial CD68 and neural caspase-3 in the brain (not otherwise described)
Bourg et al. 1985									**Cobalt Chloride**
28	RAT (Sprague-Dawley) 8M	57 days, Daily (W)	0, 20		Neuro		20		Increased latency during passive-avoidance retention testing by 342%; 972% increase in accumulation in the brain
Chetty et al. 1979									**Cobalt Chloride**
29	RAT (Sprague-Dawley) 8-12M	4 weeks, 7days/week, Daily (F)	0, 0.379, 1.9, 3.79, 7.59, 11.4	BC BW HE OF OW	Bd wt			0.38	45% reduction in body weight gain
					Cardio		11.4		
					Hemato	7.59	11.4		20% decrease in hemoglobin
					Hepatic	11.4			

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro		3.79		13% decrease in Na+-K+ ATPase activity
Clyne et al. 1988									**Cobalt Sulfate**
30	RAT (Sprague-Dawley) 5M	8 weeks, 7 days/week, Daily (F)	0, 4.2	BC BW GN HE OF WI	Bd wt			4.2	33% decrease in body weight gain
Corrier et al. 1985									**Cobalt Chloride**
31	RAT (Sprague-Dawley) 3M	14 weeks, 7 days/week, Once/day (F)	0, 20	BC HP OF RX	Hemato			20	41% increase in RBCs and 28% increase in hemoglobin
					Repro			20	Pronounced histologic alteration of seminiferous tubules (27%- 90%); sperm reserve dropped by 57%
Danzeisen et al. 2020									**Cobalt Tetraoxide**
32	Rat (Sprague-Dawley) 40M, 40F	90 days, once daily (G)	0, 0.74, 2.48, 7.44	BW FI HE, HP NX OW RX UR WI	Bd wt	220	744		Slight reduction in body weight gain (not otherwise reported)
					Hemato	73.4 F	220 F		Females showed a 5.9% increase in hemoglobin
						73.4 M	220 M		Males showed a 9.5% increase in hemoglobin, a 9.6% increase in red blood cells, and a 9.2% increase in hematocrit

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Danzeisen et al. 2020									**Cobalt(II) Chloride Hexahydrate**
33	Rat (Sprague-Dawley) 40M, 40F	90 days, once daily (G)	0, 0.74, 2.48, 7.44	BW FI HE HP NX, OW RX UR WI	Bd wt	2.48	7.44		The body weight at the end of the study at 90 days was reduced by 11% (males) and 9% (females), respectively
					Hemato	0.74			
							7.44 F		Females showed a 13.4% increase in hemoglobin, a 9.8% increase in red blood cells, and a 12% increase in hematocrit
							2.48 M		Males showed a 10.7% increase in hemoglobin, a 9.2% increase in red blood cells, and a 10.3% increase in hematocrit
Domingo et al. 1984									**Cobalt(II) Chloride Hexahydrate**
34	RAT (Sprague-Dawley) 20M	13 weeks, 7 days/week, Daily (W)	0, 30.2	BC BI CS FI GN HE OF OW UR WI	Bd wt	30.2			
					Resp		30.2		33% increase in relative lung weight
					Cardio		30.2		9.4% increase in relative heart weight
					Gastro	30.2			
					Hemato		30.2		29% increase in hematocrit, 31% increase in hemoglobin
					Musc/skel	30.2			
					Hepatic		30.2		30% decrease in liver enzyme (GPT)

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal		30.2		35% decrease in urine volume
					Immuno			30.2	43% increase in relative spleen weight
					Repro		30.2		26% decrease in relative testicular weight
					Other noncancer		30.2		Significant 13% decrease in water consumption
Garoui et al. 2011									**Cobalt Chloride**
35	RAT (Wistar) 6F	4 weeks; Daily from day 14 of pregnancy to day 14 post-delivery (W)	0, 21	BI BW DX FI LE OF OW RX UR WI	Bd wt	21			
					Hepatic			21	Liver weight decreased in pups by 10%; increase in hepatic enzymes ALT and AST by 44% and 27%, respectively; oxidative damage observed in the liver: 31% increase in MDA; decrease in SOD, CAT, GPx, and GSH by 30%, 23%, 31%, and 20%, respectively
					Other noncancer			21	Significant reduction in water (32%) and food intake (29%) were observed

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Garoui et al. 2011									**Cobalt Chloride**
36	RAT (Wistar) 4M, 4F	4 weeks; Exposed through maternal dosing- in utero and lactation daily from day 14 of pregnancy to day 14 post-delivery (W)	0, 21	BC BI BW DX FI GN OF OW UR WI	Bd wt			21	40% decrease in body weight
					Hepatic			21	Increase in hepatic enzymes ALT and AST by 133% and 75%, respectively; hepatic injury was observed with the presence of vascular congestion and infiltration of mononuclear cells by histopathology; decrease in GPx and GSH by 39% and 35%, respectively
Garoui et al. 2012									**Cobalt Chloride**
37	RAT (Wistar) 5F	28 days, Daily from day 14 of pregnancy to day 14 post-delivery (W)	0, 20.3	BI BW CS FI GN HP OW UR WI	Bd wt	20.3			
					Renal		20.3		Vascular congestion, reduction of glomerular space, and infiltration of leukocyte cells between tubules; 15% increase in plasma creatinine, 34% decrease in urine creatinine, and slight reduction in relative kidney weight (4%), compared to controls
					Other noncancer		20.3		32% lower water intake and 29% lower food intake compared to controls

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Garoui et al. 2013									**Cobalt Chloride**
38	RAT (Wistar) 4M, 4F	4 weeks; Exposed through maternal dosing- in utero and lactation daily from day 14 of pregnancy to day 14 post-delivery; (W)	0, 20.3	BI BW CS DX NX OF OW	Neuro			20.3	AChE and BuChE levels decreased in cerebrum by 33% and 36%, respectively; AChE and BuChE levels decreased in cerebellum by 33% and 47%, respectively. Decreases in antioxidant enzymes in the brain were observed- in GSH and NPSH by 23% and 50% in the cerebrum, and by 16% and 25% in the cerebellum, respectively; co-treated rats exhibited poorly differentiated purkinje cells with frequent pyknotic cells, and their number of pyknotic cells was reduced (not otherwise described)
Grice et al. 1969									**Cobalt Sulfate**
39	RAT (Wistar) 30M	8 weeks, 7 days/week, Daily (F)	0, 26	CS OF	Cardio			26	Degeneration and swelling in myocardial cells accompanied by decrease in number of myofibrils in the cells based on histopathology; damaged mitochondria were identified with electron microscopy
Haga et al. 1996									**Cobalt Sulfate**
40	RAT (Sprague-Dawley) 10M	24 weeks, 7days/week, Daily (F)	0, 8.4	BW CS FI	Bd wt			8.4	31% decrease in body weight gain

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Cardio			8.4	30% increase in the ratio of left ventricular weight to body weight; impaired ventricular function
					Hemato	8.4			
Haga et al. 1996									**Cobalt Sulfate**
41	RAT (Sprague-Dawley) 8M	16 weeks, 7days/week, Daily (F)	0, 8.4	BW CS FI	Bd wt			8.4	26% decrease in body weight
					Cardio	8.4			
					Hemato	8.4			
Holly 1955									**Cobalt Chloride**
42	RAT (Wistar) 8M	4 months, 7 days/week, 4 months, Daily (G)	0, 18	CS HE OF	Resp	18			
					Cardio	18			
					Gastro	18			
					Hemato		18		21% and 37% increases in red blood cell count and hemoglobin above controls; controls had an 18% increase in red blood cell count
					Hepatic	18			
					Renal	18			Tubular necrosis (not otherwise described)
					Endocr	18			
					Immuno	18			

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Khalil et al. 2020									**Cobalt(II) Chloride Hexahydrate**
43	RAT (Sprague-Dawley) 8M	4 weeks, Daily (W)	0, 68	BC CS LE NX OF	Hepatic		68		3.6-fold increase in LDH; 1.7, 4.5, and 1.7-fold increase in hepatic enzymes ALP, AST, and ALT, respectively; 1.9-fold increase in total bilirubin levels (these factors increase DNA damage in liver cells)
					Immuno		68		2.2-fold increase in immunoreactivity
					Neuro		68		Fatigue, lethargy, and dullness (not otherwise described)
Krasovskii and Fridlyand 1971									**Cobalt Chloride**
44	RAT (NS) 1-3NS	7 months, 6 days/week (GW)	0, 0.05, 0.5, 2.5	CS OF IX NX	Hemato	0.05	0.5		Unspecified increases in RBC, RBC diameter, and hemoglobin; mild transient polycythemia
					Hepatic	2.5			
					Renal	2.5			
					Endocr	2.5			
					Immuno	0.05	0.5		Unspecified decrease in phagocytic ability at 6-7 months
					Neuro	0.05	0.5	2.5	LOAEL: 0.5 mg/kg/day caused non-significant p<0.05 36% increase at 6-7 months SLOAEL: 2.5 mg/kg/day caused 47% increase in latent reflex at 4 months

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Mathur et al. 2011									**Cobalt(II) Chloride Hexahydrate**
45	RAT (Wistar) 8M	60 days, Daily (W)	0, 45	BC BI BW HP OW	Bd wt		45		Significant 8% decrease in body weight
					Hepatic		45		13% increase in relative liver weight; unspecified degradation, alteration in the morphology, and atrophy of liver cells; changes in liver biochemistry; 126% increase in SGOT and 122% increase in bilirubin
Mollenhauer et al. 1985									**Cobalt Metal**
46	RAT (Sprague-Dawley) 3M	14 weeks, Daily, 7 days/week (F)	0, 20	CS RX	Repro			20	Testicular degeneration and thickening of basal lamina and seminiferous tubules
Morvai et al. 1993									**Cobalt Chloride**
47	RAT (CFY) 8M	3 weeks, Daily, 7 days/week (G)	0, 12.4	BC HE HP NX OF	Bd wt	12.4			
					Cardio			12.4	~33% decrease in cardiac output; incipient, multifocal myocytolysis with degeneration of myofibrils (not otherwise described)
					Renal		12.4		8% decrease in relative kidney weight
					Neuro		12.4		10% decrease in relative brain weight

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Mutafova-Yambolieva et al. 1994									**Cobalt Nitrate**
48	RAT (Wistar) 6M	30 days, Daily (W)	0, 6.4	CS OF RX	Repro			6.4	275% increase in sympathetically-induced contractility of vas deferens (not otherwise described)
Nation et al. 1983									**Cobalt Chloride**
49	RAT (Sprague-Dawley) 6M	69 days, 7 days/week, Daily (F)	0, 5, 20	CS OW NX	Neuro	5	20		Lowered operant lever press rates (not otherwise described)
					Repro	5		20	Testicular atrophy seen in 42%
Pehrsson et al. 1991									**Cobalt Sulfate**
50	RAT (Sprague-Dawley) 12M	8 weeks, 7days/week, Daily	0, 8.4	BW CS HE OF	Bd wt			8.4	30% decrease in body weight
					Cardio	8.4			
					Hemato	8.4			
Saker et al. 1998									**Cobalt Chloride**
51	RAT (Sprague-Dawley) 6M	2 weeks, Daily (W)	0, 9.6	BC BI BW CS	Bd wt	9.6			
					Hepatic	9.6			
					Other noncancer	9.6			

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Umar et al. 2016									**Cobalt Chloride**
52	RAT (Wistar) 5B	28 days, Daily (NS)	0, 22.7	CS NX	Neuro	22.7			
Vassilev et al. 1993									**Cobalt Nitrate**
53	RAT (Wistar) 5M	30 days, Daily (W)	0, 6.44	CS NX OF	Bd wt	6.44			
					Neuro		6.44		Unspecified alterations in cholinergic sensitivity
Anderson et al. 1992									**Cobalt Chloride**
54	MOUSE (CD-1) 10M	13 weeks, 7 days/week, Daily (W)	0, 24.6	BW HP OF OW RX	Bd wt	24.6			
					Hepatic	24.6			
					Renal	24.6			
					Repro			24.6	Unspecified increase in the number of Leydig cells and changes in the peritubular area; increased folding in the germinal epithelium accompanied with changes in cell morphology
Anderson et al. 1993									**Cobalt Chloride**
55	MOUSE (CD-1) 10 M	13 weeks, 7days/week, Daily (W)	0, 43.4	BW HP OF OW RX	Bd wt		43.4		Significant 7% decrease in body weight

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro			43.4	Irreversible testicular degeneration demonstrated by damage to seminiferous tubules and hypercellularity of the interstitial areas
Bryan and Bright, 1973									**Cobalt Chloride**
56	MOUSE (Swiss-Webster) 3 M	Once/day, 7 days/week, 13 weeks (W)	0, 763	BC BW HE	Hemato	763			
Bryan and Bright, 1973									**Cobalt Chloride**
57	MOUSE (Swiss-Webster) 3M	Once/day, 7 days/week, 3 weeks (W)	0, 763	BC BW HE	Hemato	763			
Gluhcheva et al. 2014									**Cobalt(II) Chloride Hexahydrate**
58	MOUSE (ICR) 7B	In utero for 2-3 days + 25 days via breastmilk + 65 days orally (W)	0, 18.6, 31	BW HE OW	Hemato		18.58		Unspecified hemoglobin changes and hematopoiesis
					Hepatic			18.58	Significant decrease (21.5%) of liver weight index in mice sacrificed on day 90, compared to controls

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal		18.58	30.96	LOAEL: Increase (14.3%) of liver weight index in mice sacrificed on day 30, compared to controls at 18.58 SLOAEL: Significant increase (28.6%) of kidney weight index in mice sacrificed on day 30, compared to controls at dose 30.96
					Immuno			18.58	Significant decrease (43-53%) of spleen weight index (measure of relative weight) in mice sacrificed on day 60-90, compared to controls
Gluhcheva et al. 2020									**Cobalt(II) Chloride Hexahydrate**
59	MOUSE (ICR) 7-8B (W)	20-21 days, In utero and breastmilk; mothers exposed daily 2-3 days before birth and to post-natal day 18	0, 18.6	BI HE HP OW	Bd wt		18.57 F		17% decrease in body weight compared to controls
					Hemato		18.57 F		Statistically significant 17% increase in erythrocyte count; 19% decrease in mean corpuscular hemoglobin; and 10% decrease mean corpuscular volume, compared to controls
					Hepatic		18.57 F		Leukocyte infiltration; increased number of binucleated hepatocytes; abundant Kupffer cells; and apoptotic bodies in liver

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Immuno		18.57 F		Reduced red pulp in spleen; 55% decrease in spleen weight index (measure of relative weight), compared to controls
Legostaeva et al. 2012									**Cobalt Chloride**
60	MOUSE (BALB/c) 8M, 8F	5 weeks, 7days/week, Daily (W)	0, 56	BI HE OF	Immuno		56		2-fold decrease in the concentration of the total blood protein and 1.5-fold decrease of total immunoglobulin G
Madzharova et al. 2010									**Cobalt Chloride**
61	MOUSE (BALB/c) 6-13 M	18 days, Daily	0, 34, 56	RX	Repro	56			
Pedigo and Vernon et al. 1993									**Cobalt Chloride**
62	MOUSE (B6C3F1) 10M	10 weeks, Daily (W)	0, 15	BW CS LE RX	Repro			15	Reduction in pregnancy in females by 57% when mated with males treated with Co; 28% decrease in implantation of embryos when mated with Co exposed males; 458% increase in preimplantation losses in pregnant females mated with Co-exposed males; sperm concentration decreased to 15.3% and sperm motility to 18.3%
Pedigo et al. 1988									**Cobalt Chloride**
63	MOUSE (B6C3F1) 20M	13 weeks, Daily (W)	0, 15	BW HE RX	Bd wt	15			

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hemato	15			
					Repro			15	Testicular weights as a % of body weight decreased to 14%, 21%, 57%, and 71% at 7, 9, 11, and 13 weeks, respectively; sperm concentration decreased to 81.3% after 9 weeks of treatment; 82% decrease in sperm motility after 11 weeks of exposure
Pedigo et al. 1988									**Cobalt(II) Chloride Hexahydrate**
64	MOUSE (B6C3F1) 5M	12 weeks, Daily (GW)	0, 23, 42, 72	BW CS HE OW RX	Bd wt	11	18		Significant decrease in body weight by 13%
					Hemato	6			
					Repro		6		Decrease in testicular weight (expressed as % of body weight) by 14%; 11% decrease in sperm concentration; 80% increase in serum testosterone
Shrivastava et al. 1996									**Cobalt Chloride**
65	MOUSE (Parkes) 6F	45 days, Daily (W)	0, 26	HP	Endocr			26	Time dependent effects of exposure; treated mice showed low epithelial lining with degenerated nuclei; degeneration in thyroid was observed 30 and 45 days after the exposure ceased; not otherwise described

Table 2-2. Levels of Significant Exposure to Cobalt – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Zaksas et al. 2013									**Cobalt(II) Chloride Hexahydrate**
66	MOUSE (BALB/c) 19B	2-3 day in-utero + 25 days via breastmilk + 35 days orally (W)	0, 56.7	BC BW CS LE	Bd wt			56.7	33% decrease in average body weight by day 60, compared to controls
					Neuro	56.7			
Mohiuddin et al. 1970									**Cobalt Sulfate**
67	GN PIG 20M	5 weeks, Daily, 7 days/week (F)	0, 20	BW OB GN HP CS	Death			20	4/20 died
					Cardio		20		32% increase in relative heart weight; lesions observed in 75% of the samples examined

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration oral MRL of 0.03 mg Co/kg/day; dose was divided by an uncertainty factor of 30 (10 for human variability, 3 for use of a minimal LOAEL).
[c]Used to derive an intermediate-duration oral MRL of 0.03 mg Co/kg/day; dose was divided by an uncertainty factor of 10 for human variability and a modifying factor of 3 for limited database.
Studies listed in the table could potentially have examined more than one endpoint.

Anephric = without functioning kidneys; BC = serum (blood) chemistry; BI = biochemical changes; BW or bd wt = body weight; (C) = capsule; Cardio = cardiovascular; CS = clinical signs; DX = developmental toxicity; Endocr = endocrine; F = female(s); (F) = feed; FI = food intake; (G) = gavage – not specified; Gastro = gastrointestinal; GN = gross necropsy; (GW) = gavage – water intraperitoneal; HE = hematological; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = Musculo/skeletal; Neuro = neurological; NOAEL = no-observed-adverse- effect-level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; Resp = respiratory; polycythemia = author reported term associated with increased hemoglobin or erythrocyte count; RX = reproductive function; UR = urinalysis; (W) = water; WI = water intake

Figure 2-3. Levels of Significant Exposure to Cobalt–Oral

Acute (≤14 days)

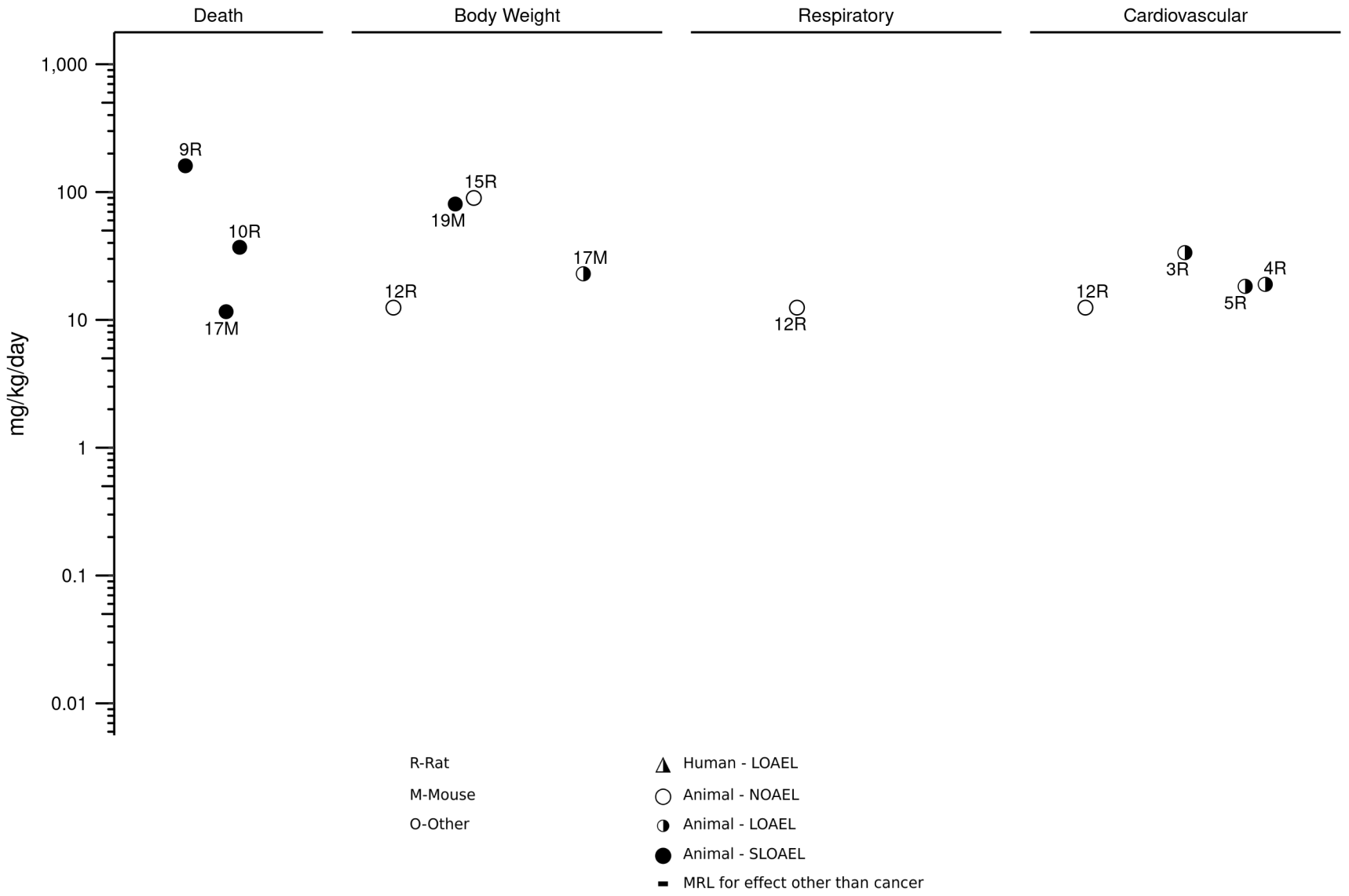


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral

Acute (≤14 days)

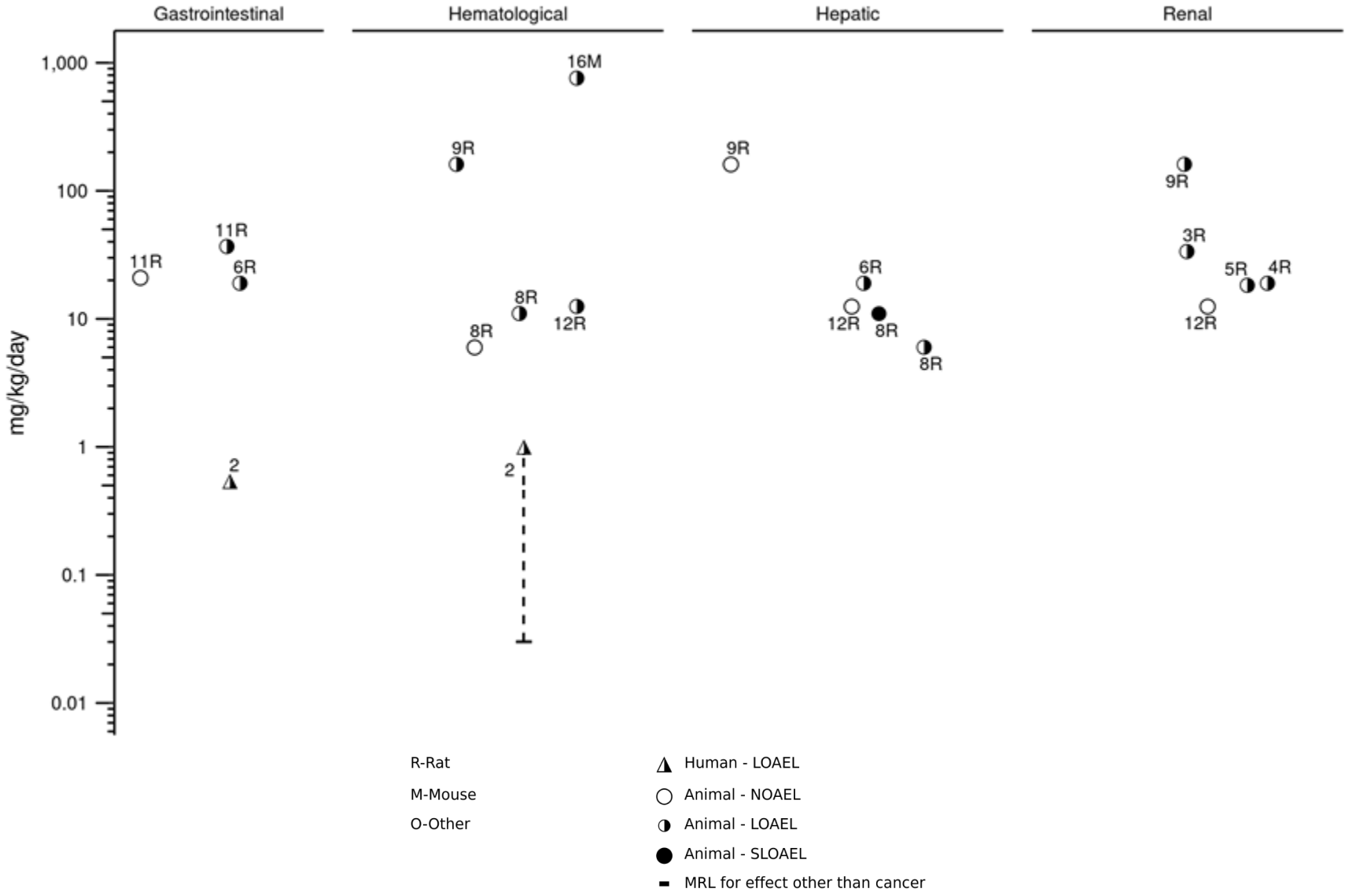


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral

Acute (≤14 days)

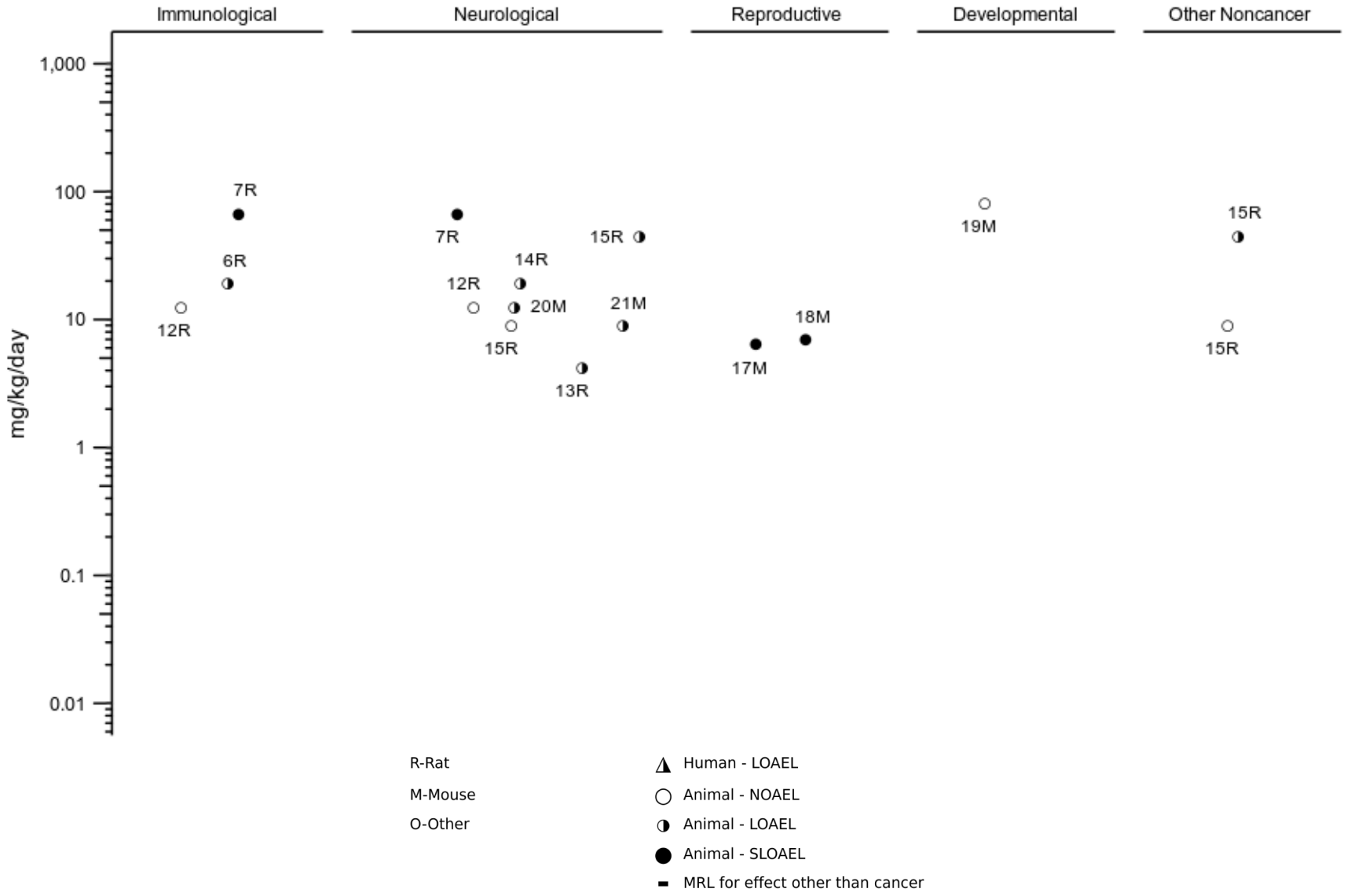


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral
Intermediate (15-364 days)

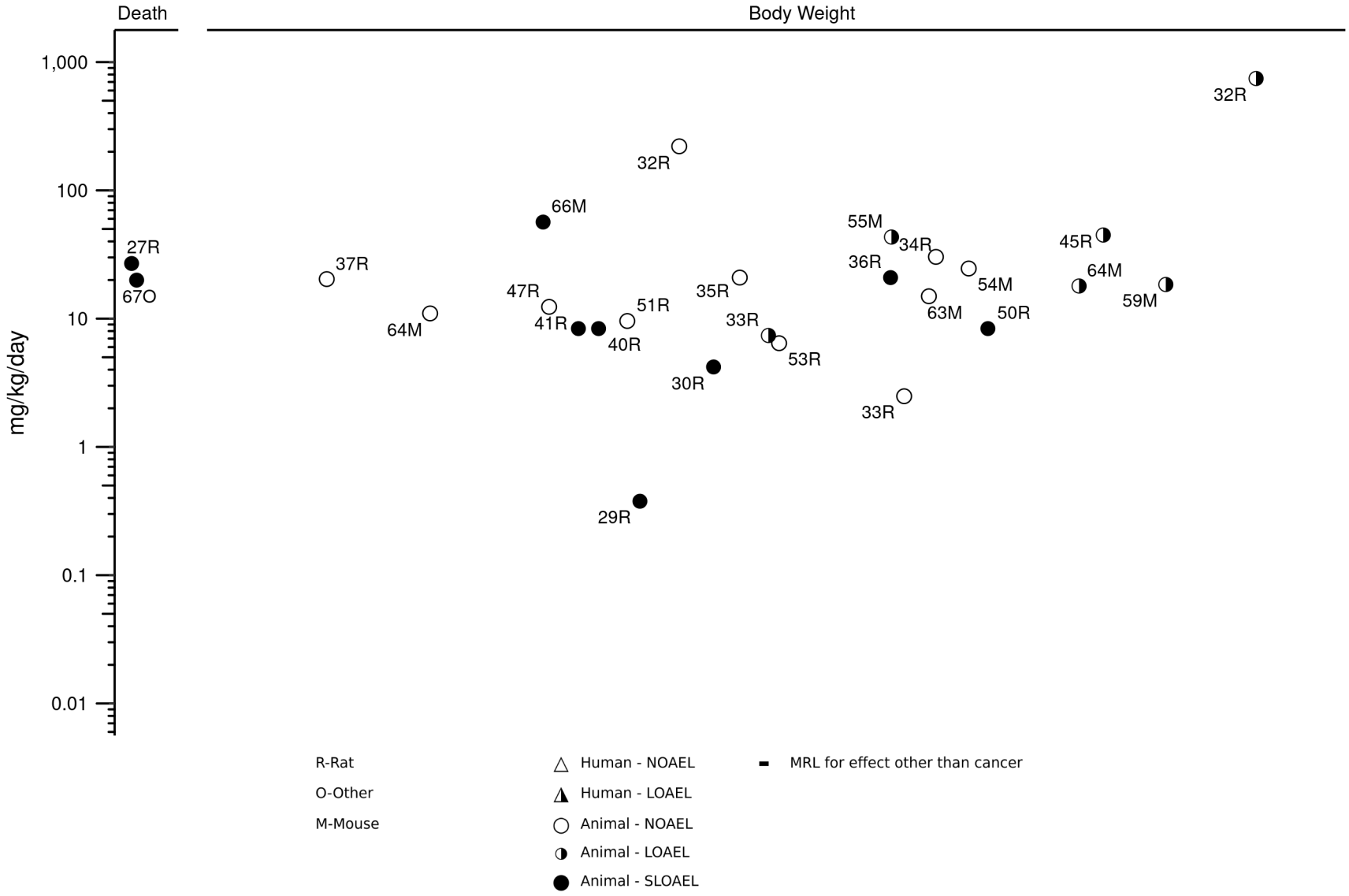


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral

Intermediate (15-364 days)

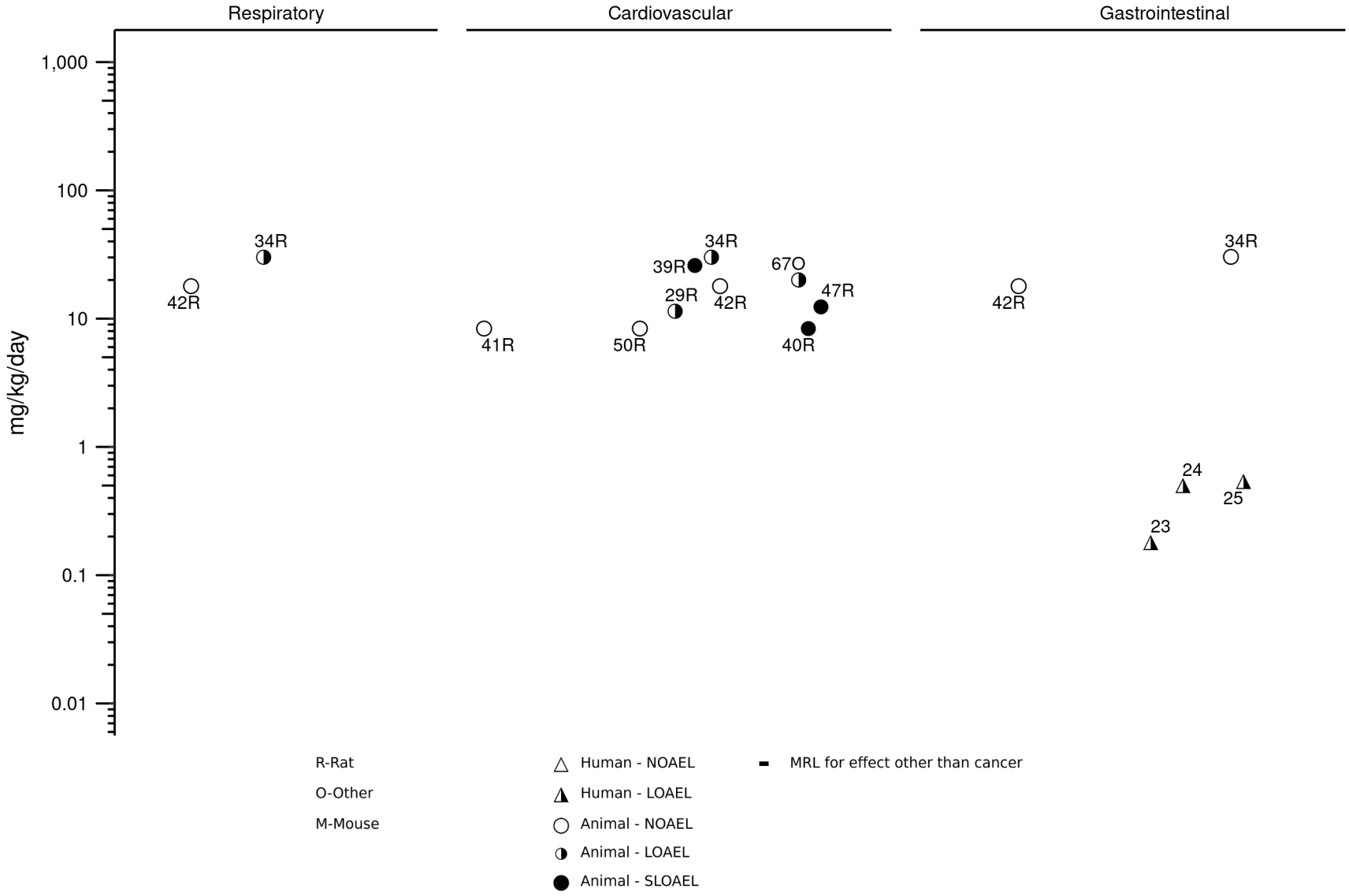


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral
Intermediate (15-364 days)

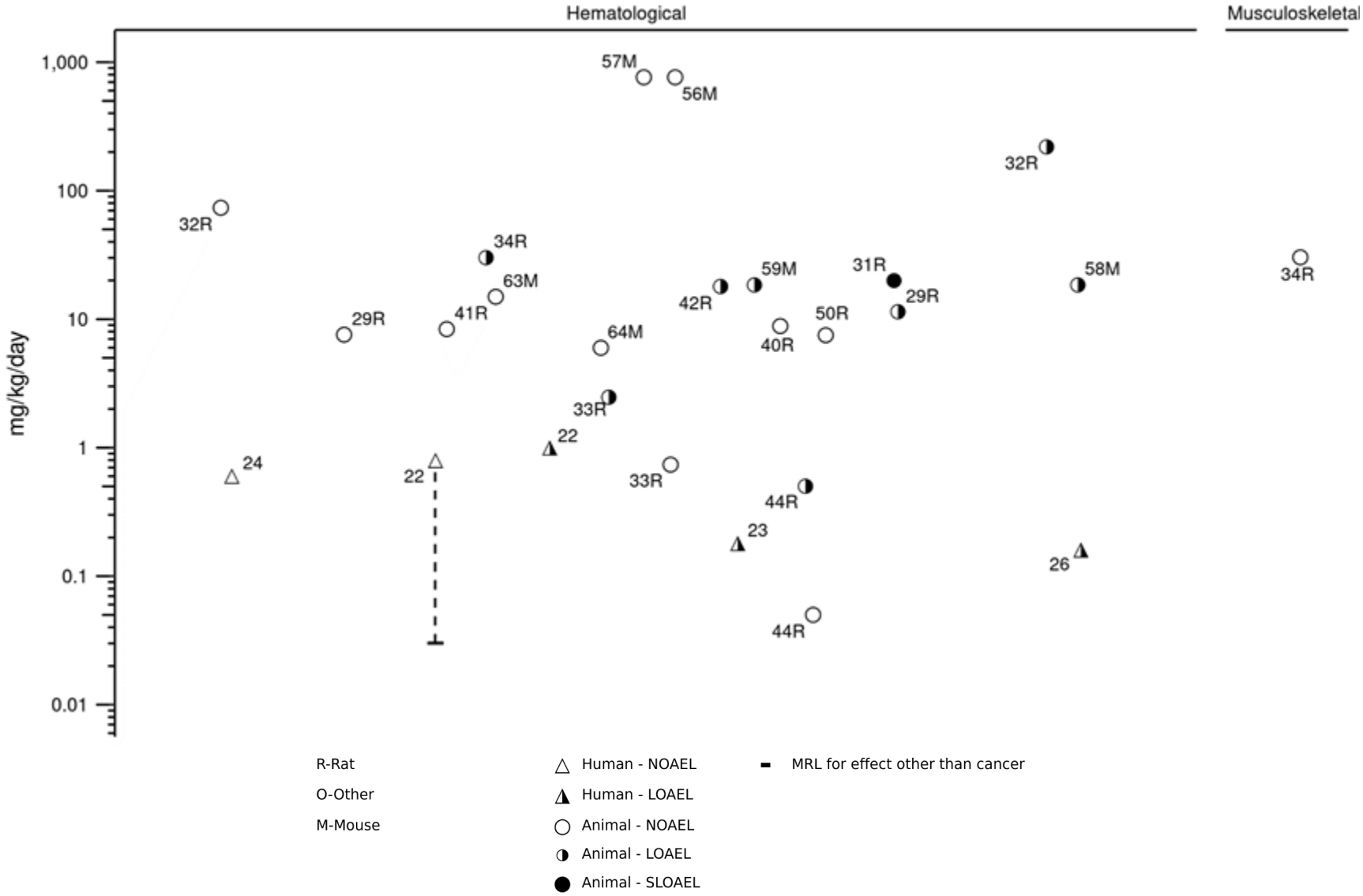


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral

Intermediate (15-364 days)

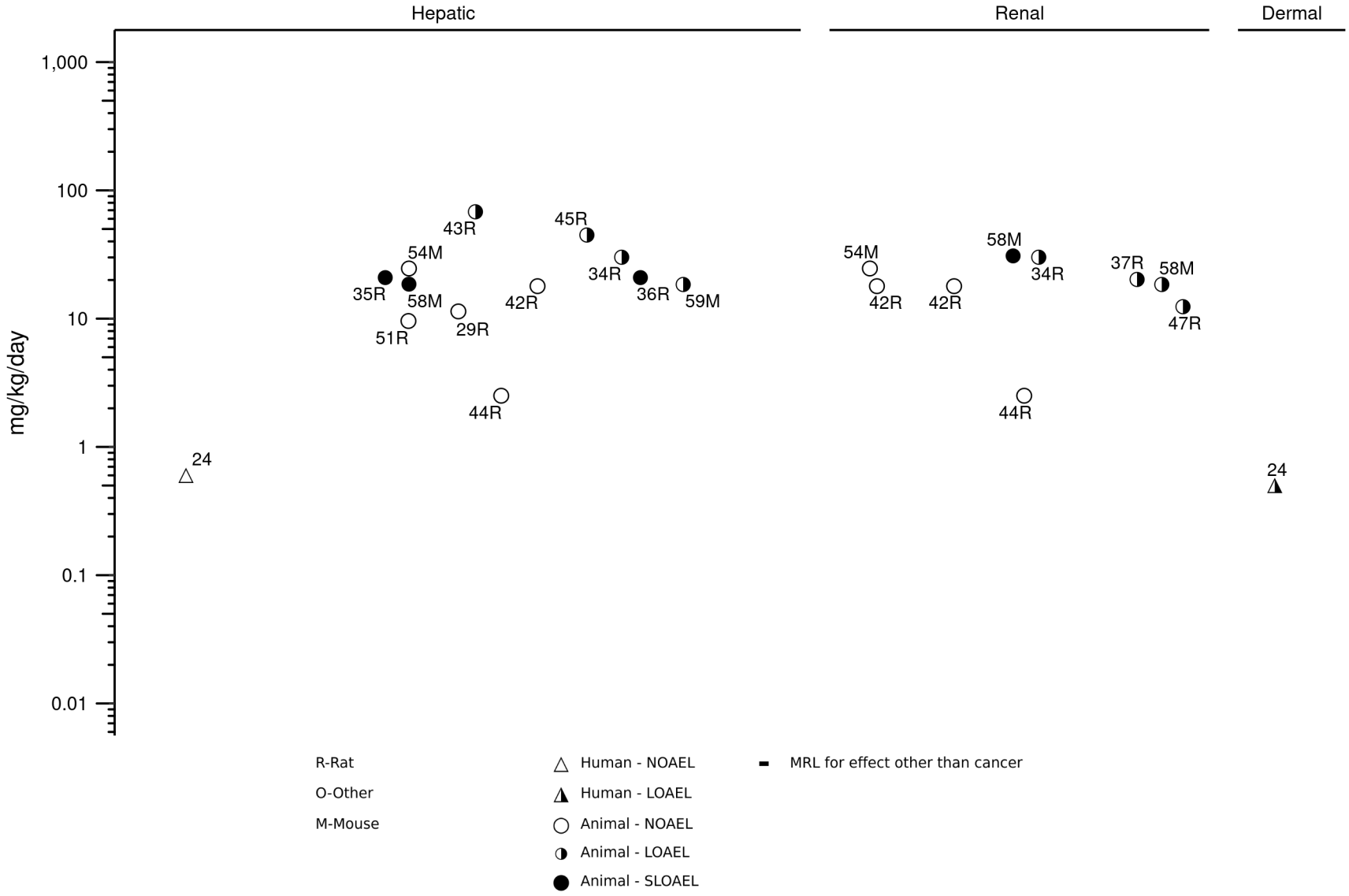


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral

Intermediate (15-364 days)

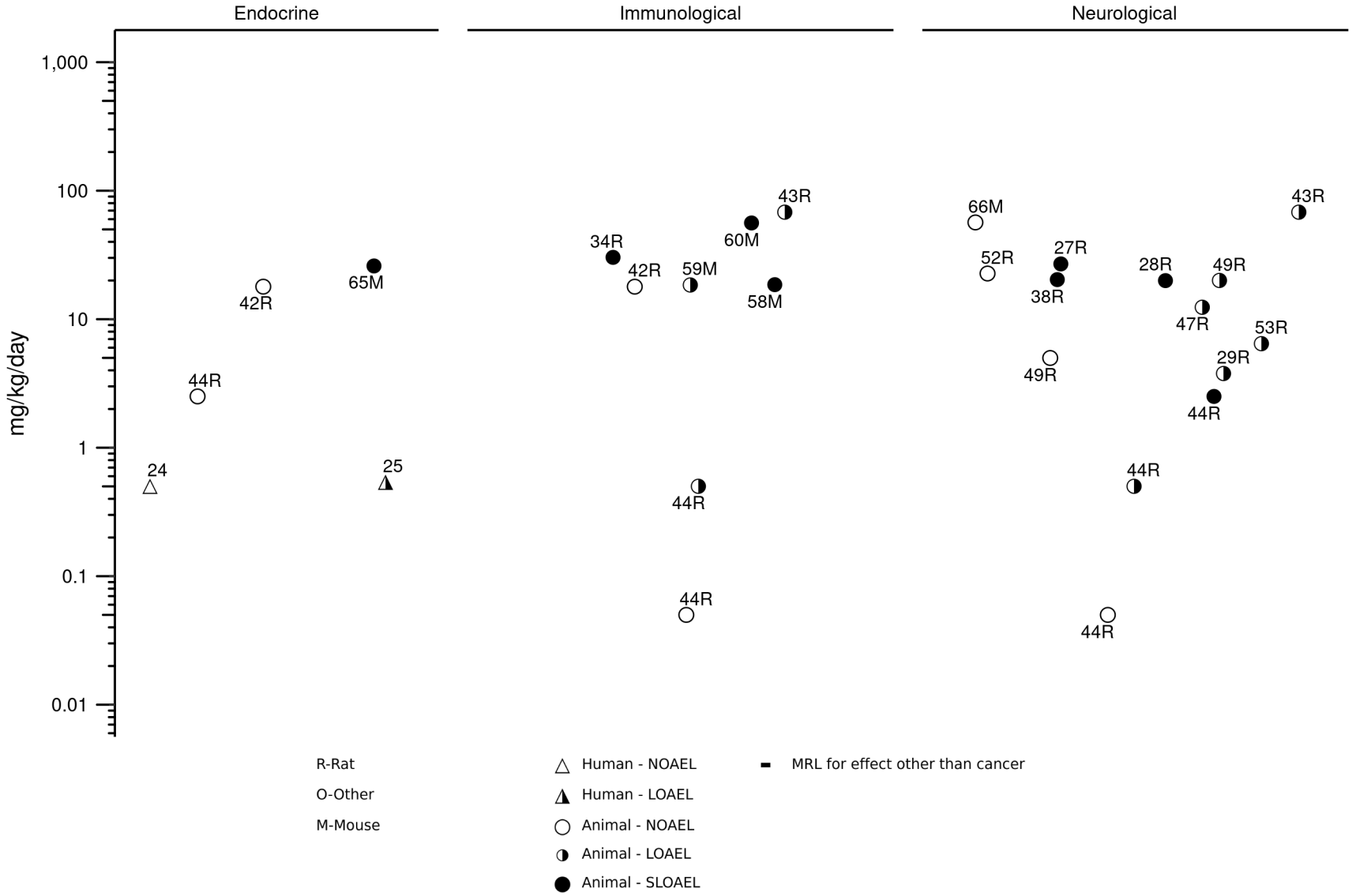


Figure 2-3. Levels of Significant Exposure to Cobalt–Oral

Intermediate (15-364 days)

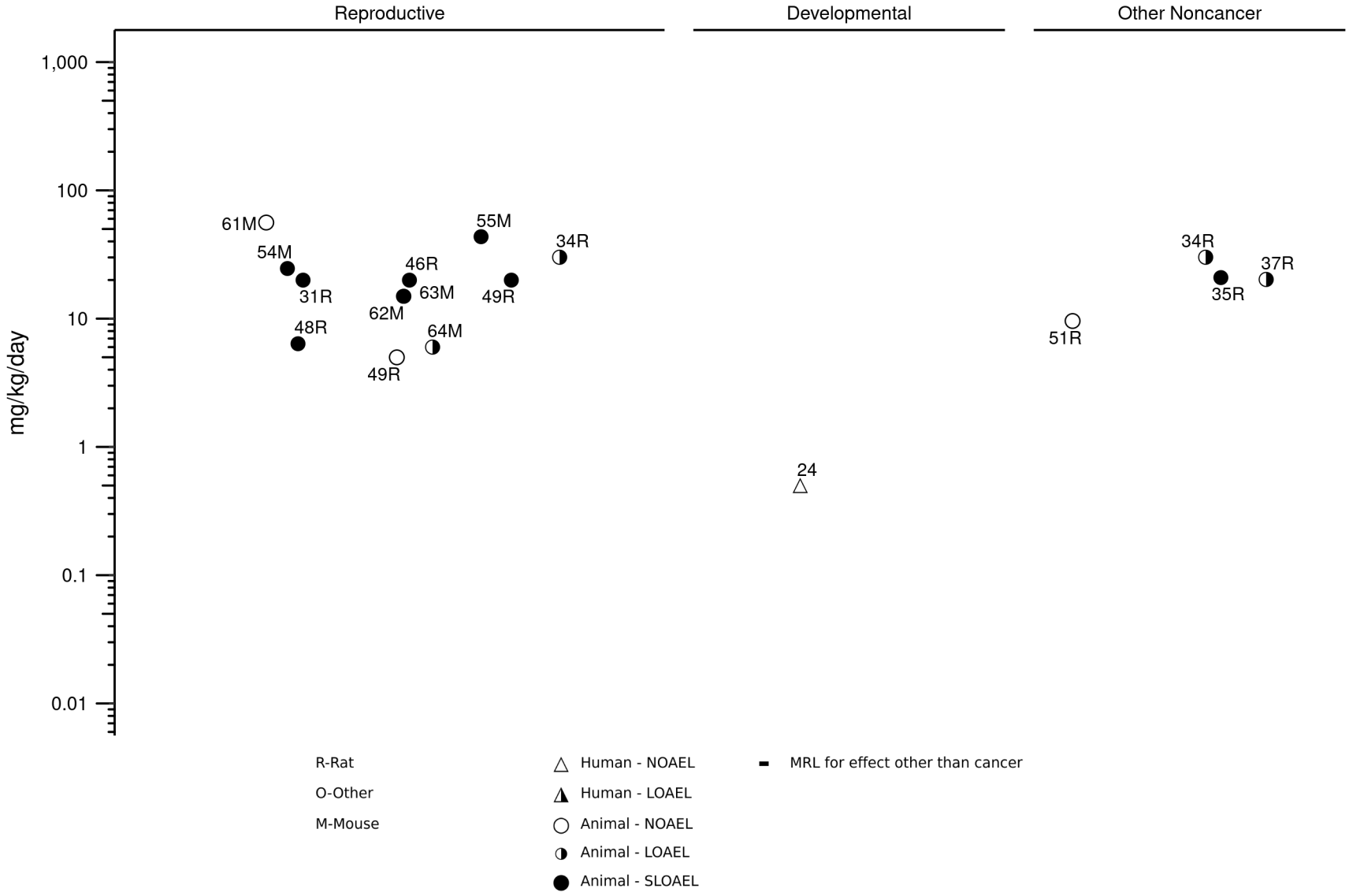


Table 2-3. Levels of Significant Exposure to Cobalt – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (%)	Parameters monitored	Endpoint	NOAEL (%)	Less serious LOAEL (%)	Serious LOAEL (%)	Effects
ACUTE EXPOSURE									
Ikarashi et al. 1992a									**Cobalt Chloride**
1	RAT (Fischer-344) 3F	Once/day, 3 days w/v%	0, 0.5, 1, 2.5, 5%	CS IX OF	Immuno	1	2.5		Increased proliferation of lymphatic cells at dose of 2.5% w/v% solution of DMSO by a factor of 3.8
Ikarashi et al. 1992b									**Cobalt Chloride**
2	RAT (Fischer-344) 3F	Once/day, 3 days	0, 1, 5, 10%	CS IX OF	Immuno		1		Increased proliferation of lymphatic cells by factors of 1.5, 2.5, and 4.1 for 1%, 5%, and 10% doses, respectively
Ikarashi et al. 1992b									**Cobalt Chloride**
3	RAT (Fischer-344) 3F	Once/day 1 or 3 days in DMSO without or with abrasion	0, 5%	CS IX OF	Immuno		5		Increased proliferation of lymphatic cells by factor of 1.9 (after 1 dose) or 4.3 (after 3 doses without abrasion); pre-abrasion enhanced the 3-dose response another factor of 2.1
Bonefeld et al. 2015									**Cobalt Chloride**
4	MOUSE (NS) NS	Daily, 2 days	0, 10%	CS OF	Dermal		10		Swelling at the application site on the ears (increased ear thickness) by 1% for initial dose, 5% after challenge dose
					Immuno		10		Proliferation of B, CD4, and CD8 cells was approximately 40% for each cell type by initial plus challenge doses

Table 2-3. Levels of Significant Exposure to Cobalt – Dermal

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (%)	Parameters monitored	Endpoint	NOAEL (%)	Less serious LOAEL (%)	Serious LOAEL (%)	Effects
Ikarashi et al. 1992a									**Cobalt Chloride**
5	MOUSE (CBA/N) 3F	Once/day, 3 days	0, 0.5, 1, 2.5, 5 w/v%	CS IX OF	Immuno		0.5		Increased proliferation of lymphatic cells at a dose of 0.5 w/v% solution of DMSO by a factor of 2.1
Ikarashi et al. 1992a									**Cobalt Chloride**
6	GN PIG (Hartley) 3F	Once/day, 3 days	0, 0.5, 1, 2.5, 5% w/v%	CS IX OF	Immuno	2.5	5		Increased proliferation of lymphatic cells at dose of 5% w/v% solution of DMSO by a factor of 3.3
INTERMEDIATE EXPOSURE									
Kincaid et al. 1954									**Cobalt Dicobalt octacarbonyl**
7	GN PIG (NS) 3NS	Once/day, 5 days/week, 18 days	0, 2.4 %	CS	Dermal		2.4		Skin lesions, scabs, and denuded areas after dermal application at application site

CS = clinical signs; F = female(s); Immuno = immunological; IX = immune function; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function

Table 2-4. Occupational Exposures to Cobalt and Health Outcome Associations

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, Covariates Considered and Adjustments	Outcomes and Limitations
Hematological		
Lantin et al. 2011 **Study Type:** Cross-sectional study of RBC and thyroid function in 249 workers in a cobalt refinery in Belgium, February 2008-August 2009.	**Exposure:** Blood and urine cobalt were assessed. Median blood and urine cobalt were 0.1 µg/100 mL and 3.9 µg/g creatinine, respectively. An integrated exposure index (IEI) based on historical biomonitoring records was used to assess long-term exposure, with a median of 106 µg/g creatinine × years. **Inclusion/Exclusion Criteria:** Retired workers were included only if they experienced substantial cobalt exposures in the past (minimum 5 to 8 years). Workers who were on chemotherapy or had hemochromatosis or hyperthyroidism were excluded. **Covariates Considered/Other Regression Adjustments:** Age, exercise, alcohol intake, cigarette smoking, and ethnicity.	**Outcomes:** No significant effects of cobalt exposure were observed on RBC measures or thyroid function. **Limitations:** Potential bias from residual confounding and healthy worker effect. Cross-sectional design precludes inferences of temporality.
Cardiovascular		
Lantin et al. 2013 **Study Type:** Cross-sectional study of cardiomyopathy in 237 workers in a cobalt refinery in Belgium, February 2008-August 2009.	**Exposure:** Recent exposures were assessed via urinary cobalt. Chronic exposure was assessed using an integrated exposure index (IEI) based on historical biomonitoring records. Median was approx. 4 µg/g creatinine for urinary cobalt and 100 µg/g creatinine × years for IEI. **Inclusion/Exclusion Criteria:** Participants with valvular heart disease, history of myocardial infarction, haemochromatosis or chemotherapy were excluded from the analysis. **Covariates Considered/Other Regression Adjustments:** Body mass index, height, age, heart rate, exercise, thyroid function, arterial hypertension,	**Outcomes:** Urinary cobalt was associated with decreased left ventricle volume, but not with any signs of dilated cardiomyopathy. No associations were found between IEI and echocardiographic or electrocardiographic parameters. **Limitations:** Potential bias from residual confounding and healthy worker effect. Cross-sectional design precludes inferences of temporality.

Table 2-4. Occupational Exposures to Cobalt and Health Outcome Associations

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, Covariates Considered and Adjustments	Outcomes and Limitations
	smoking, alcohol intake, diabetes, ferritin, abnormal ECG, emphysema, ethnicity, retirement status, and several types of heart disease.	
Linna et al. 2003a **Study Type:** Cross-sectional study of cardiotoxicity in 297 factory workers (203 exposed and 94 controls) in Finland, 1999	**Exposure:** Cumulative exposure was assessed using job-exposure matrices and ambient air measurements. Exposed workers had mean cobalt exposure of 0.82 mg-years. **Inclusion/Exclusion Criteria:** Employees with at least one year of exposure were included in the study. Workers with co-exposure to potential confounding chemicals (e.g., arsenic), history of myocardial infarction, or cardiac valvular disease were excluded. **Covariates Considered/Other Regression Adjustments:** Age, smoking status, blood pressure, alcohol overuse, physical activity, BMI, and heart rate.	**Outcomes:** Significant increases in left ventricular isovolumetric relaxation time and in deceleration time of the velocity of the early rapid filling wave were associated with cobalt exposure, indicating altered diastole. No differences in ECG findings, conduction parameters, or blood pressure were observed. **Limitations:** Relatively small number of participants in the control group. Control group was comprised of factory workers exposed to zinc.
Linna et al. 2020 **Study Type:** Cross-sectional study of cardiotoxicity in 142 factory workers (93 exposed and 49 controls) in Finland, 2006	**Exposure:** Cumulative exposure was assessed using job-exposure matrices and ambient air measurements. Exposed workers had mean cobalt exposure of 0.82 mg-years. **Inclusion/Exclusion Criteria:** Workers with co-exposure to potential confounding chemicals (e.g., arsenic), history of myocardial infarction, or cardiac valvular disease were excluded. **Covariates Considered/Other Regression Adjustments:** Age, smoking, BMI, hypertension, alcohol use, athleticism, and heart rate.	**Outcomes:** Prevalence of heart diseases, hypertension, and stroke were similar in exposed and unexposed workers. Exposed workers were more likely to report asthma and pulmonary diseases. No significant differences in blood pressure, heart rate, or ECG findings were observed by cobalt exposure. **Limitations:** Relatively small number of participants in the control group. Control group was comprised of zinc factory workers.

Table 2-4. Occupational Exposures to Cobalt and Health Outcome Associations

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, Covariates Considered and Adjustments	Outcomes and Limitations
Respiratory		
Hamzah et al. 2014 **Study Type:** Cross-sectional study of respiratory health in 436 factory workers in Malaysia, 2013	**Exposure:** Personal air sampling was conducted. TWA 8-hour cobalt concentrations in different job categories ranged from 0.01 mg/m^3 to 0.19 mg/m^3. **Inclusion/Exclusion Criteria:** Male factory workers aged 18 to 56 years old and over 1 year of employment were included. **Covariates Considered/Other Regression Adjustments:** Smoking status.	**Outcomes:** Exposure to cobalt was associated with significant increases in chronic phlegm and decreases in FVC and FEV1 ($p<0.05$). **Limitations:** Workers were co-exposed to high levels of chromium. Lung function tests may not have been able to identify all potential lung abnormalities, particularly in the small airways. Potential for bias from healthy worker effect.
Linna et al. 2003b **Study Type:** Cross-sectional study of cardiotoxicity in 110 factory workers (85 exposed and 25 controls) in Finland, 2006	**Exposure:** Cumulative exposure was assessed based on historical monitoring. Mean exposure to cobalt was 1.0 mg-years (range 0.1-4.6). **Inclusion/Exclusion Criteria:** Workers with a history of welding or work in other metallurgic plants were excluded. **Covariates Considered/Other Regression Adjustments:** Age and smoking status.	**Outcomes:** Symptoms of asthma such as phlegm, cough, and shortness of breath were more common in exposed participants. Compared to controls, the exposed group had significantly higher prevalence of suspected asthma (17.3% vs. 5.8%, $p<0.01$) and work-related asthma (14% vs. 3%, $p<0.008$). Respiratory flow rates at 50% and 25% of vital capacity were significantly lower in exposed smokers than in unexposed smokers. **Limitations:** Workers were co-exposed to irritants such as SO_2. Relatively small number of participants in the control group.
Sauni et al. 2010 **Study Type:** Case study of occupational asthma in cobalt plant workers in Finland, 1967-2003	**Exposure:** Mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m^3. **Inclusion/Exclusion Criteria:** None. **Covariates Considered/Other Regression Adjustments:** None.	**Outcomes:** In departments with higher air concentrations of cobalt, incidence of asthma was higher and latency period before symptoms occurred was shorter. Upon bronchial challenge tests for cobalt, workers displayed immediate, delayed, and dual asthmatic reactions. **Limitations:** Cases were diagnosed over a long-time span; challenge tests were not standard over

Table 2-4. Occupational Exposures to Cobalt and Health Outcome Associations

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, Covariates Considered and Adjustments	Outcomes and Limitations
		the study period. Co-exposures to irritant gases such as SO_2 occurred.
Walters et al. 2013 **Study type:** Case report of occupational asthma (n=4) and cross-sectional study (n=62) of factory workers in Alabama, 2010	**Exposure:** Urinary cobalt concentrations and excretion were assessed. Mean values were 0.6 µg/L and 0.6 µg/g creatinine, respectively. **Inclusion/Exclusion Criteria:** None. **Covariates Considered/Other Regression Adjustments:** None.	**Outcomes:** One case was attributed to cobalt exposure. Urinary cobalt concentrations were significantly higher in workers with probable/definite occupational asthma than in asymptomatic workers ($t<0.001$). No associations between cobalt exposure and occupational rhinitis were observed. **Limitations:** Workers were co-exposed to metals including chromium. Potential bias from confounding and healthy worker effect. Cross-sectional design precludes inferences of temporality.
Dermal		
Wahlqvist et al. 2020 **Study Type:** Cross-sectional study of 71 metal factory workers in Sweden, March 2017 to October 2018	**Exposure:** Air sampling of inhalable dust and biological sampling of blood, urine, and skin. Geometric mean breathing air cobalt concentrations ranged from 0.0001 to 0.019 mg/m^3. Mean blood cobalt concentrations were 6.2 nmol/L pre-shift, 6.9 nmol/L post-shift, and 6.6 nmol/L after 2 days. **Inclusion/Exclusion Criteria:** None. **Covariates Considered/Other Regression Adjustments:** None.	**Outcomes:** Many workers reported dry skin (42%). Prevalence of eczema on hands, face, and arms was 6-7%. **Limitations:** Dermal effects assessed via self-report. High percentage of exposed workers (14%) had eczema as a child.

BMI = body mass index, ECG = electrocardiogram, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RBC = red blood cell, TWA = time-weighted average

Table 2-5. Environmental Exposure to Cobalt and Health Outcome Associations in Human Studies

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, Covariates Considered and Adjustments	Outcomes and Limitations
Hematological		
Jefferson et al. 2002 **Study Type:** Case-control study of cobalt levels and excessive erythrocytosis in 80 Peruvian men (21 high-altitude cases, 25 high-altitude controls, and 28 sea-level controls).	**Exposure:** Measured serum cobalt. Normal cobalt concentrations were considered to be 1.7 to 5.1 nmol/L. In the subset of cases with packed-cell volume >75%, concentrations ranged from 22 to 71 nmol/L. **Inclusion/Exclusion Criteria:** Men who smoked more than five cigarettes per day or had phlebotomy conducted within the past year were excluded from the study. **Covariates Considered/Other Regression Adjustments:** Altitude.	**Outcomes:** Serum cobalt was significantly elevated in cases (defined as packed-cell volume >65%) as compared to sea-level controls ($p = 0.002$) and high-altitude controls ($p = 0.002$). In cases, serum cobalt was correlated with packed-cell volume (erythrocytosis) ($r = 0.4$, $p = 0.01$). **Limitations:** Small sample size. Serum cobalt is only indicative of recent exposure; controls may have had past cobalt exposure.

Table 2-6. Oral Exposure to Cobalt and Health Outcome Associations in Human Studies

Reference, Study Type, and Study Population	Exposure, Inclusion/Exclusion Criteria, Covariates Considered and Adjustments	Outcomes and Limitations
Hematological		
Finley et al. 2013 **Study Type:** Human controlled exposure study of cobalt ingestion in 10 adults in the United States	**Exposure:** Volunteers ingested 1.0 mg/day of cobalt (0.08-0.19 mg/kg/day) for 31 days. Male and female participants had mean serum cobalt concentrations of 16 µg/L and 33 µg/L, respectively. **Inclusion/Exclusion Criteria:** Exclusion criteria were use of vitamins or dietary supplements; history of cobalt allergy; prior total joint replacement; history of cardiovascular, thyroid, kidney, or liver disease; insulin-dependent diabetes; weight <45 kg; and pregnancy or lactation. **Covariates Considered/Other Regression Adjustments:** None.	**Outcomes:** Cobalt ingestion was not associated with overt adverse health effects or biochemical indicators of thyroid, cardiac, liver, or kidney functions. In males only, there was a non-clinically significant (<5%) increase in hemoglobin, hematocrit, and RBC counts at 7 days after dose termination. **Limitations:** Small sample size and homogenous sample of healthy adults.
Tvermoes et al. 2014 **Study Type:** Human controlled exposure study of cobalt ingestion in 10 adults in the United States	**Exposure:** Volunteers ingested 1.0 mg/day of cobalt (0.08-0.19 mg/kg/day) for up to 90 days. Mean serum cobalt concentrations in men and women were 25 µg/L and 71 µg/L, respectively. **Inclusion/Exclusion Criteria:** Exclusion criteria were use of vitamins or dietary supplements; history of cobalt allergy; prior total joint replacement; history of cardiovascular, thyroid, kidney, or liver disease; insulin-dependent diabetes; weight <45 kg; and pregnancy or lactation. **Covariates Considered/Other Regression Adjustments:** None.	**Outcomes:** No significant changes in hematological parameters or biomarkers of cardiac, liver, or kidney function were observed. One female participant had elevated TSH and decreased T4 levels. Cobalt was not associated with cardiac, auditory, or visual changes. Some participants showed non-significant decreases in sensory nerve conduction velocity and amplitude. **Limitations:** Small sample size and homogenous sample of healthy adults.

RBC = red blood cell, TSH = thyroid-stimulating hormone, T4 = free thyroxine

2.2. DEATH

No studies were identified regarding death in humans after inhalation, oral, or dermal exposure to cobalt at any duration.

Inhalation

In laboratory animal studies, high dose acute- and intermediate-duration exposure to cobalt appeared to cause mortality but chronic-duration exposure to lower concentrations had no effect on survival. Acute inhalation of cobalt hydrocarbonyl was examined in albino rats by Palmes et al (1959) and it established that the LC_{50} for a two-week exposure was 165 mg Co/m^3. A 30-minute exposure to 78 mg Co/m^3 resulted in death of 3/5 albino rats (Palmes et al. 1959). In NTP (2014), lethal effects were seen in F344/N rats and B6C3F_1 mice exposed to 20 and 40 mg Co/m^3, respectively, after a 60-hour exposure. At 20 mg Co/m^3 5/5 males and 3/5 female rats died and at 40 mg Co/m^3, 4/10 mice died (NTP 2014). Intermediate-duration exposure to 6.29 mg Co/m^3 for 13 weeks was lethal only to B6C3F_1 mice and not to F344/N rats (Bucher et al. 1990; NTP 1991). A 3-month exposure to 9 mg Co/m^3 did not cause death in albino rats or guinea pigs (species not specified) (Palmes et al. 1959), and exposure to cobalt sulfate heptahydrate for 13 weeks did not affect the survival of either male and female Fisher-344 rats (Bucher et al. 1990). After a 16-day exposure to 19 mg Co/m^3 of cobalt sulfate, 2/5 male rats and 0/5 female rats died, while 5/5 male and 5/5 female mice died (NTP 1991). Chronic exposure for 105 weeks to cobalt sulfate heptahydrate did not have a significant effect on death in F344/N rats at 0.63 mg Co/m^3 (Bucher et al. 1999; NTP 1998). No increase in mortality in F344/N rats or B6C3F_1 mice of either sex was seen following 104-weeks of exposure to 1.14 mg Co/m^3 as cobalt sulfate (Bucher et al. 1999; NTP 1998). Chronic-duration exposure to cobalt metal for 105 weeks showed a reduced survival probability in male mice and female (F344/N) rats exposed to 2.5 mg Co/m^3, compared to controls (NTP 2014). Lethal levels for each species and duration category are presented in Table 2-1 and plotted in Figure 2-2.

Oral

In animals, acute-duration oral administration of cobalt at high doses caused death. Doming and Llobet (1984) showed that a single oral exposure to 161 mg Co/kg caused death in 5/20 Sprague-Dawley rats. Acute oral exposure to cobalt chloride tetrahydrate at a dose of 149 mg Co/kg/day killed 10 out of 20 Sprague-Dawley rats in the treatment group (Domingo et al. 1985a).

Oral intermediate-duration exposure to cobalt compounds in animals resulted in death. In an intermediate-duration exposure study, 4/10 Wistar rats died following exposure to 27 mg Co/kg/day for 60 days (Abdel-Rahman Mohamed et al. 2019). Elbetieha et al. (2008) demonstrated that a 12-week exposure to

11.61 mg Co/kg/day as cobalt chloride hexahydrate caused the death of 1 Swiss mouse during the 10th week (Elbetieha et al. 2008). The authors in Elbetieha et al. (2008) did not specify whether this death was treatment related. No death was observed at 20.3 mg Co/kg/day as cobalt chloride in Wistar rat dams and pups exposed for 2 weeks during gestation and then additionally for 2 weeks of lactation (Garoui et al. 2013). Death of 1 mouse was observed during the 10th week in a study where ICR mice were orally exposed to 6.4 mg Co/kg/day in water for 12 weeks (Gluhcheva et al. 2020). The authors of Gluhcheva et al. (2020) did not specify whether this effect was treatment related. Following a 5-week exposure to 20 mg Co/kg/day as cobalt sulfate by gavage, 4 out of 10 guinea pigs (species not specified) died (Mohiuddin et al. 1970). No death was reported among BALB/c mice exposed to cobalt in utero, via breastmilk, and then orally (Zaksas et al. 2013). In this study, dams were exposed to 56.7 mg Co/kg/day as cobalt chloride hexahydrate for 2-3 days during gestation, followed by 25 days during breastfeeding, and then offspring were orally exposed for 35 days through drinking water (Zaksas et al. 2013). A 4-week exposure to 68 mg Co/kg/day as cobalt chloride hexahydrate did not cause any death in Sprague-Dawley rats (Khalil et al. 2020).

Dermal

Two studies in animals reported no death following dermal exposures to cobalt compounds. Acute 3-day dermal exposure to 0.5-10% cobalt chloride did not cause death in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). Intermediate dermal exposure once a day for 18 days to 51.7 mg Co/kg/day as dicobalt octacarbonyl did not cause death in guinea pigs (species not specified) (Kincaid et al. 1954).

Other

Acute-duration exposure by subcutaneous injection of 45 mg Co/kg/day as dicobalt octacarbonyl did not cause death in guinea pigs (Kincaid et al. 1954). Acute-duration exposure to cobalt chloride tetrahydrate at a dose of 12 mg Co/kg/day in the form of intraperitoneal injection killed 13 Sprague-Dawley rats out of 20 in the treatment group (Domingo et al. 1985a). No Wistar rats died after a single subcutaneous injection of 7 mg Co/kg (Horiguchi et al. 2004). Doming and Llobet (1984) showed that a single intraperitoneal injection of cobalt chloride at 12 mg Co/kg/day caused the death of 5 Sprague-Dawley rats in a treatment group of 20 (Domingo and Llobet 1984).

2.3. BODY WEIGHT

No studies in humans examined changes in body weight following inhalation, oral, or dermal exposure to cobalt.

Inhalation

Several studies in animals indicate that inhalation exposure to cobalt and cobalt compounds results in decreased body weight. Intermediate exposure to 20 mg Co/m^3 for 16 days resulted in 45% and 20% decreases in body weight in female and male F344/N rats, respectively, compared to control rats (NTP 2014). Similar effects were seen in B6C3F_1 mice, where females showed a 37% decrease, and males a 26% decrease in body weight after exposure to 40 mg Co/m^3 (NTP 2014). Inhalation exposure to 30 mg Co/m^3 as cobalt sulfate heptahydrate for 13 weeks, 5 days a week, 6 hours/day reduced the mean body weights in male F344/N rats; however, no differences were seen in female rats when compared to control animals (Bucher et al. 1990). A 3-month exposure to cobalt metal for 5 days a week, 6 hours/day at 0.1 mg Co/m^3 resulted in a 16% decrease in body weight in pigs (strain not specified) (Kerfoot 1974). B6C3F_1 mice exposed to 19 mg Co/m^3 as cobalt sulfate heptahydrate for 16 days, 5 days a week, 6 hours/day showed a 33% and 20% decrease in body weight in males and females, respectively (NTP 1991). A 13-week 5 days a week, 6 hours/day exposure to 6.29 mg Co/m^3 as cobalt sulfate heptahydrate caused a 22% decrease in female B6C3F_1 mice and a 14% decrease in male mice (NTP 1991). A 14-week, 5 days a week, 6 hours/day exposure to cobalt metal at 10 mg Co/m^3 decreased body weight by 13-14% in B6C3F_1 mice (NTP 2014). No weight loss was seen in albino rats or guinea pigs (strain not specified) exposed for 3 months to cobalt at a level of 9 mg Co/m^3 as cobalt hydrocarbonyl (Palmes et al. 1959).

Continuous chronic-duration exposure to 5 mg Co/m^3 for 105 weeks (5 days a week, 6 hours/day) caused a decrease in body weight in both male (~23%) and female (21%) F344/N rats and in male (11%) and female (25%) B6C3F_1 mice (NTP 2014). Lifetime continuous exposure, (5 days a week, 7 hours/day) to 7.9 mg Co/m^3 as cobalt oxide did not result in decreased body weight gain in hamsters (ENG:ELA) (Wehner et al. 1977).

Oral

Decreased body weight was commonly observed in animals orally exposed to cobalt and its compounds. Intermediate-duration exposure of 30 days to 0.379 mg Co/kg/day as cobalt chloride caused a 45% decrease in body weight gain in male Sprague-Dawley rats (Chetty et al. 1979). Rats showed a 33% decrease in body weight gain after exposure to 4.2 mg Co/kg/day as cobalt sulfate for 4 weeks (Clyne et al. 1988). Exposure of Sprague-Dawley rats to 8.4 mg Co/kg/day as cobalt sulfate for 8-24 weeks resulted in a 30% to 31% decrease in body weight (Haga et al. 1996; Pehrsson et al. 1991). At 9.6 mg Co/kg/day as cobalt chloride for 2 weeks there were no effects on body weight in Sprague-Dawley rats (Saker et al. 1998). Elbetieha et al. (2008) demonstrated that a 12 week exposure to 23 mg Co/kg/day as cobalt chloride hexahydrate induced a significant 7% increase of body weight in Swiss mice, which is not

considered biologically significant based on ATSDR guidelines (ATSDR 2018). A 7.1% decrease in body weight gain compared to controls was observed in a study where ICR mice were orally exposed to 6.36 mg Co/kg/day in water for 12 weeks (Gluhcheva et al. 2020). An in utero dose of 56.73 mg Co/kg/day as cobalt chloride hexahydrate for 2-3 days, followed by an equivalent dose for 25 days via breastmilk, followed by the same dose for 35 days orally via drinking water significantly decreased the average body weight of offspring BALB/c mice by 33% by day 60 of exposure when compared to control animals (Zaksas et al. 2013). The body weight at autopsy was reduced by 11% (males) and 9% (females), respectively, at 7.44 mg Co/kg bw/day as $CoCl_2$. At the end of the 4-week recovery period (test day 118), the body weight of the male and female animals exposed to the highest dose was still reduced by 17% or by 13%, respectively, compared with the control group (Danzeisen et al. 2020). Danzeisen et al. (2020) also examined the effects of oral exposure to Co_3O_4 at the dose of 734 mg Co/kg/day for 90 days and observed there were marginal effects on body weight in male and female rats.

Dermal

Dermal exposure to cobalt did not induce body weight changes in laboratory animal studies. Acute-duration dermal exposure to 0.5-10% cobalt chloride (dissolved in DMSO) did not induce any changes in body weight in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No body weight changes were observed after intermediate-duration dermal exposure to 51.70 mg Co/kg/day as dicobalt octacarbonyl in methyl ether ketone in guinea pigs (Kincaid et al. 1954). Bonefeld et al. (2015) and Ikarashi et al. (1992a, 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Acute-duration exposure by subcutaneous injection to 45 mg Co/kg/day as dicobalt octacarbonyl did not affect body weight in guinea pigs (strain not specified) (Kincaid et al. 1954). A daily 6-week subcutaneous injection study in albino rats caused a 24% weight loss following administration of cobalt chloride at a dose of 2.5 mg Co/kg/day (Stanley et al. 1947).

2.4. RESPIRATORY

Inhalation

Inhalation exposure to cobalt and its compounds resulted in altered spirometry and increased evidence of pulmonary irritation and dyspnea in human occupational exposure studies. In laboratory animal studies, acute-duration inhalation exposure to cobalt increased inflammation, edema, and necrosis in the lungs.

Intermediate-duration exposure caused an increase in lung weight and inflammation and chronic-duration exposure increased neoplasms and hyperplasia along with lung inflammation.

Several occupational studies have found respiratory effects associated with cobalt exposures. In Malaysian factory workers exposed to 8-hour cobalt concentrations ranging from 0.01 to 0.19 mg/m^3, exposure to cobalt was associated with significant increases in chronic phlegm and decreases in forced vital capacity and forced expiratory volume ($p<0.05$) (Hamzah et al. 2014). Cobalt exposure has also been linked to increased risk of occupational asthma (Linna et al. 2003a; Sauni et al. 2010; Walters et al. 2013). Compared to controls, exposed factory workers in Finland had significantly higher prevalence of suspected asthma (17.3% vs. 5.8%, $p<0.01$) and work-related asthma (14% vs. 3%, $p<0.008$) (Linna et al. 2003a). Sauni et al. (2010) conducted a case study of occupational asthma in cobalt plant workers in Finland from 1967-2003 where the mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m^3. Until 1987, cobalt was being produced from pyrite ore concentrate which led to co-exposures with irritant gases like sulfur dioxide (SO_2) and ammonia (NH_3) that are known respiratory irritants (Andersson et al. 2006; ATSDR 1998; Huber and Loving 1991). After 1987, cobalt was produced using by-products of the metallurgic industry as raw material which eliminated the co-exposure to the irritant gases and the incidence of asthma decreased to only 1 case between 1987-2003 compared to 21 cases between 1967-1987 (Sauni et al. 2010). Therefore, it is likely that the health effects observed in Sauni et al. (2010) were due to the co-exposure to sulfur dioxide and ammonia and not cobalt alone. Walters et al. (2013) found that urinary cobalt concentrations were significantly higher in workers with probable or definite occupational asthma than in asymptomatic workers ($t<0.001$). Morfeld et al. (2017) reported an increase in non-malignant respiratory diseases in a cohort working in a German hard metal industry after occupational exposure. In the studies detailed above, all the factory workers were subjected to co-exposures with other metals like nickel and chromium and irritant gases, therefore the health effects observed might not be caused by cobalt alone (Hamzah et al. 2014; Linna et al. 2003a; Sauni et al. 2010; Walters et al. 2013). Respiratory effects of exposure to cobalt, tungsten, and nickel were evaluated in an international cohort of hard metal production workers (Marsh et al. 2017a; Marsh et al. 2017b).Workers from 3 companies, 17 sites among 5 countries, including the United States, Austria, Germany, Sweden, and the United Kingdom were evaluated. Information on respiratory parameters were obtained from various national datasets, and phone interviews were completed for participants when possible. These interviews provided information on demographics and lifestyle factors. The exposed workers showed chronic obstructive pulmonary disease, bronchitis, emphysema, and asthma (Marsh et al. 2017a; Marsh et al. 2017b).

An acute 6-hour exposure to cobalt dust at 0.038 mg Co/m^3 decreased lung function in exposed workers compared to non-exposed workers (Kusaka et al. 1986a). Chronic 3-year exposure to 0.126 mg Co/m^3 caused a 2.7% decrease in lung function, specifically FEV1% in exposed workers, while 0.085 mg Co/m^3 did not affect the pulmonary function (Kusaka et al. 1986a). Occupational exposure to cobalt metal for unspecified periods at 0.0152 and 0.1355 mg Co/m^3 decreased lung parameters FEV1 and FVC by ~10% and increased cough, sputum, and dyspnea in exposed workers, and these parameters correlated with their urinary cobalt levels (Gennart and Lauwerys 1990). In this study by Gennart and Lauwerys (1990), cobalt air concentrations were measured from 2 rooms that workers moved freely between during the work shift and no individual worker stay times or exposures were provided. The absence of this information did not allow accurate estimation of the average exposure per worker. However, at a similar concentration of 0.0175 mg Co/m^3, there were no effects observed in workers after a chronic occupational exposure for 3 years (Deng et al. 1991). Occupational exposure to cobalt at the concentration of 0.0151 mg Co/m^3 decreased FEV1 (5%) and FVC (5%) in exposed workers. The exposed workers also exhibited increased incidence of cough (11/91), wheezing (4/91), and upper airway irritation (40/91) (Nemery et al. 1992). Among the workers subjected to work-related exposure, upper airway effects were seen in 30% of controls, 26% of low dose individuals, and 43% of high dose individuals. Work-related cough was not observed in the control subjects, but was observed in 4% of low exposure individuals and in 12% of high exposure individuals. While the respiratory effects appeared at a greater rate in individuals who were exposed to higher concentrations of Co, the study collected but did not report the smoking status of this treatment group. There was no correlation between cobalt exposure and respiratory effects on an individual level within this group; correlations occurred only on a group level: low, high, control. Therefore, smoking may have caused or contributed to the increase in cough in the 12% of individuals in the higher concentration exposure group. Personal and area air samples correlated well based on results of monitoring a set of individuals in each primary work area; correlations occurred on a group level: low, high, control. The lower exposure concentration of 0.0053 mg Co/m^3 did not alter pulmonary function in the exposed workers.

Animal studies have also observed respiratory effects consistent with the effects seen in human studies. Following a 30-minute exposure to 90 mg Co/m^3 all albino rats showed pulmonary irritation with dose-dependent edema and damage in the lungs (Palmes et al. 1959). The albino rats also exhibited labored breathing and disturbed respiration (Palmes et al. 1959). In this study, all animals (albino rats and guinea pigs) exposed to concentrations ≥106 mg Co/m^3 showed lung inflammation. A 2-week exposure to cobalt chloride at 2.4 mg Co/m^3 increased lung weight by 20% and retention of lavage fluid by 53% in female

Hartley guinea pigs (Camner et al. 1993). As per the authors, the significance of retained lavage fluid is unclear.

Male albino rats exposed to 9 mg Co/m^3 intermittently for 3 months showed lung inflammation, edema, congestion, and bronchitis (Palmes et al. 1959). In F344/N rats exposed to cobalt concentrations as low as 0.21 mg Co/m^3 for 13 weeks, relative lung weights increased by 14% compared to controls (Bucher et al. 1990; NTP 1991). B6C3F1 mice exposed to cobalt at 19 mg/m^3 for 16 days showed lesions and degeneration of the olfactory epithelium, squamous metaplasia in the respiratory epithelium, inflammation in the nose, and metaplasia of the trachea (Bucher et al. 1990; NTP 1991). Necrosis and inflammation of the respiratory tract epithelium (nasal turbinates, larynx, trachea, and bronchioles) were reported in F344/N rats exposed to 19 mg Co/m^3 and in mice exposed to concentrations ≥1.9 mg Co/m^3 for 16 days (Bucher et al. 1990; NTP 1991).

Intermittent exposure of F344/N rats and $B6C3F_1$ mice to cobalt as cobalt sulfate for 13 weeks, resulted in adverse effects on all parts of the respiratory tract, with the larynx being the most sensitive part (Bucher et al. 1990; NTP 1991). NTP (1991) observed an increase in lung weights in both male (7%) and female (14%) rats along with histiocytic infiltrates in the lung reported at similar levels in both the rats and mice. Severe edema and lung inflammation were observed in albino rats following exposure to a concentration of 90 mg Co/m^3 for 3-months (Palmes et al. 1959). A continuous intermediate 3-month exposure to 0.1 mg Co/m^3 as cobalt metal in pigs decreased specific respiratory compliance by 29% (Kerfoot 1974). At a concentration of 20 mg Co/m^3, F344/N rats of both sexes showed abnormal breathing, increased incidence of lung hemorrhage, and acute inflammation (Behl et al. 2015; NTP 2014). An intermediate 16-day intermittent inhalation exposure to cobalt metal at 2.5 mg Co/m^3 in F344/N rats and B6C3F1 mice of both sexes induced necrosis in the respiratory epithelium and atrophy of olfactory epithelium (Behl et al. 2015; NTP 2014). A 14-week intermittent intermediate exposure to 0.625 mg Co/m^3 caused an increase in the incidence of chronic active inflammation in lungs and an increase in relative lung weight in both male and female F344/N rats (Behl et al. 2015; NTP 2014). Both male and female B6C3F1 mice exposed to 0.625 mg Co/m^3 for 14 weeks showed cytoplasmic vacuolization of the bronchiole epithelium (Behl et al. 2015; NTP 2014). A 17-week intermittent exposure in male rabbits to 0.4 mg Co/m^3 caused inflammation in lungs, accumulation of macrophages, and at 2 mg Co/m^3, caused severe inflammation and an increase in lung lobe weight by 25% (Johansson et al. 1987). Johansson et al. (1992) also observed alterations in pulmonary tissues, alterations in BAL parameters, and a 22% decrease in macrophages in male rabbits after a 4-month intermittent exposure to cobalt metal.

In F344/N rats, chronic exposure to cobalt sulfate for 105 weeks caused inflammation of the larynx at ≥0.21 mg Co/m^3, and more severe effects on the nose, larynx, and lung were reported at concentrations

≥0.21 mg Co/m^3 (NTP 1998). In B6C3F1 mice, acute inflammation of the nose was observed at ≥0.63 mg Co/m^3 along with atrophy, metaplasia, or hyperplasia in the larynx and olfactory epithelium (NTP 1998). Exposure of F344/N rats and mice to aerosols of cobalt (as cobalt sulfate) at concentrations from 0.06 to 0.63 mg Co/m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of males and females (Bucher et al. 1999; NTP 1998). A 2-year intermittent chronic exposure to cobalt metal at 1.25 mg Co/m^3 increased the incidence of lung neoplasm and non-neoplastic lesions in the lungs and nose in rats and mice of both sexes (Behl et al. 2015; NTP 2014). Lifetime intermittent exposure to cobalt oxide at 7.9 mg Co/m^3 caused lung inflammation and emphysema in male ENG:ELA hamsters (Wehner et al. 1977).

Oral

No studies examined respiratory toxicity in humans following oral exposure to cobalt.

A significant 33% increase in the weight of the lungs, without morphological or histological changes, was observed in Sprague-Dawley rats that received 30.2 mg Co/kg/day as cobalt chloride in drinking water for 3 months, as compared with controls (Domingo et al. 1984). No morphological changes were seen in the lungs of Wistar rats treated with 18 mg Co/kg/day for 4 months (Holly 1955).

Dermal

No studies were identified that examined respiratory effects in humans or animals following dermal exposure to cobalt.

2.5. CARDIOVASCULAR

Inhalation

Several studies were identified that examined cardiovascular effects in humans after occupational inhalation exposure to cobalt which provided contradictory evidence of cardiovascular toxicity. A study of cobalt refinery workers in Belgium, Lantin et al. (2013) found no association between cumulative cobalt exposures and any changes in echocardiographic or electrocardiographic parameters. Increased urinary cobalt was associated with decreased left ventricle volume, but not with any signs of dilated cardiomyopathy (Lantin et al. 2013). In a study of Finnish factory workers and a 6-year follow-up, no differences in electrocardiogram findings or blood pressure were observed from cobalt exposure (Linna et al. 2003b, 2020). Exposed workers did show significant changes in left ventricular relaxation and filling, indicating altered diastole (Linna et al. 2003b). However, at follow-up, prevalence of heart disease, hypertension, and stroke were similar in exposed and unexposed workers (Linna et al. 2020). Morfeld et

al. (2017) reported an increase in heart disease in a cohort working in a German hard metal industry after occupational exposure. Cardiovascular effects of exposure to cobalt, tungsten, and nickel were evaluated in an international cohort of hard metal production workers (Marsh et al. 2017a; Marsh et al. 2017b). Workers from 3 companies, 17 sites among 5 countries, including the United States, Austria, Germany, Sweden, and the United Kingdom were evaluated. Information on cardiovascular parameters were obtained from various national datasets, and phone interviews were completed for participants when possible. These interviews provided information on demographic and lifestyle factors. The exposed workers showed increased incidences of cardiovascular diseases as a result of occupational exposure (Marsh et al. 2017a; Marsh et al. 2017b). Exposure to 20 mg Co/m^3 did not cause cardiovascular effects in F344/N rats after a 16-day intermittent exposure (NTP 2014). In contrast, female B6C3F1 mice similarly exposed showed a 39% increase in heart weight at 40 mg Co/m^3 (NTP 2014). Intermittent exposure to cobalt metal at 0.1 mg Co/m^3 for 3 months caused a 14% increase in heart rate, a 38% decrease in QRS amplitude, and electrocardiogram abnormalities that may reflect ventricular impairment in pigs (strain not specified) (Kerfoot 1974). No signs of cardiovascular toxicity were observed in experimental studies where animals were exposed to concentrations ranging from 0.625 to 19 mg Co/m^3 for intermediate and chronic-durations in F344/N rats and 0.625 to 41.72 mg Co/m^3 for intermediate and chronic-duration exposures in B63F1 mice (NTP 1991, 1998, 2014).

Oral

No studies were identified that examined cardiovascular effects in humans after oral exposure to cobalt.

Animal studies indicate that oral exposure to cobalt induces cardiovascular effects for multiple animal species exposed to cobalt for acute and intermediate durations. In Wistar rats, oral exposure to 650 mg Co/L of cobalt chloride in drinking water (34 mg Co/kg/day) induced effects on the cardiovascular system (Ajibade et al. 2017). In this study, exposure to 33.7 mg Co/kg/day decreased glutathione (GSH) and glutathione peroxidase (GPx) expression in the heart by 2.2% and 11%, respectively (Ajibade et al. 2017). Cobalt exposure also increased mean blood pressure by 50% and Nf-kB expression by 67% (Ajibade et al. 2017). Acute-duration oral exposure to 18.38 mg Co/kg/day in Wistar rats caused cardiac damage in a study by Akinrinde et al. (2016). This study examined histopathology of the heart and observed hemorrhagic lesions with congestion of coronary blood vessels and mild infiltration of the myocardium and atrium by inflammatory cells. Additionally, a 12% decrease in systolic blood pressure, a 150% increase in lactate dehydrogenase, and a 67% increase in AST were also observed (Akinrinde et al. 2016b). A second acute-duration exposure study by Akinrinde et al. (2016) also corroborated their previous study as exposure to 19 mg Co/kg/day caused inflammation of the myocardium and areas of

myocardial infarction along with a 17, 24, and 21% decrease in systolic blood pressure, diastolic blood pressure, and mean arterial pressure, respectively, in Wistar rats (Akinrinde et al. 2016c).

Clyne et al. (2001) reported that exposure of Sprague-Dawley rats to 8.4 mg Co/kg/day, as cobalt sulfate, in the diet for 24 weeks resulted in significant reductions in a number of enzymes in cardiac tissues, including manganese-superoxide dismutase, succinate-cytochrome c oxidase, NADH-cytochrome c reductase, and cytochrome c oxidase, as well as reducing the mitochondrial ATP production rate (Clyne et al. 2001). Exposure of Sprague-Dawley rats to 8.4 mg Co/kg/day as cobalt sulfate resulted in left ventricular hypertrophy and impaired left ventricular systolic and diastolic functions (Haga et al. 1996). Conversely, in Sprague-Dawley rats exposed to 8.4 mg Co/kg/day as cobalt sulfate for 8 weeks, there were no effects on cardiac function (Pehrsson et al. 1991). A 3-week exposure to 12.4 mg Co/kg/day as cobalt chloride in male CFY rats resulted in cardiac damage, presenting as multifocal myocytolysis with myofibril degeneration (Morvai et al. 1993). Two to three months of daily exposure to 26 to 30.2 mg Co/kg/day in drinking water resulted in degenerative heart lesions (Grice et al. 1969) and a 9.4% increase in relative heart weight (Domingo et al. 1984) in Wistar and Sprague-Dawley rats, respectively.

An oral exposure to 20 mg Co/kg/day for 5 weeks as cobalt sulfate in guinea pigs (strain not specified) resulted in a 32% increase in relative heart weight along with pericardial effusion in 45% of the animals and combined endocardial, myocardial, and pericardial lesions in 75% of the samples examined histopathologically. Exposure also caused an increase in relative bradycardia, decrease in QRS voltage, and a significant increase in abnormal ECG findings (Mohiuddin et al. 1970). While there were no control groups included, Wistar rats exposed to a single dose of 176.6 mg Co/kg administered by gavage as cobalt fluoride or a single dose of 795 mg Co/kg administered as cobalt oxide showed a proliferation of interstitial tissue, swollen muscle fibers, and focal degeneration in the cardiac tissues in males and females (Speijers et al. 1982).

Dermal

No studies were identified regarding cardiovascular toxicity in humans after dermal exposure to cobalt.

No cardiovascular effects have been observed after dermal exposure to cobalt in animals. Acute-duration dermal exposure to 0.5-10% cobalt chloride did not induce any cardiovascular effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No cardiovascular effects were observed after intermediate-duration dermal exposure to 51.70 mg Co/kg/day as dicobalt octacarbonyl in guinea pigs (Kincaid et al. 1954).

Other

Acute-duration exposure by subcutaneous injection of 45 mg Co/kg/day as dicobalt octacarbonyl did not cause cardiovascular toxicity in guinea pigs (Kincaid et al. 1954).

2.6. GASTROINTESTINAL

No studies were identified that examined gastrointestinal effects in humans after inhalation, oral, or dermal exposure to cobalt.

Inhalation

No histological lesions were reported in the esophagus, stomach, duodenum, ileum, jejunum, cecum, colon, or rectum of rats or mice of both sexes exposed to 0.4 mg Co/m^3 to 41.72 mg Co/m^3 for 16 days, 0.06 to 6.29 mg Co/m^3 for 13-14 weeks, and 5 mg Co/m^3 and 0.63 mg Co/m^3 for 105 weeks (Behl et al. 2015; NTP 1991, 1998, 2014).

Oral

Studies showed that oral exposure to cobalt resulted in gastric distress in humans and changes in gut microbiota along with signs of intestinal injury in animals. Twice a day, daily oral exposure to 0.18 mg Co/kg/day for 12 weeks in humans caused gastric distress manifested as nausea and constipation in anephric patients (with non-functioning kidneys) (Duckham and Lee 1976). Intestinal injury in the form of loss of epithelial cells in the intestines were observed in Wistar rats exposed to 29 mg Co/kg/day as cobalt chloride (Akinrinde et al 2016). Acute-duration oral exposure to cobalt chloride at 37 mg Co/kg/day altered the gut microbiota composition in treated Sprague-Dawley rats which were quantified using 16s rRNA amplicon sequences (Richardson et al. 2018). No morphological changes in the gastrointestinal system were observed following exposure of 20 Sprague-Dawley male rats exposed to 30.2 mg Co/kg/day in drinking water for 3 months (Domingo et al. 1984) or in Wistar rats exposed to 18 mg Co/kg/day for 4 months (Holly 1955).

Dermal

No gastrointestinal effects have been observed after dermal exposure to cobalt in animals. Acute-duration dermal exposure to 0.5-10% cobalt chloride (in DMSO) did not induce gastrointestinal effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No gastrointestinal effects were observed after intermediate dermal exposure for 18 days, 5 days/week, once/day to 2.4% cobalt as dicobalt octacarbonyl (in methyl ethyl ketone) in guinea pigs (Kincaid et al. 1954).

Other

Acute exposure by subcutaneous injection of 45 mg Co/kg/day as dicobalt octacarbonyl did not cause any gastrointestinal illness or alter physiology in the gastrointestinal tract of guinea pigs (Kincaid et al. 1954).

2.7. HEMATOLOGICAL

Inhalation

One occupational study examined hematological effects in humans from inhalation exposure to cobalt. Chronic-duration exposure to cobalt in refinery workers was not associated with changes in red blood cell parameters such as hemoglobin and hematocrit even though exposure resulted in increased urinary cobalt levels. The workers used protective masks since 2002 which lowered the urinary cobalt levels compared to workers without protective gear (Lantin et al. 2011).

Inhalation exposure of cobalt induced changes in hematological parameters mainly in erythrocytes, hematocrit, and hemoglobin. An intermittent 3-month intermediate-duration exposure to 9 mg Co/m^3 as cobalt hydrocarbonyl increased levels of hemoglobin, numbers of basophils, and monocytes in albino rats and guinea pigs (strain not specified), but not in dogs (beagles) (Palmes et al. 1959). Bucher et al. (1990) showed that male and female F344/N rats developed polycythemia (as reported in the study) following exposure to 10 and 3 mg/m^3, respectively, after 13 weeks of intermittent exposure. Both sexes also had increased hemoglobin and hematocrit levels at 10 mg/m^3. The reticulocyte count increased only in female rats exposed to 30 mg/m^3 (Bucher et al. 1990). No hematological effects were seen in pigs (strain not specified) after a 3-month exposure to cobalt metal (Kerfoot 1974). Polycythemia (as reported in the study) was reported in F344/N rats, but not B6C3F1 mice, exposed to 1.14 mg Co/m^3 as cobalt sulfate for 13 weeks (NTP 1991). A 5% decrease in hemoglobin, a 3% decrease in hematocrit, and a 4% decrease in platelet count were seen in female and male B6C3F1 mice after a 13-week exposure (NTP 1991). After a 14-week intermittent exposure, female F344/N rats showed a 9% increase in hematocrit, hemoglobin, and erythrocyte levels, compared to controls at 1.25 mg Co/m^3 and male F344/N rats showed a 4.5% increase in hemoglobin levels and 5.2% increase in erythrocytes, compared to controls at 0.625 mg Co/m^3. Female and male B6C3F1 mice showed a significant 4.7% and 3% increase in erythrocytes, respectively (Hong et al. 2015).

Oral

Oral exposure to cobalt altered hematological parameters including hemoglobin, hematocrit, and erythrocytes. Finley et al. (2013) administered 1.0 mg/day of cobalt (0.08-0.19 mg/kg/day) to volunteers (n=10) for 31 days. At 7 days post-exposure, a non-clinically significant (<5%) increase in hemoglobin,

hematocrit, and red blood cell counts was observed in males only (Finley et al. 2013). Tvermoes et al. (2014) found no significant changes in hematological parameters following 90-day exposure to 1.0 mg/day of cobalt (0.08-0.19 mg/kg/day) in 10 volunteers. Acute oral exposure to 1 mg Co/kg/day for 6-14 days increased red blood cells by 8.7% in humans and intermediate exposure to 0.8 mg Co/kg/day for 15 days did not influence the levels of red blood cells but 1 mg Co/kg/day for 22-23 days increased the red blood cells by 9.7% (Davis and Fields 1958). Acute oral exposure to 1 mg Co/kg/day for 6-14 days increased red blood cells by 8.7% in humans and intermediate exposure to 0.8 mg Co/kg/day for 15 days did not have an effect on the red blood cells, but 1 mg Co/kg/day for 22-23 days increased the red blood cell count by 9.7% (Davis and Fields 1958). Twice a day, daily oral exposure to 0.18 mg Co/kg/day for 12 weeks in anephric (with non-functioning kidneys), hemoglobin deficient patients increased hemoglobin in male and female human subjects by 26-70% and eliminated the need for transfusions in 4/12 individuals (Duckham and Lee 1976). Daily oral exposure to 0.16 mg Co/kg/day in humans for 12-32 weeks caused an increase in hemoglobin which was not quantified in the study (Taylor et al. 1977). A 13 week daily oral exposure to 0.6 mg Co/kg/day in humans did not cause any hematological effects (Holly 1955). A study by Roche and Layrisse (1956) examined iodine uptake in 12 euthyroid (normal thyroid) patients who were orally exposed to 1mg Co/kg-day (assuming a body weight of 70 kg) for 2 weeks which resulted in a greatly reduced uptake of 48-hour radioactive iodine by the thyroid when measured after 1 week of exposure to cobalt. The decreased uptake is likely resulting from cobalt blocking the organic binding of iodine (Paley et al. 1958). This effect was reversed by the second week of exposure nearly completely (Roche and Layrisse, 1956). No other clinical details (e.g., including effects on thyroid stimulating hormone [TSH]) were provided for the human subjects in this study, therefore, the mechanism for the effect of cobalt on thyroidal iodine uptake cannot be ascertained.

Acute-duration oral exposure to cobalt has also led to hematological effects in rats. A single oral exposure to cobalt chloride of 161 mg Co/kg caused an 8% increase in hematocrit levels in Sprague-Dawley rats (Domingo and Llobet 1984). Acute 5-day exposure to cobalt in albino rats caused a dose-dependent increase in the frequency of micronucleated polychromatic erythrocytes with a 400% increase at 11 mg Co/kg/day (Awoyemi et al. 2017). The NOAEL dose of 6 mg Co/kg/day used in Awoyemi et al. (2017) where no effects were observed is a dose that is rather high for humans to be exposed to cobalt via oral exposure. The average daily intakes are often in the microgram range. Oral acute-duration exposure to 12.5 mg Co/kg/day resulted in 60%, 10%, and 8% increased red blood cells, hematocrit, and hemoglobin, respectively, in Sprague-Dawley rats (Shrivastava et al. 2008; Shrivastava et al. 2010). A single oral dose of 161 mg Co/kg caused significant increases in erythrocyte count (polycythemia, as reported by the study authors), hematocrit, and hemoglobin in Sprague- Dawley rats (Domingo et al. 1984).

Intermediate-duration oral exposure to cobalt caused hematological effects in rats and mice. Rats were exposed to 0.74, 2.48, and 7.44 mg Co/kg/day as cobalt chloride hexahydrate orally daily for 90 days (Danzeisen et al. 2020). In this study, male rats showed no alterations in hematological parameters at 0.74 mg Co/kg/day; however, at a dose of 2.48 mg Co/kg day there was a 10.7%, 9.2%, and 10.2% increase in hemoglobin, erythrocytes, and hematocrit, respectively. While the male rats were more sensitive and showed changes in hematological parameters at lower doses, female rats showed an increase of 13.4% and 9.8% in hemoglobin and erythrocytes, respectively, only at a dose of 7.44 mg Co/kg/day (Danzeisen et al. 2020). Danzeisen et al. (2020) also examined effects of Co_3O_4 on hematological parameters. They observed that a daily oral dose of 220 mg Co/kg/day increased hemoglobin, erythrocytes, and hematocrit by 9.5%, 9.6%, and 9.2%, respectively, in male rats, and a 5.9% increase in hemoglobin level in female rats. At the highest dose of 734 mg Co/kg/day, males and female rats showed an increase in hemoglobin (25.4% males and 16.4% females), erythrocytes (22.7% males and 12.9% females), and hematocrit (24.2% males and 13.9% females) (Danzeisen et al. 2020). Krasovskii and Fridyland (1971) exposed groups of rats to 0, 0.05, 0.5 and 2.5 mg Co/kg/day as cobaltous chloride, daily for 7 months. The group treated with 2.5 mg Co/kg/day showed a persistent increase in erythrocytes, the 0.5 mg Co/kg/day group showed a transient increase, and the lowest exposure group showed no effect. This study provided qualitative findings but did not report numerical data and their statistical significance. An intermediate exposure of cobalt chloride in dogs for a 4-week period to daily doses of 5- 30 mg Co/kg/day and a dose ≤ 15 mg Co/kg/day caused a significant increase in erythrocyte number and hemoglobin level, when compared to preexposure levels (Brewer 1940). Minimal changes in the levels of blood proteins (transferrin, several haptoglobulins, and ceruloplasmin) were noted in male Swiss mice following 4, 24, and 48 hours of treatment with 76.4 mg Co/kg as cobalt chloride in the drinking water (Bryan and Bright 1973). Exposure for an intermediate-duration (3 weeks or 3 months) to 76.4 mg Co/kg as cobalt chloride in the drinking water resulted in no alterations in serum proteins examined in Swiss mice (Bryan and Bright 1973). Intermediate exposure to 18 and 0.5 mg Co/kg/day for 4 and 7 months, respectively, in water caused an increase in red blood cells and hemoglobin (Holly 1955; Krasovskii and Fridlyand 1971), and induced polycythemia in Wistar rats (reported as mild transient polycythemia by study authors) (Krasovskii and Fridlyand 1971). A 30-day exposure to 11.4 mg Co/kg/day as cobalt chloride caused a 20% decrease in hemoglobin in male Sprague-Dawley rats (Chetty et al. 1979). Hematological parameters in Sprague-Dawley rats exposed to 20 to 30 mg Co/kg/day as cobalt chloride for 13 to 14 weeks in food or drinking water resulted in an increase in red blood cells (41%), hemoglobin (28-31%) and hematocrit (29%) (Corrier et al. 1985; Domingo et al. 1984). Pregnant ICR mouse dams were orally treated with 18.6 mg Co/kg/day as cobalt chloride hexahydrate which resulted in the offspring being exposed in utero for 2-3 days followed by 25 days via breastmilk; after weaning they were exposed orally for 65 days which

altered levels of hemoglobin and hematopoiesis (Gluhcheva et al. 2014). Pedigo et al. (1988) observed that a 6 mg Co/kg/day exposure resulted in no hematological effects in male mice after a daily exposure for 13 weeks in B6C3F1 mice (Pedigo et al. 1988). A 6-week study in albino rats showed a dose- and time-related increase in erythrocyte number following oral administration of 2.5 mg Co/kg/day (Stanley et al. 1947).

Dermal

No studies were identified regarding hematological effects in humans after dermal exposure to cobalt.

No hematological effects have been observed after dermal exposure to cobalt in animals. Acute dermal exposure to 0.5-10% cobalt chloride (in DMSO) did not induce hematological effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No hematological effects were observed after intermediate dermal exposure to 51.70 mg Co/kg/day as dicobalt octacarbonyl (in methyl ethyl ketone) in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992a, 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Acute-duration exposure to cobalt chloride by 10 subcutaneous injections in a controlled exposure human study (9 days gap between 2 blocks of 5 consecutive injections) of 18 mg Co/kg/day increased triglycerides by 49%, caused lipemia, and increased erythropoietin (Taylor et al. 1977). In a human case study of cobalt exposure of unknown origin, Jefferson et al. (2002) found a correlation between serum cobalt and excessive erythrocytosis ($p=0.002$) and packed-cell volume ($r = 0.4$, $p = 0.01$). Doming and Llobet (1984) showed that single intraperitoneal injections of cobalt chloride at a dose of 12 mg Co/kg caused a 10% increase in hematocrit levels in Sprague-Dawley rats (Domingo and Llobet 1984). Wistar rats were exposed to a single dose of cobalt chloride by a subcutaneous injection (7 mg Co/kg) which resulted in an approximately 17% increase in excretion of methemoglobin within 3 hours of exposure (Horiguchi et al. 2004). A 6-week subcutaneous injection study in albino rats showed an increase in erythrocyte number following administration of cobalt chloride at a dose of 0.6 mg Co/kg/day (Stanley et al. 1947).

2.8. MUSCULOSKELETAL

No studies were identified regarding toxicity of cobalt on musculoskeletal effects in humans after inhalation, oral, or dermal exposure to cobalt.

Inhalation

No histological lesions were reported in the sternebrae (unpaired segments of the sternum), including the bone marrow, of rats or mice exposed to 0.06-41.72 mg Co/m^3 as cobalt sulfate for 16 days, 0.06 to 6.29 mg Co/m^3 for 13 weeks, and 0.06 to 0.63 mg Co/m^3 for 104 weeks (NTP 1991, 1998, 2014).

Oral

No morphological changes were found in the skeletal muscle of rats exposed to 30.2 mg Co/kg/day as cobalt chloride in the drinking water for 3 months (Domingo et al. 1984).

Dermal

No musculoskeletal effects have been observed after dermal exposure to cobalt in animals. Acute dermal exposure to 0.5-10% cobalt chloride (in DMSO) did not induce musculoskeletal effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No musculoskeletal effects were observed after intermediate-duration dermal exposure to 51.70 mg Co/kg/day as dicobalt octacarbonyl (in methyl ethyl ketone) in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992a, 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Acute-duration exposure by a single subcutaneous injection of 45 mg Co/kg/day as dicobalt octacarbonyl did not cause musculoskeletal effects in guinea pigs (Kincaid et al. 1954).

2.9. HEPATIC

No studies were identified regarding hepatic effects in humans after inhalation, oral, or dermal exposure to cobalt.

Inhalation

Intermediate-duration inhalation exposure to cobalt in rats and mice altered liver weight, caused necrosis and congestion. Sixteen days of intermittent exposure to 20 mg Co/m^3 increased relative liver weight by 13% and 16% in male and female F344/N rats, respectively, and in both male and female B6C3F1 mice by 10-11% (NTP 2014). Necrosis and congestion of the liver were observed in both F344/N rats and B6C3F1 mice that died following intermittent exposure to 19 mg Co/m^3 as cobalt sulfate over 16 days (NTP 1991). A significant decrease in relative liver weights were observed in female and male B6C3F1 mice at 2.5 and 10 mg Co/m3, respectively, after 14 weeks of intermittent inhalation exposure (NTP 2014). No histological effects on the liver were found in pigs (strain not specified) exposed ≤1.0 mg

Co/m^3 as cobalt metal dust intermittently for 3 months (Kerfoot 1974). No effects on hepatic function were seen in F344/N rats following intermittent exposure to 5 mg Co/m^3 for 14 weeks (NTP 2014). In NTP (1998), a chronic intermittent exposure of 105 weeks to cobalt sulfate heptahydrate did not alter hepatic function in both F344/N rats and B6C3F1 mice (NTP 1998). Chronic intermittent 105-week exposure to 1.25 and 5 mg Co/m^3/day increased the incidence of basophilic focus in male and female F344/N rats, respectively, but had no effect in B6C3F1 mice (NTP 2014).

Oral

Acute-duration oral exposure to cobalt caused necrosis, congestion, changes in liver weight, and inflammation of the liver in animal studies. Domingo and Llobet (1984) showed that a single oral exposure to 161 mg Co/kg did not alter hepatic function in Sprague-Dawley rats (Domingo and Llobet 1984). Akinrinde et al. (2016) observed necrosis, cytotoxicity, and abnormal morphology in Wistar rat hepatocytes following exposure to 29 mg Co/kg/day as cobalt chloride. This study also noted a 14% decrease in relative liver weight, and 50% and 40% decrease in GSH and GPx, respectively (Akinrinde et al. 2016a). An acute 1-week exposure to 6 mg Co/kg/day in albino rats caused moderate congestion in the hepatocytes as well as very mild infiltration by inflammatory cells, focal areas of necrosis, and congestion of vessels in rats (Awoyemi et al. 2017). Awoyemi et al. (2017) reported statistically significant changes in several hepatic parameters, e.g., GSH, SPx, and ALT, at doses ranging from 6 to 22 mg Co/kg/day. Additionally, immunohistochemistry of liver in albino rats showed a dose dependent increase in hepatic expressions of cyclooxygenase 2 (COX-2) and BCL-2- associated protein (BAX) relative to the control. Changes in oxidative stress markers along with altered liver enzymes were observed, namely a 19% increase in H_2O_2, 5% decrease in GSH, 37% decrease in GPx, and 16% increase in ALT in Wistar rats (Awoyemi et al. 2017).

Intermediate-duration oral exposure to cobalt altered liver enzymes and caused inflammation of the liver in animals. A 13-week exposure to 30.2 mg Co/kg/day as cobalt chloride in the drinking water caused a 30% decrease in liver enzymes in rats (Domingo et al. 1984). A dose of 9.6 mg Co/kg/day for 2 weeks produced no effects on hepatic function in Sprague-Dawley rats (Saker et al. 1998). Garoui et al (2011) demonstrated that daily exposure, 2 weeks during gestation and 2 weeks post-delivery, to 21 mg Co/kg/day as cobalt chloride decreased liver weight in Wistar rat pups by 10%, and the dams (rats) showed an increase in hepatic enzymes ALT and AST by 44% and 27%, respectively, and a decrease in SOD, CAT, GPx and GSH by 30%, 23%, 31%, and 20%, respectively (Garoui el et al. 2011). The same study showed that, in pups exposed to cobalt in utero and through lactation, there was an increase in hepatic enzymes ALT and AST by 133 and 75%, respectively, and hepatic injury was observed with the presence of vascular congestion and infiltration of mononuclear cells by histopathology, along with a

decrease in GPx and GSH by 39% and 35%, respectively (Garoui el et al. 2011). No morphological or enzymatic changes were found in the livers of rats (Sprague-Dawley, Wistar, and albino, respectively) exposed to doses of 2.5 to 30.2 mg Co/kg/day as cobalt chloride by gavage or as cobalt chloride in the drinking water for 3 to 7 months (Domingo et al. 1984; Holly 1955; Krasovskii and Fridlyand 1971). At a dose of 18.6 mg Co/kg/day as cobalt chloride hexahydrate in utero for 2-3 days, followed by 25 days via breastmilk, and lastly 65 days orally, there was a significant decrease (21.5%) of liver weight index in ICR mice sacrificed on day 90, compared to controls (Gluhcheva et al. 2014). Mathur et al. (2011) performed a 60-day exposure to 45 mg Co/kg/day as cobalt chloride hexahydrate in Wistar rats, which showed an increase in relative liver weight by 13% along with degradation and alteration in the morphology and atrophy of liver cells (Mathur et al. 2011). This study showed alterations in liver biochemistry which included a 126% increase in AST and a 122% increase in bilirubin (Mathur et al. 2011). A 4-week exposure to 68 mg Co/kg/day in water as cobalt chloride hexahydrate increased LDH by 3.6-fold; hepatic enzymes ALP, AST, and ALT by 1.7, 4.5, and 1.7-fold, respectively, and total bilirubin levels by 1.9-fold, all of which contributed to an increase in DNA damage in Sprague-Dawley hepatocytes (Khalil et al. 2020). While there were no controls included in this study, hyperemia of the liver and cytoplasmic changes in hepatocytes (clumpy cytoplasm located along the cell membrane) were found in Wistar rats administered a single dose of 68.2 mg Co/kg as cobalt fluoride or a single dose of 157.3 mg Co/kg as cobalt oxide (Speijers et al. 1982).

Dermal

No hepatic effects have been observed after dermal exposure to cobalt in animals. Acute-duration dermal exposure to 0.5-10% cobalt chloride (in DMSO) did not induce hepatic effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No hepatic effects were observed after intermediate-duration dermal exposure to 51.70 mg Co/kg/day as dicobalt octacarbonyl (in methyl ethyl ketone) in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992a, 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

In guinea pigs and rats exposed to a single intraperitoneal injection of 27 and 36 mg Co/kg, respectively, altered antioxidant markers like malondialdehyde increased by approximately 160% and 36%, GSH levels decreased by 12% and 25%, and increased glutathione reductase levels by 36% and 27% were seen in guinea pigs and rats, respectively (Christova et al. 2002).

2.10. RENAL

No studies were identified regarding renal effects in humans after inhalation, oral, or dermal exposure to cobalt.

Inhalation

Inhalation exposure to cobalt caused changes in kidney weight and creatinine levels in rats and mice. Sixteen-day intermittent exposure to 10 and 20 mg Co/m^3 as cobalt metal caused a significant 7.5% decrease of relative left kidney weight and an 80% increase in urinary creatinine in male F344/N rats, and a 291% increase in urinary creatinine levels and 23.5% increase in relative kidney weight in female rats, and had no effect in B6C3F1 mice (NTP 2014). No histological effects on the kidneys were found in pigs exposed ≤1.0 mg Co/m^3 as cobalt metal for 3 months (Kerfoot 1974). A significant increase in the relative weight of the kidneys was reported in male rats exposed to ≥0.06 mg Co/m^3 for 13 weeks (NTP 1991). An intermediate intermittent exposure for 14 weeks to cobalt metal at 5 mg Co/m^3 increased kidney weights in female F344/N rats and increased 24% urinary creatinine in males (NTP 2014). No effects were observed upon histological examination of the kidneys in F344/N rats or B6C3F1 mice following intermittent exposure to ≤41.72 mg Co/m^3 as cobalt sulfate for 16 days, up to 6.29 mg Co/m^3 for 13 weeks, or ≤5 mg Co/m^3 for 104 to 105 weeks (NTP 1991, 1998, 2014).

Oral

Acute oral exposure to cobalt caused changes in kidney weight, altered renal morphology and physiology in rats. Domingo and Llobet (1984) showed that a single oral exposure to 161 mg Co/kg caused a 68% increase in urea and a 57% decrease in uric acid, which indicates alterations in renal function in the Sprague-Dawley rats exposed to cobalt (Domingo and Llobet 1984). Oral exposure to 33.7 mg Co/kg/day of cobalt chloride in Wistar rats induced effects on the renal system (Ajibade et al. 2017). Oral exposure to 33.7 mg Co/kg/day decreased GPx expression in the kidneys by 15%. Co exposure also increased the Nf-κB expression by 300% (Ajibade et al. 2017). Acute-duration oral exposure to 18.4 mg Co/kg/day of cobalt chloride hexahydrate in Wistar rats caused renal damage (Akinrinde et al. 2016a). This study examined histopathology of the kidney and observed a severe loss of normal morphology, loss of tubular and glomerular outlines with marked peri-tubular inflammatory cell infiltration, and vascular congestion. The authors also noted an approximate increase in urea by 33% and creatinine by 19% (Akinrinde et al. 2016b). A second acute-duration exposure study by Akinrinde et al. (2016b) also corroborated their previous study where 19 mg Co/kg/day caused inflammation in the peri- tubular and peri-vascular areas along with focal tubular necrosis (Akinrinde et al. 2016c).

Intermediate-duration oral exposure to cobalt caused changes in kidney weight, altered renal morphology, function, and physiology in rats and mice. Abdel-Daim et al. (2020) showed altered renal function in Sprague-Dawley rats after a 4 week oral exposure to 16.2 mg Co/kg/day caused an increase in urea and creatinine by 105% and 137%, respectively, and a decrease in GSH by 63% (Abdel-Daim et al. 2020). A single oral dose of 161 mg Co/kg caused alterations in renal function by increasing urea production by 68% and decreasing uric acid by 57% in Sprague-Dawley rats (Domingo et al. 1984). Morvai et al. (1993) observed a 10% decrease in relative kidney weight change after exposure to 12.4 mg Co/kg/day as cobalt chloride for 3 weeks in CFY rats (Morvai et al. 1993). After a 13-week exposure to 30.2 mg Co/kg/day as cobalt chloride in the drinking water, a 35% decrease in urine volume in Sprague-Dawley rats was seen (Domingo et al. 1984). Garoui et al (2012) observed that daily exposure, 2 weeks during gestation and 2 weeks post-delivery, to 20.26 mg Co/kg/day in water as cobalt chloride caused vascular congestion, reduction of glomerular space, and infiltration of leukocyte cells between tubules based on histology. A 15% increase in plasma creatinine, 34% decrease in urine creatinine, and a slight reduction in relative kidney weight (4%), compared to controls were also reported in Wistar rats (Garoui el et al. 2012). ICR mice were exposed to doses of 18.6 and 31 mg Co/kg/day in utero for 2-3 days followed by 25 days via breastmilk, and lastly 65 days orally (Gluhcheva et al. 2014). The lower dose group of 18.6 mg Co/kg/day showed an increase (14.3%) in kidney weight index in mice sacrificed on day 30, compared to controls. There were serious effects observed at 31 mg Co/kg/day where there was a 28.6% of kidney weight index in mice sacrificed on day 30, compared to controls (Gluhcheva et al. 2014). Histopathology of the kidney revealed peritubular and periglomerular inflammation and focal glomerular necrosis following Co exposure at 18.6 mg Co/kg/day (Gluhcheva et al. 2014). While there are no control animals in this study, renal injury, evidenced by histologic alteration of the proximal tubules, was observed in Wistar rats after a single oral exposure to 42 mg Co/kg as cobalt fluoride (Speijers et al. 1982) and after exposure to 10 to 18 mg Co/kg/day as cobalt chloride for 4 to 5 months (Holly 1955; Murdock 1959). A slightly decreased urinary output was observed in Wistar rats exposed to 19.4 mg Co/kg as cobalt sulfate, but not in Wistar rats exposed to 4.24 mg Co/kg as cobalt chloride (Singh and Junnarkar 1991).

Dermal

No renal effects have been observed after dermal exposure to cobalt in animals. Acute-duration dermal exposure to 0.5-10% cobalt chloride (in DMSO) did not induce renal effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No renal effects were observed after intermediate dermal exposure to 2.4% Co as dicobalt octacarbonyl (in methyl ethyl ketone) in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992a, 1992b) tested both an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Domingo and Llobet (1984) showed that a single intraperitoneal injection of cobalt chloride at a dose of 12 mg Co/kg did not alter renal function in Sprague-Dawley rats (Domingo and Llobet 1984). Wistar rats were exposed to a single dose of cobalt chloride by a subcutaneous injection (7 mg Co/kg). This acute exposure resulted in an approximately 10-fold increase in excretion of methemoglobin within 3 hours from the renal tissues in Wistar rats (Horiguchi et al. 2004). An intermediate exposure to 1.6 mg Co/kg/day as subcutaneous injections of cobalt nitrate for 4 weeks caused glomerulo-tubular nephrosis with degenerative changes and was toxic to the renal tubule cells in albino rats (Hanafy and Soltan 2004).

2.11. DERMAL

Inhalation

One study examined dermal effects in humans after occupational inhalation exposure to cobalt. Metal factory workers (n=71) exposed to air cobalt concentrations ranging from 0.0001 to 0.019 mg/m^3 had high self-reported prevalence of dry skin (42%) and eczema (6-7%) (Wahlqvist et al. 2020).

Oral

No studies examining dermal effects in humans or animals after oral exposure to cobalt were identified.

Dermal

Dermal exposure to cobalt has been associated with eczema and contact dermatitis in several case reports (Alinaghi et al. 2019, Krecisz et al. 2009; Laing et al. 2005). Four cases of eczema of the hands, feet and/or limbs were associated with exposure to objects ranging from 0.01% to over 10% cobalt by weight (Alinaghi et al. 2019). Clothing dye containing 0.32 mg/kg cobalt caused pruritic rash in a 20-year-old female (Krecisz et al. 2009). In another case study, exposure to blue paint containing cobalt caused eczema, hives, swelling, and anaphylactic reaction (Laing et al. 2005).

In an intermediate dermal exposure study where guinea pigs (strain not specified) were exposed to 2.4% cobalt for 18 days, scabs and denuded areas were formed around the area where dicobalt octacarbonyl was applied (Kincaid et al. 1954). Bonefeld et al. (2015) showed acute exposure to 10% cobalt chloride (in petrolatum) in mice (strain not specified) caused no swelling on the ears where it was applied but the ears showed inflammation with the same dose after being sensitized with a dose of 10% $CoCl_2$.

Other

Ulcerations were observed at the site after a single subcutaneous injection of 45 mg Co/kg as dicobalt octacarbonyl in guinea pigs (strain not specified) (Kincaid et al. 1954).

2.12. OCULAR

No studies examined ocular effects in humans following inhalation, oral, or dermal exposure to cobalt. Additionally, no studies in animals examined ocular effects following oral exposure to cobalt.

Inhalation

Inhalation studies of cobalt inhalation exposure in animals showed mixed results for ocular effects. Intermediate-duration exposure to 19 mg Co/m^3/day as cobalt sulfate heptahydrate caused chromodacryorrhea in F344/N rats and B6C3F1 mice after 16 days of intermittent exposure (NTP 1991). No histological lesions were reported in the eyes of F344/N rats or B6C3F1 mice intermittently exposed to ≤41.72 mg Co/m^3 as cobalt sulfate for 16 days, up to 6.29 mg Co/m^3 for 13 weeks, up to 0.63 mg Co/m^3 for 104 weeks (5 days/week, 6 hours/day), or up to 5 mg Co/m^3 for 105 weeks (Behl et al. 2015; NTP 1991, 1998, 2014).

Dermal

No ocular effects have been observed after dermal exposure to cobalt in animals. Acute-duration dermal exposure to 0.5-10% cobalt chloride (in DMSO) did not induce ocular effects mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No ocular effects were observed after intermediate-duration dermal exposure to 2.4% as dicobalt octacarbonyl (in methyl ethyl ketone) in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992 & 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Acute-duration exposure by a single subcutaneous injection of 45 mg Co/kg as dicobalt octacarbonyl did not cause ocular effects in guinea pigs (species not specified) (Kincaid et al. 1954).

2.13. ENDOCRINE

Inhalation

Two studies examined endocrine effects in humans after inhalation exposure to cobalt and showed alterations in thyroid function. In a study of cobalt refinery workers in Belgium, Lantin et al. (2013) found

no association between cumulative cobalt exposures and thyroid function. One volunteer out of 10 who ingested 1.0 mg Co/day for up to 90 days showed elevated TSH and decreased T4 (Tvermoes et al. 2013).

In animal studies minimal effects of acute-duration cobalt exposure were seen on the endocrine system. No effects were observed on the endocrine system in an intermediate-duration exposure in F344/N rats for up to 20 mg Co/m^3 and in B6C3F1 mice for up to 40 mg Co/m^3, exposed as cobalt metal after a 16 day intermittent exposure (NTP 2014). Intermediate-duration exposure to 4 mg Co/m^3 lowered T3 in female F344/N rats and 11 mg Co/m^3 lowered TSH in male rats after a 13-week intermittent exposure (NTP 1991).

Intermediate-duration exposure to cobalt caused no effects on endocrine function while chronic-duration exposure to cobalt altered adrenal morphology. No effects were seen after a 14-week intermittent exposure to 5 and 10 mg Co/m^3 as cobalt metal in F344/N rats and B6C3F1 mice, respectively (NTP 2014). No effects were observed after 16 days of intermittent exposure to 19 mg Co/m^3 as cobalt sulfate heptahydrate in F344/N rats (NTP 1991). Chronic intermittent exposure for 105 weeks to 1.25 and 2.5 mg Co/m^3 increased the incidence (13/50 males and 8/50 females) of bilateral benign pheochromocytoma in F344/N rats (NTP 2014). An increased incidence of medullary hyperplasia in the adrenal gland was seen in 27 female F344/N rats after chronic exposure to 1.25 mg Co/m^3 (NTP 2014). Exposure to 0.63 mg Co/m^3 as cobalt sulfate heptahydrate intermittently for 105 weeks and 5 mg Co/m^3 as cobalt metal for 105 weeks did not alter endocrine function in B6C3F1 mice (NTP 1998, 2014).

Oral

No studies were identified regarding endocrine effects in humans after oral exposure to cobalt.

A single study was identified that examined endocrine effects in animals after oral exposure to cobalt in animals. Female Parkes mice exposed to 26 mg Co/kg-day as cobalt chloride in the drinking water for 45 days showed histopathological changes to the thyroid gland i.e. low epithelial lining with degenerated nuclei (Shrivastava et al. 1996). The study also observed a time-dependent effect on the degeneration seen within the thyroid and the degradation persisted 30 and 45 days after the exposure ceased (Shrivastava et al. 1996).

Dermal

No studies were identified regarding endocrine effects in humans after dermal exposure to cobalt.

No endocrine effects have been observed after dermal exposure to cobalt in animals. Acute-duration dermal exposure to 0.5-10% (in DMSO) cobalt chloride did not induce endocrine effects in mice

(Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No endocrine effects were observed after intermediate-duration dermal exposure to 2.4% cobalt as dicobalt octacarbonyl (in methyl ethyl ketone) in guinea pigs (Kincaid et al. 1954). Bonefeld et al. (2015) and Ikarashi et al. (1992 & 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Fifteen day intermediate exposure of 30 mg Co/kg/day as cobalt chloride by intraperitoneal injections in guinea pigs (strain not specified) altered hormones in the pancreas and had cytotoxic effects on the alpha cells in the pancreas (Beskid 1963). Single intravenous doses of 25-40 mg Co/kg as cobalt chloride in female rabbits (strain not specified) also caused cytotoxicity in the alpha cells in the pancreas (Goldner et al. 1952). Another acute-duration study that exposed pigmented guinea pigs to cobalt chloride parenterally by single intravenous dose, corroborated the results described in the previous studies by showing damages to alpha cells in pancreatic islets (Hakanson et al. 1974). A similar study in dogs (strain not specified) also showed damage to alpha cells in the pancreatic islets after an acute-duration intravenous exposure to cobalt chloride (Lazarus et al. 1953). Acute exposure to cobalt nitrate salts subcutaneously was detrimental to the alpha cells in the pancreas in guinea pigs (strain not specified) (Van Campenhout 1955). An acute-duration 10-day subcutaneous exposure in ICR mice to 0.59 mg Co/kg/day as cobalt chloride resulted in increased adipocyte mRNA by nearly 100% and adiponectin levels by 42% (Kawakami et al. 2012). These effects were directly related with decreases in white adipose tissue weight and size which were potentially a direct result of cobalt toxicity (Kawakami et al. 2012). The relevance of these effects to human health are currently unknown as they have not been studied in humans.

2.14. IMMUNOLOGICAL

No studies were identified that examined immunotoxicity in humans following inhalation, oral, or dermal exposure to cobalt.

Inhalation

Inhalation exposure to cobalt reduced thymus weight, caused accumulation of macrophages, and resulted in necrosis. Sixteen-day intermittent exposure to 20 mg Co/m^3 decreased thymus weight in female rats by 64%, but had no effect in male F344/N rats. In the lung, at the lower exposure of 5 mg Co/m^3, the incidence of minimal to moderate alveolar histiocytic cellular infiltration (accumulation of macrophages within the alveolar spaces and septa) was seen in 5/5 male and 5/5 female B6C3F1 mice (NTP 2014).

No effects were seen in pigs (strain not specified) after a 3 month intermittent exposure to 0.1 mg Co/m^3 (Kerfoot 1974). No effects were seen in F344/N rats, but B6C3F1 mice showed hyperplasia in lymph nodes after an intermittent exposure of 11 mg Co/m^3 for 13 weeks (NTP 1991). At a higher dose of 19 mg Co/m^3 as cobalt sulfate heptahydrate intermittently for 16 days, F344/N rats showed necrosis and decreased weight of the thymus in both males and females, whereas B6C3F1 mice only showed a decrease in thymus weight (NTP 1991).

Alveolar histiocytic cellular infiltration characterized by the presence of low to moderate numbers of histiocytes (macrophages) were observed after a chronic exposure to 0.625 mg Co/m^3 for 104 weeks (NTP 2014). Macrophages accumulated around alveolar/bronchial neoplasms after chronic exposure to 5 mg Co/m^3 as cobalt metal intermittently for 105 weeks in female F344/N rats and in B6C3F1 mice (NTP 2014). Tests of immunological function, however, were not performed on the rats or mice.

Oral

Acute-duration oral exposure to cobalt altered the immune response and thymus weight in rats. Akinrinde et al. (2019) showed that 1-week oral exposure to cobalt chloride hexahydrate caused a 300% increase in 1L-1β and a 100% increase in TNF- α at 67.5 mg Co/kg/day in Wistar rats (Akinrinde and Adebiyi 2019). In an acute 7-day oral exposure study by Akinrinde et al (2016), Wistar rats exposed to 19 mg Co/kg/day as cobalt chloride showed an increase in TNF- α by 60% and a decrease in IL1- β by 25% (Akinrinde et al. 2016a). Abdel-Daim et al. (2020) revealed alterations in immune function after a 4 week intermediate oral exposure to 16.24 mg Co/kg/day as cobalt chloride hexahydrate, this caused a 1400% increase in TNF-α in Sprague-Dawley rats (Abdel-Daim et al. 2020). Atrophy of the thymus was reported in male Sprague-Dawley rats exposed to 3.8 mg Co/kg/day as cobalt chloride in the feed for 4 weeks (Chetty et al. 1979).

Intermediate-duration oral exposure to cobalt altered the immune response and spleen weight in rats and mice. After a 13 week exposure to 30.2 mg Co/kg/day as cobalt chloride in the drinking water, a 43% decrease in spleen weight in Sprague-Dawley rats was seen (Domingo et al. 1984). At doses of 18.6 and 31 mg Co/kg/day as cobalt chloride hexahydrate in utero for 2-3 days, followed by 25 days via breastmilk, and then 65 days orally, ICR mice showed a significant decrease in the spleen weight index by 43-53% (measure of relative weight) on day 60-90, compared to controls (Gluhcheva et al. 2014). A 2-fold decrease in the concentration of the total blood protein and a 1.5-fold decrease of total immunoglobulin G was observed in both male and female BALB/c mice at 56 mg Co/kg/day after an oral exposure for 5 weeks (Legostaeva et al. 2013). A 4-week exposure to 68 mg Co/kg/day in water as cobalt

chloride hexahydrate caused a 2.2-fold increase in immunoreactivity in Sprague-Dawley rats (Khalil et al. 2020).

Dermal

Dermal exposure to cobalt altered the immune response in Guinea pigs and mice. Acute 3 day dermal exposure to 0.5-5 % cobalt chloride (in DMSO) in mice caused an increase in cellular proliferation in the local lymph node assay in a dose dependent manner (Ikarashi et al. 1992b; Ikarashi et al. 1992a). Three consecutive exposures to increasing doses of cobalt chloride in Balb/c mice and Hartley guinea pigs elicited lymph node cell proliferation (Ikarashi et al. 1992b). Bonefeld et al. (2015) showed that sensitizing the mice (strain not specified) with 10% cobalt chloride (in petrolatum) and exposing them to a dermal challenge with the same dose of cobalt chloride, elicited an immune response in the mice and caused an increase in proliferation of B cells and T cells (Bonefeld et al. 2015).

2.15. NEUROLOGICAL

No studies were identified that examined neurotoxicity in humans following inhalation, oral, or dermal exposure to cobalt.

Inhalation

Inhalation exposure to cobalt caused congestion in the cranial vasculature but did not alter neurological function in rats and mice. A 16 day intermittent exposure to 20 and 40 mg Co/m^3 as cobalt metal caused lethargy in male and female F344/N rats, respectively, and in male and female B6C3F1 mice at 20 and 10 mg Co/m^3, respectively (NTP 2014). Congestion in the vessels of the brain in rats and mice were observed after a 16 day intermittent exposure to 19 mg Co/m^3 as cobalt sulfate heptahydrate (NTP 1991). No effects were seen in F344/N rats and B6C3F1 mice exposed to 11 mg Co/m^3 for 13 weeks as cobalt sulfate heptahydrate (NTP 1991). A 14 week intermittent exposure to 5 and 10 mg Co/m^3 as cobalt metal did not affect neurological function in F344/N rats and B6C3F1 mice, respectively (NTP 2014). A chronic 105 week intermittent exposure to 5 mg Co/m^3 as cobalt metal did not affect neurological function in either F344/N rats or B6C3F1 mice (NTP 2014).

Oral

Acute-duration oral exposure to cobalt produces neurological effects in animals. A study by Wellman et al. (1984) that examined acute-duration oral exposure to 45 mg Co/kg/day as cobalt chloride showed increased saccharin aversion in Long-Evans rats in an operant chamber task during the training phase. These effects in Wellman et al. (1984) were also accompanied with significant food aversion, which

resulted in a decrease in body weight in the rats treated with cobalt (Wellman et al. 1984). Acute-duration oral exposure to cobalt sulfate in both Wistar rats and Swiss-Webster mice at a dose of 19.4 mg Co and 12.3 mg Co per kg body weight, respectively, caused a decrease in motor activity and impairments in reflexes, ultimately resulting in anoxic convulsions (Singh and Junnarkar 1991). The dose also had CNS depressant effects which were indicated by mild hypothermic effects, moderate reduction in spontaneous activity, muscle tone, touch response, and respiration, and increased sleeping time by 19% in rats (Singh and Junnarkar 1991).

Similar effects were seen when both Wistar rats and Swiss-Webster mice were exposed to cobalt chloride at respective doses of 4.2 and 8.9 mg Co/kg body weight (Singh and Junnarkar 1991). The doses also had CNS depressant effects which were indicated by mild hypothermic effects and increased sleeping time by 31% in rats (Singh and Junnarkar 1991). Akinrinde et al. (2019) showed that exposure to cobalt chloride hexahydrate caused deficits in performance on a battery of neurobehavioral tests along with an increase in expression by 60% of AChE activity as compared to controls at 67.5 mg Co/kg/day in Wistar rats (Akinrinde and Adebiyi 2019). Abdel-Rehman et al. (2019) conducted an intermediate-duration exposure study at a dose of 27 mg Co/kg/day in Wistar rats where there was a 251% increase in Co accumulation in the brain accompanied by decreases in neurotransmitters levels- 23% in serotonin, 26% in norepinephrine, 48% in dopamine, and 39% in GABA. The authors observed an increase in encephalopathy of the cerebral cortex. This was also accompanied with an upregulation of microglial CD68 and neural caspase-3 in the brain which indicates that there was an upregulation of inflammatory response in the brain (Abdel-Rahman Mohamed et al. 2019).

In an intermediate-duration oral exposure study where Sprague-Dawley rats were exposed to 20 mg Co/kg/day as cobalt chloride for 80 days in water, there was increased latency during memory retention testing by 342% (Bourg and Nation 1985). Intermediate-duration exposure to cobalt chloride for 7 months in water caused a significant increase in the conditioned latent reflex at 2.5 mg Co/kg/day and a pronounced neurotropic effect (disturbed conditioned reflexes and loss of memory retention) in albino rats as investigated by the motor-alimentary method (Krasovskii and Fridlyand 1971). The decrease in memory retention observed in the rats was determined by the authors to be a function of dose and exposure duration. Morvai et al. (1993) observed a 10% decrease in relative brain weight after exposure to 12.4 mg Co/kg/day as cobalt chloride for 3 weeks in CFY rats (Morvai et al. 1993). Sprague-Dawley rats exposed to 20 mg Co/kg/day via food for 69 days showed varied deficits in neurobehavioral tasks. For example, there was a slower rate of lever pressing than controls, but no change in behavioral reactivity to stress (Nation et al. 1983). Taken together, the differences in the study are driven by variability in the control group. Wistar rats exposed to 6.44 mg Co/kg/day as cobalt nitrate in the drinking

water for 30 days showed an increased sensitivity and decreased maximal response to a cholinergic agonist (Vassilev Peter P. et al. 1993). Intermediate exposure of 30 days to 3.79 mg Co/kg/day as cobalt chloride caused a 13% decrease in Na+- K+ ATPase activity in male Sprague-Dawley rats (Chetty et al. 1979).

Wistar pups were exposed in-utero and during lactation for 2 weeks each to 20.3 mg Co/kg/day as cobalt chloride which caused a decrease in the levels of AChE and BuChE in the cerebrum by 33% and 36%, respectively, and the cerebellum by 33% and 47%, respectively (Garoui et al. 2013). The authors of this study also observed a decrease in antioxidant enzymes in the brain, namely GSH and NPSH by 23% and 50% in the cerebrum and by 16% and 25% in the cerebellum, respectively, in the Wistar rat pups (Garoui et al. 2013). Purkinje cells in the cerebellum of the Wistar rat pups exposed to Co in utero and via lactation were poorly differentiated with frequent pyknotic cells and had fewer cells (Garoui et al. 2013). At a dose of 56.73 mg Co/kg/day as cobalt chloride hexahydrate in utero for 2-3 days followed by 25 days via breastmilk and lastly 35 days orally did not alter neurological function in both male and female Balb/c mice (Zaksas et al. 2013). Khalil et al. (2020) showed that a 4-week exposure to 68 mg Co/kg/day in water as cobalt chloride hexahydrate caused fatigue, lethargy, and dullness in the treated Sprague-Dawley rats (Khalil et al. 2020). No neurological effects were seen at 22.7 mg Co/kg/day as cobalt chloride when dosed for 28 days in Wistar rats (Umar et al. 2016).

Dermal

Dermal exposure to cobalt did not produce neurological effects in animals. Acute-duration dermal exposure to 0.5-10% cobalt chloride did not induce neurological effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No neurological effects were observed after intermediate-duration dermal exposure to 52 mg Co/kg/day as dicobalt octacarbonyl in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992 & 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Acute-duration exposure to 6 mg Co/kg/day as cobalt chloride via intraperitoneal injections resulted in a 25% decrease in response latency in Balb/c mice (Alexa et al. 2015). In another study, rats (strain not specified) were exposed by intraperitoneal administration of cobalt sulfate at 114 mg Co/kg/day for 5 consecutive days resulting in a decrease in avoidance response (Inozemtsev et al. 2008). Balb/c mice showed a decrease in auditory brainstem response thresholds after an intraperitoneal injection of 22.7 mg Co/kg/day once as cobalt chloride. This effect indicates that Co is potentially ototoxic (Lee et al. 2016). Singh and Junnarkar (1991) examined the effects of intraperitoneal and intravenous injections on both

Wistar rats and Swiss-Webster mice and observed that it increased urine volume at various doses of cobalt chloride and cobalt sulfate (Singh and Junnarkar 1991). Single intraperitoneal injection of 25 mg/kg/day did not alter brain serotonin levels in Swiss albino mice, but did cause hypothermia (Burke et al. 1978).

2.16. REPRODUCTIVE

No studies were identified that examined reproductive toxicity in humans following inhalation, oral, or dermal exposure to cobalt.

Inhalation

Inhalation exposure to cobalt produces reproductive effects in some animals studied. Intermittent exposure to 10 and 40 mg Co/m^3 as cobalt metal in male and female rats and mice, respectively, for 5 hr/day, 6 days/week, for 16 days did not affect reproductive function (NTP 2014). Another 16 day intermittent exposure to 19 mg Co/m^3 as cobalt sulfate heptahydrate did not alter reproductive function in female F344/N rats and B6C3F1 mice, but in male rats it caused testicular atrophy along with a decrease in number of cells in the seminiferous tubules and atypical germinal epithelial cells in the epididymal ducts (NTP 1991). Intermediate-duration exposure to 11 mg Co/m^3 as cobalt sulfate heptahydrate intermittently for 13 weeks did not affect reproductive function in male and female F344/N rats, but in female B6C3F1 mice the same exposure increased the length of the estrous cycle by 19%; sperm motility decreased by 79% in male mice at 1.1 mg Co/m^3 (NTP 1991). Male F344/N rats and B6C3F1 mice showed decreased reproductive function after intermittent exposure to 2.5 mg Co/m^3 for 14 weeks; however, only female mice showed longer estrous cycles (NTP 2014). Bucher et al. (1990) demonstrated that an intermediate-duration inhalation exposure of cobalt sulfate heptahydrate caused reproductive deficits in male B6C3F1 mice. There was a marked decrease in sperm motility in male B6C3F1 mice at 3 mg Co/m^3 and increased numbers of abnormal sperm were observed at 3, 10, and 30 mg Co/m^3 after 13 weeks of intermittent exposure (Bucher et al. 1990; NTP 1991). Intermittent exposure at a higher dose of 30 mg Co/m^3 for 13 weeks was associated with decreased epididymal and testis weights (Bucher et al. 1990; NTP 1991). Estrous cycle length increased to 5 days in female B6C3F1 mice exposed to 30 mg Co/m^3 (Bucher et al. 1990). Chronic intermittent 105-week exposure to cobalt-containing aerosols caused deficits in reproductive functioning and resulted in effects on reproductive end points. A chronic intermittent 105 week exposure to 2.5 and 5 mg Co/m^3 was associated with decreased reproductive function in both male F344/N rats and B6C3F1 mice, respectively, but not in the female rats or mice (NTP 2014).

Oral

Oral exposure to cobalt produces reproductive effects in animals. An acute-duration 5 day exposure to 7 mg Co/kg/day as cobalt chloride increased abnormal sperm in male Swiss mice by 126% (Hassan et al. 2006). Intermediate-duration 13 week oral exposure to 24.6 mg Co/kg/day as cobalt chloride in water induced reproductive effects in male CD-1 mice which included an unspecified increase in the number of Leydig cells, degeneration in the peritubular area of the seminiferous tubules, and increased folding in the germinal epithelium of seminiferous tubules of the testicles were accompanied with changes in epithelial cell morphology (Anderson et al. 1992). In a follow up study by Anderson et al. (1993) with intermediate-duration exposure for 13 weeks to 43.4 mg Co/kg/day in water, irreversible testicular degeneration occurred demonstrated by damage to seminiferous tubules and hypercellularity of the interstitial areas in CD-1 mice (Anderson et al. 1993).

Mollenhauer et al. (1985) demonstrated that an exposure to cobalt metal through food at 20 mg Co/kg/day for 14 weeks caused deterioration of cell architecture and a decrease in testicular volume in Sprague-Dawley rats. This damage included thickening of basal lamina and basement membranes, increased packing of red blood cells in veins and arteries, change in sperm morphology, and degeneration in sperm mitochondria (Mollenhauer et al. 1985). Testicular atrophy was observed at a dose of 20 mg Co/kg/day in Sprague-Dawley rats after exposure for nearly 2 months via food (Nation et al. 1983). A 30 day exposure to 6.4 mg/Co/kg/day as cobalt nitrate in water caused a 275% increase in sympathetically-induced contractility of the vas deferens (Mutafova-Yambolieva et al. 1994). Testicular degeneration and atrophy which includes alteration in seminiferous tubules (27-90%), drop in sperm reserves (57%), and a marked decrease in testicular weight (26%) have been reported in Sprague-Dawley rats exposed to 20-30 mg Co/kg/day as cobalt chloride for 13-14 weeks in food or drinking water (Corrier et al. 1985; Domingo et al. 1984). Elbetieha et al. (2008) demonstrated that a 12 week exposure to 6.36 mg Co/kg/day as cobalt chloride hexahydrate in drinking water induced a significant 16.8% increase of relative preputial gland weight, a 13.3% decrease in sperm count, and decreased male fertility compared to controls in Swiss mice (Elbetieha et al. 2008). When males Swiss mice exposed to 6.3 mg Co/kg/day were mated with females, the number of implantations was reduced in those females and the number of viable fetuses also decreased significantly (Elbetieha et al. 2008). Additionally, the number of resorptions and the number of mice with resorptions were increased in females mated with the exposed males at all three concentrations of cobalt chloride (Elbetieha et al. 2008). A significant 16.8% increase of relative preputial gland weight, 13.3% decrease in sperm count, and decreased male fertility compared to controls was observed in a study where ICR mice were orally exposed to 6.36 mg Co/kg/day in water for 12 weeks (Gluhcheva et al. 2020). Pedigo et al. (1988) observed that a dose of 6 mg Co/kg/day as cobalt chloride hexahydrate in

drinking water decreased testicular weight (expressed as % of body weight) by 14% with an 11% decrease in sperm concentration, and an 80% increase in serum testosterone in B6C3F1 mice (Pedigo et al. 1988). In the same study, a dose of 15 mg Co/kg/day for 13 weeks caused a decrease in testicular weights as a % of body weight by 14%, 21%, 57%, and 71% at 7, 9, 11, and 13 weeks, respectively, a reduction in sperm concentration to 81.3% after 9 weeks of treatment, and an 82% decrease in sperm motility after 11 weeks of exposure (Pedigo et al. 1988). A subsequent 10 week study by Pedigo et al. (1993) where male B6C3F1 mice were exposed to 15 mg Co/kg/day showed a reduction in pregnancy in females by 57% when mated with males treated with Co, a 28% decrease in implantation of embryos when mated with Co exposed males, a 458% increase in preimplantation losses in pregnant females mated with Co- exposed males, a decrease in sperm concentration to 15.3%, and a decrease in sperm motility to 18.3% (Pedigo and Vernon 1993).

No reproductive function was altered in in male Balb/c mice after exposure to 56 mg Co/kg/day for 18 days (Madzharova et al. 2014).

Dermal

No studies were identified regarding reproductive effects in humans after dermal exposure to cobalt for any duration.

Acute-duration dermal exposure to 0.5-10% cobalt chloride did not induce reproductive effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No reproductive effects were observed after intermediate-duration dermal exposure to 52 mg Co/kg/day as dicobalt octacarbonyl in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992 & 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

No studies were identified regarding reproductive effects in animals after intermediate- and chronic-duration parenteral exposure to cobalt. Acute-duration exposure by intraperitoneal injections to cobalt chloride resulted in structural and functional alterations of the testes in Syrian hamsters (Lukac et al. 2007).

2.17. DEVELOPMENTAL

No studies were identified that examined developmental toxicity in humans following inhalation, oral, or dermal exposure to cobalt.

Inhalation

No studies were identified regarding developmental effects in animals after inhalation exposure to cobalt for any duration.

Oral

Oral exposure to cobalt produces developmental effects in animals. Acute-duration oral exposure to 81 mg Co/kg/day as cobalt chloride for 5 days during gestation days 8–12 was reported to have no effect on fetal growth or mortality in the pups, but did decrease maternal weight gain by 32% in ICR mice (Seidenberg et al. 1986). Oral exposure of female Sprague-Dawley rats to cobalt chloride at 5.4 or 21.8 mg Co/kg/day from gestation day 14 through lactation day 21 resulted in stunted growth and decreased survival, respectively, of newborn pups (Domingo et al. 1985a). Maternal toxicity was observed at these same doses making it unclear if the observed findings were due to a potential indirect effect of maternal toxicity or a direct effect of cobalt on the fetus (Domingo et al. 1985a).

In a study without a control group, no effects on fetal growth or survival were found following exposure to 24.8 mg Co/kg/day as cobalt chloride during gestation days 6–15 in Sprague-Dawley rats (Paternian and Domingo 1988).

Dermal

No developmental effects were observed after dermal exposure to cobalt. Acute-duration dermal exposure to 0.5-10% cobalt chloride did not induce developmental effects in mice (Bonefeld et al. 2015; Ikarashi et al. 1992b; Ikarashi et al. 1992a). No developmental effects were observed after intermediate-duration dermal exposure to 2.4% cobalt as dicobalt octacarbonyl in guinea pigs (Kincaid et al. 1954). Bonefeld et al (2015) and Ikarashi et al. (1992 & 1992b) tested an unspecified strain of mouse and ICR mice, respectively, and did not observe any differences.

Other

Acute-duration exposure by subcutaneous injection of 45 mg Co/kg/day as dicobalt octacarbonyl did not cause developmental effects in guinea pigs (Kincaid et al. 1954).

2.18. OTHER NONCANCER

No studies were identified that examined other noncancer effects in humans following inhalation, oral, or dermal exposure to cobalt.

Inhalation

No studies were identified regarding other noncancer effects in animals after inhalation exposure to cobalt for any duration.

Oral

Oral exposure to cobalt produced other noncancerous effects in animals. Acute-duration exposure of 45 mg Co/kg/day as cobalt chloride in food for 3 consecutive days decreased food consumption in Sprague-Dawley rats (Wellman et al. 1984). Intermediate-duration exposure of 30.2 mg Co/kg/day as cobalt chloride hexahydrate for 13 weeks decreased water intake in Sprague-Dawley rats (Domingo et al. 1984). Garoui et al (2012) observed decreased water and food intake in Wistar rats exposed to 20.26-21 mg Co/kg/day as cobalt chloride (Garoui el et al. 2011; Garoui el et al. 2012).

Dermal

No studies were identified regarding other noncancer effects in animals after dermal exposure to cobalt for any duration.

2.19. CANCER

No studies were identified that reported significant cancerous effects in humans following inhalation, oral, or dermal exposure to cobalt.

Inhalation

EPA has not classified cobalt for carcinogenicity. IARC has classified cobalt as *Group 2B- possibly carcinogenic to humans.* Exposure to cobalt, tungsten, and nickel and cancer mortality risk was evaluated in an international cohort of hard metal production workers (Marsh et al. 2017b). Workers (32,534) from 3 companies, 17 sites among 5 countries, including the United States, Austria, Germany, Sweden, and the United Kingdom were evaluated. Information on deaths was obtained from various national datasets, and phone interviews were completed for participants when possible. These interviews provided information on demographic and lifestyle factors. Kennedy et al. (2017) described the job class plus exposure matrix that was used and reported the estimated cobalt, nickel, and tungsten exposures. Employee history was obtained from occupational records. Among the US cohort which included eight sites, there was no increased lung cancer mortality risk or trends in SMRs from long term exposure to cobalt or from the other metals studied (Marsh et al. 2017a). Standardized mortality ratios were not statistically higher by sex and while two plants observed excess lung cancer mortality, this was not statistically significant (Marsh et al. 2017a). Study authors state that the lung cancer risks were higher in females than in males in

Germany, the US, and Sweden likely due to lifestyle and behavioral factors, such as increased smoking and not from occupational exposure (Marsh et al. 2017a). When pooling data from all international cohorts, there was a slight excess in all cancer and lung cancer mortality; however, there was no evidence of an exposure-response relationship for lung cancer (Marsh et al. 2017b). Additionally, there was no indication that occupation duration nor cumulative exposure to cobalt impacted lung cancer mortality risk. In other studies conducted at hard metal production factories in the United Kingdom and Europe, the study authors found no significant exposure-response relationship between cancer and inhalation exposure to cobalt (McElvenny et al. 2017; Morfeld et al. 2017; Sauni et al. 2017; Wallner et al. 2017; Westberg et al. 2017a; Westberg et al. 2017b).

Inhalation exposure to cobalt metal produces cancerous effects in animals. An intermediate-duration 13 week intermittent exposure to 0.06 mg Co/m^3 caused squamous metaplasia in the larynx in F344/N rats and B6C3F1 mice (Bucher et al. 1990; NTP 1991). At concentrations ≥0.06 mg Co/m^3 for 13 weeks, rats and mice also developed squamous metaplasia of the larynx (Bucher et al. 1990; NTP 1991). Chronic intermittent exposure to cobalt sulfate heptahydrate for 105 weeks at 0.06 mg Co/m^3 caused alveolar/bronchiolar neoplasms along with granulomatous inflammation and metaplasia in the nose and epiglottis in F344/N rats and B6C3F1 mice of both sexes (NTP 1998). Chronic intermittent exposure at 0.06 mg Co/m^3 for 105 weeks also caused hyperplasia in the adrenal medulla in F344/N rats of both sexes (NTP 1998). Increased incidence of alveolar/bronchiolar neoplasms was noted following lifetime exposure of male rats to 0.63 mg Co/m^3 and in female F344/N rats exposed to 0.21 mg Co/m^3 (Bucher et al. 1999; NTP 1998). Statistical analysis revealed that tumors occurred with significantly positive trends in both sexes of rats (NTP 1998). Similarly, B6C3F1 mice of both sexes exposed to 0.63 mg Co/m^3 showed an increase in alveolar/bronchiolar neoplasms, again with lung tumors occurring with significantly positive trends (NTP 1998). Another chronic study with intermittent exposure (105 weeks) to cobalt metal caused a significantly increased incidence of mononuclear cell leukemia in female rats at 1.25 mg Co/m^3 compared to controls (adjusted incidence rate: 62.4% in exposed, 35.7% in controls) (Behl et al. 2015; NTP 2014). In B6C3F1 mice of both sexes, exposure at 1.25 mg Co/m^3 for 105 weeks intermittently increased the rate of alveolar/bronchiolar carcinoma in exposed mice compared to controls (Adjusted rates in exposed: 79.4% in males, 53.8% in females; adjusted rates in controls: 22.8% in males, 11.3% in females) (Behl et al. 2015; Hong et al. 2015; NTP 2014).

Oral

No studies were identified regarding cancer effects in animals after oral exposure to cobalt.

Dermal

No studies were identified regarding cancer effects in animals after dermal exposure to cobalt.

2.20. GENOTOXICITY

No studies were identified regarding genotoxic effects in humans following oral or dermal exposure to cobalt. No studies were identified regarding genotoxic effects in animals following inhalation and dermal exposure to cobalt.

Gennart et al. (1993) examined a cohort of 26 male workers who had been occupationally-exposed to cobalt and observed that analysis of variance on sister-chromatid exchange rank values revealed that exposure status (exposed vs. controls) had statistically significant effects (Gennart et al. 1993). De Boeck et al. (2000) reported no significant change in the comet assay on lymphocytes from nonsmoking workers who had been occupationally exposed to cobalt (De Boeck et al. 2000). The genotoxic effects of Co showed that metallic Co induced a statistically significant concentration dependent increase in micronucleated binucleates quantified by the comet assay in blood samples from two donors (De Boeck et al. 2003). In Hengsteler et al. (2003) blood samples from 78 subjects (62 men and 16 women) exposed to cobalt in occupational settings were collected. The concentration of cobalt in air was quantified 6 h immediately before blood samples were collected for DNA –SSB analysis and the air concentration of cobalt of the work areas of the 78 individuals examined in this study varied widely ranging from 0 to 10 µg /m3 for cobalt (Hengstler et al. 2003). Hengstler et al. (2003) showed a correlation between increased air concentration of cobalt and levels of single stranded DNA binding protein (DNA- SSB). Mateuca et al. (2005) collected blood from 21 cobalt exposed and 26 matched controls to examine the genotoxic effects of cobalt exposure on lymphocytes by using a Comet assay. The workers who were exposed to cobalt showed chromosomal rearrangements resulting from chromosome loss or acentric fragments assessed as micronucleated mononucleates and binucleates (Mateuca et al. 2005). Welders exposed to cobalt in occupational settings showed a significant increase of OTMχ^2 distribution along with a significant induction of DNA strand breaks (Iarmarcovai et al. 2005). The micronucleus assay showed that the exposed welders had higher frequency of chromosomal damage, in particular, the XRCC1 variant allele coding Gln amino acid at position 399 was found to be associated with a higher number of DNA breaks as revealed by the comet assay (Iarmarcovai et al. 2005). Uboldi et al (2016) showed a dose- dependent increase in genotoxic effects caused by $CoCl_2$ in human bronchial epithelial cells. The underlying cause for the observed genotoxic effects in the bronchial epithelial cells is oxidative DNA damage as evidenced by modification in FPG (DNA-formamidopyrimidine glycosylase) and hOGG1 enzymes (Uboldi et al. 2016). Xi et al (2016) exposed human bronchial epithelial cells to cobalt oxide and cobalt chloride and

observed a dose dependent increase in cytotoxicity and genotoxicity. Cobalt oxide and cobalt chloride induced chromosome damage in human bronchial epithelial cells where the greatest aberration observed for both were chromatid lesions (Xie et al. 2016). Exposing lung fibroblast cells to cobalt oxide and cobalt chloride hexahydrate resulted in increased cytotoxic effects by cobalt chloride hexahydrate, but they both had similar effects on genotoxicity in a study by Smith et al. (2014). Increased chromosome damage, i.e. increased percent of metaphases and total aberrations in 100 metaphases, was observed when the cells were exposed to cobalt chloride hexahydrate which is more soluble than cobalt oxide (Smith et al. 2014). Cobalt chloride induced DNA fragmentation in both a dose- and time- dependent manner in human submandibular gland cells (Akita et al. 2007). γH2AX is an early and sensitive marker of genotoxicity in Hep G2 (liver cells) and LS-174T (colon cells) cell lines that did not show any changes upon exposure to cobalt chloride and cobalt oxide (Kopp et al. 2018). An acute 1-week oral exposure to cobalt chloride in albino rats showed a dose- dependent increase in frequency of micronucleated polychromatic erythrocytes. This oral administration led to hepatic damage through induction of oxidative stress, inflammation, and apoptosis (Awoyemi et al. 2017). Genotoxic effects of *in vivo* exposure to cobalt are presented in Table 2-7.

Single oral exposures of male Swiss mice to 0, 4.96, 9.92, or 19.8 mg Co/kg as cobalt chloride resulted in significantly increased percentages of both chromosomal breaks and chromosomal aberrations in bone marrow cells with significant linear trends toward increased aberrations with increased exposure (Palit et al. 1991a, 1991b; Palit et al. 1991c; Palit et al. 1991d). Thirty hours following a single intraperitoneal injection of cobalt(II) chloride in BALB/c mice, an increase in micronucleus formation was seen at doses of 12.4 or 22.3 mg Co/kg (as cobalt chloride), but not at 6.19 mg/kg (Suzuki et al. 1993). Single intraperitoneal injection of 50 mg Co/kg (as cobalt chloride) resulted in significantly increased micronucleus formation at 24 hours post-injection, but not at 12, 48, 72, or 96 hours (Suzuki et al. 1993). Two or 10 days following intraperitoneal injection of male and female F344 rats with 3 or 6 mg Co/kg, increased levels of oxidatively-damaged DNA bases were noted in the liver, kidney, and to a lesser extent, the lung (Kasprzak et al. 1994). *Drosophila melanogaster* exposed to cobalt chloride showed mutagenic activity resulting in malformed wings (Kaya et al. 2002). Oral exposure to cobalt compounds studied by Kirkland et al. (2015) did not elicit any chromosomal aberrations in the bone marrow or sperm.

Cobalt was found to be non-mutagenic in bacteria (*Salmonella typhimurium*, *Escherichia coli*) and yeast (Arlauskas et al. 1985; Fukunaga et al. 1982; Kanematsu et al. 1980; Kharab and Singh 1985; Ogawa et al. 1986; Singh 1983; Tso and Fung 1981). A very weak mutagenic response was found with *Bacillus subtilis* (Kanematsu et al. 1980). A mutagenic response to cobalt was found when compounds with a valence state of III were tested in *S. typhimurium* and *E. coli* (Schultz et al. 1982). The authors suggested

that this may be due to the formation of cobalt(III) complexes that are inert to ligand substitution, allowing optimal interaction of cobalt with genetic material (Schultz et al. 1982). Other studies have shown cobalt to be a co-mutagen in combination with 4-substituted pyridines in *S. typhimurium* (Ogawa et al. 1988). It also has been reported that cobalt acts as an anti-mutagen in bacterial (*S. typhimurium*, *B. subtilis*, *E. coli*) and yeast test systems. (*Saccharomyces cerevisiae*) (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). A possible explanation is that cobalt acts by correcting the error-proneness of deoxyribonucleic acid (DNA) replicating enzymes by improving their performance during DNA synthesis (Inoue et al. 1981; Kada et al. 1986; Kuroda and Inoue 1988). However, cobalt has also been shown to increase the frequency of genetic conversions in *S. cerevisiae* (Kharab and Singh 1985; Singh 1983). The reasons for this apparent dichotomy in yeast cells is not known.

In contrast to the results seen in bacteria, cobalt compounds were generally found to be genotoxic or mutagenic in mammalian assay systems. Exposure to cobalt compounds (metal, salts, or hard metal) can produce clastogenic effects in mammalian cells, including human lymphocytes (Anard et al. 1997; Hamilton-Koch et al. 1986; Painter and Howard 1982); transformation in hamster cells (Costa et al. 1982); sister chromatid exchanges in human lymphocytes (Andersen 1983); and micronucleus formation in rodent bone marrow cells (Suzuki et al. 1993) and human lymphocytes (Capomazza and Botta 1991; Olivero et al. 1995; Van Goethem et al. 1997). Hard metal is generally more genotoxic in *in vitro* tests than other cobalt compounds. Cobalt ions are thought to inhibit DNA repair in mammalian cells by interaction with zinc-finger proteins involved in DNA excision repair (De Boeck et al. 1998; Hartwig et al. 1991; Kasten et al. 1997; Sarkar 1995). Genotoxic effects of *in vitro* exposure to cobalt are represented in Table 2-8.

Table 2-7. Genotoxicity of Cobalt In Vivo

Species (test system)	End Point	Results	Reference
Drosophila Melanogaster (wing spot test)	Clastogenicity resulting in malformed wings	+	Kaya et al. 2002
Sprague-Dawley rats	Clastogenicity	+	Kirkland et al. 2015
Sprague-Dawley rats	Chromosomal aberration	+	Kirkland et al. 2015
Albino rats	DNA damage	+	Awoyemi et al. 2017
Human peripheral blood mononucleated cells	DNA damage	+	DeBoeck et al. 2003
Human mononuclear blood cells	DNA damage	+	Hengstler et al. 2003
Human lymphocytes	DNA damage	+	Mateuca et al. 2005
Human lymphocytes	Breakage of DNA strands	+	Iarmarcovai et al. 2005

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid;

Table 2-8. Genotoxicity of Cobalt In Vitro

Species (test system)	End Point	Results		Reference
		With Activation	Without Activation	
Prokaryotic organisms				
Salmonella typhimurium (plate incorporation)	Gene mutations	No data	-	Tso and Fung 1981
Salmonella typhimurium (plate incorporation)	Gene mutations	No data	-	Arlauskas et al. 1985
Salmonella typhimurium (plate incorporation)	Gene mutations	No data	-	Ogawa et al. 1986
Salmonella typhimurium (plate incorporation)	Gene mutations	No data	+	Schultz et al. 1982
Salmonella typhimurium (plate incorporation)	Gene mutations	-	-	Kirkland et al. 2015
Salmonella typhimurium (pre incubation)	Gene mutations	-	-	Kirkland et al. 2015
Bacillus subtilis (rec assay)	Gene mutations	No data	(+)	Kanematsu et al. 1980
Escherichia coli (reversion assay)	DNA damage	No data	-	Kanematsu et al. 1980
E. coli (repair assay)	Reversion	No data	+	Schultz et al. 1982
Eukaryotic organisms				
Saccharomyces cerevisiae (plate assay)	Reversion	No data	-	Kharab and Singh 1985
S. cerevisiae (plate assay)	Reversion	No data	-	Fukunaga et al. 1982
S. cerevisiae (plate assay)	Conversion	No data	-	Singh 1983
S. cerevisiae (plate assay)	Conversion	No data	+	Kharab and Singh 1985
S. cerevisiae (plate assay)	Conversion	No data	+	Fukunaga et al. 1982
S. cerevisiae (plate assay)	Conversion	No data	+	Singh 1983
Mammalian cells				
Hamster ovary cells	Clastogenic effects	No data	+	Hamilton-Koch et al. 1986
Hamster embryo cells	Transformation	No data	+	Costa et al. 1982
Mouse lymphoma cells	Clastogenic effects	+	+	Kirkland et al. 2015
Human lymphocytes	Sister chromatid exchange	No data	+	Andersen 1983
Human lymphocytes	Gene mutations	-	-	Kirkland et al. 2015

Table 2-8. Genotoxicity of Cobalt In Vitro

Species (test system)	End Point	Results		Reference
		With Activation	Without Activation	
Human lymphocytes	Chromosomal aberration	+	+	Kirkland et al. 2015
Human HeLa cells	Inhibition of DNA synthesis	No data	+	Painter and Howards 1982
Human diploid fibroblasts	DNA damage	No data	+	Hamilton-Koch et al. 1986
Human bronchial epithelial cells	DNA damage	No data	+	Uboldi et al 2016*
Human bronchial epithelial cells	Chromosome aberration and chromatid lesions	No data	+	Xie et al. 2016
Human lung fibroblast cells	Induces cell cycle arrests and absence of metaphase	No data	+	Smith et al 2014
Human sub mandibular gland ductal cell line	DNA fragmentation	No data	+	Akita et al. 2007
Human hepatoblastoma cells	DNA damage	No data	-	Kopp et al. 2018
Human epithelial colorectal adenocarcinoma cells	DNA damage	No data	-	Kopp et al. 2018

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; *= hOGG1- 8-Oxoguanine glycosylase also known as OGG1 is a DNA glycosylase enzyme that, in humans, is encoded by the OGG1 gene. It is involved in base excision repair. It is found in bacterial, archaeal, and eukaryotic species; FPG-DNA-formamidopyrimidine glycosylase is a base excision repair enzyme which recognizes and removes a wide range of oxidized purines from correspondingly damaged DNA

2.21. MECHANISM OF ACTION

Soluble and insoluble forms of cobalt give rise to toxicity and carcinogenicity in animal models following cellular uptake of the metal and subsequent release of cobalt ions from its salts. These ions elicit a cascade of downstream biological effects. The extracellular release of cobalt ions from water-soluble compounds is transported into the cells thorough the ion channels or via endocytosis of poorly soluble cobalt compounds. The poorly soluble cobalt compounds are then solubilized in the acidic environment and then released as ionic cobalt in the intracellular space. While the exact mechanism(s) for the transport of cobalt cations through cellular membranes are unknown, the natural resistance-associated macrophage protein 2 (NRAMP 2)/divalent metal transporter 1 (DMT1) can play a role in this transport (Forbes and Gros 2003). There are several plausible ways through which these ions can cause toxicity *in vivo.* These include inhibition of DNA repair, genotoxicity, generation of reactive oxygen species (ROS) resulting in oxidative damage, and stabilization of hypoxia-inducible factor 1α (HIF-1α), a protein that increases the expression of genes that promote survival of cells when they receive less oxygen (NTP 2016).

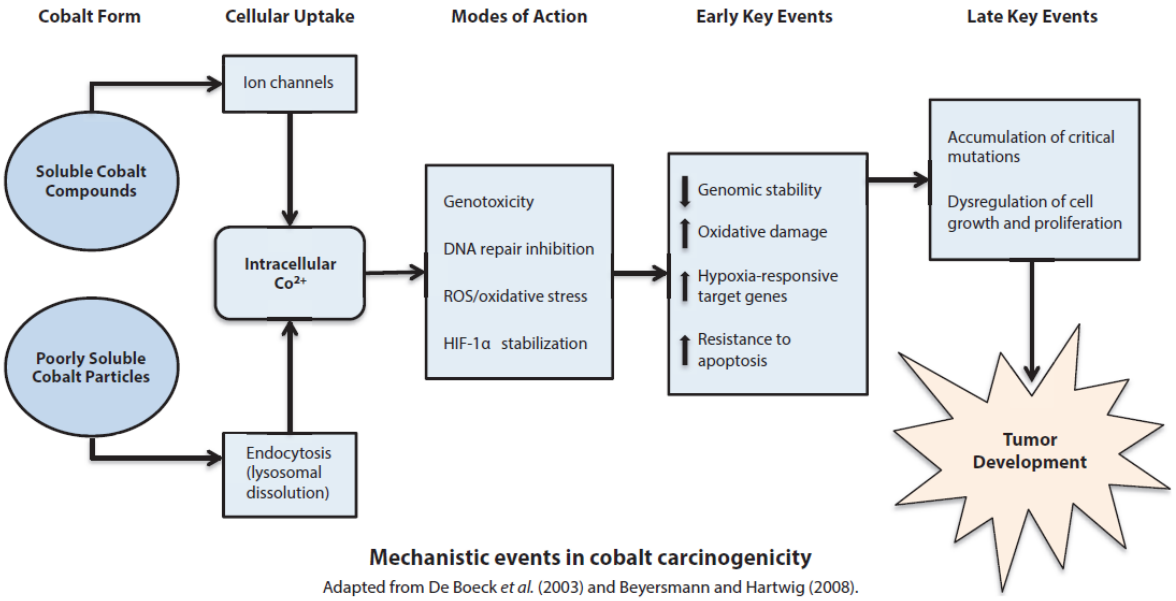
Calcium influx in cells is known to be altered by soluble cobalt when it blocks the inorganic calcium channels in cells harvested from rodent models (Henquin and Lambert 1975; Moger 1983; Yamatani et al.

1998). Blocking these channels is associated with a decrease in steroidogenesis in mouse Leydig cells (Moger 1983). The ubiquitous calcium channels in liver cells harvested from rats (Yamatani et al. 1998) and pancreatic cells harvested from mice (Henquin and Lambert 1975) also get blocked by cobalt. Cobalt also affects neuromuscular calcium transmission because muscle tissues have an abundance of calcium ion channels in an *in vitro* sartorius nerve muscle preparation (Weakly 1973). An in vitro study of $CoCl_2$ on postnatal day 3 rat cochlear organotypic cultures reported damage to cochlear hair cells and peripheral auditory nerve fibers along with loss of spiral ganglion neurons that were concentration and duration dependent; these occurred along with increased expression of superoxide radicals and increased expression of caspase-3 in hair cells indicative of apoptotic mediation (Li et al. 2015).

Cobalt is also known to interfere with the hypoxia inducible factor α (HIF- α) and degrading it, thus, exposure to cobalt can often mimic hypoxic conditions in *in vitro* models (Yuan et al. 2003). The testicular degeneration seen as a result of cobalt exposure is often a result of the testis itself becoming hypoxic due to blockage of veins and arteries by increases in the number of red blood cells, alterations in permeability due to thickening of basal lamina and basement membranes, and enlargement of interstitial Leydig cells in a rodent model (Elbetieha et al. 2008; Mollenhauer et al. 1985). Hypoxia can also be observed in other tissues such as cardiac, brain, liver, and renal from rats and mice (Mayfield et al. 1994; Morelli et al. 1994). Cobalt ions are also responsible for stabilizing HIF-1α and HIF-2α and thus increasing the production of red blood cells, and increasing hemoglobin concentrations in human male participants (Hoffmeister et al. 2018).

Cobalt ions can damage DNA by inhibiting DNA polymerization thus affecting DNA repair in human fibroblasts (Kasten et al. 1997). It can also cause induction of oxidative damage in a mouse model and human lung fibroblast cells (Lison 2015; Smith et al. 2014). Changes in hepatic enzymes like superoxide dismutase, catalase, glutathione peroxidase, and heme oxygenase are associated with an increase in lipid peroxidation in the liver which is a direct result of an increase in oxidative damage in *in vivo* animal models (Akinrinde et al. 2016a; Awoyemi et al. 2017; Christova et al. 2001).

Figure 2-4. Mechanistic Events Associated with Cobalt Toxicity and Carcinogenicity



Source: Beyersmann and Hartwig 2008; De Boeck et al. 2003; NIEHS 2016

2.22. COBALT NANOPARTICLES

The following section provides a brief overview of cobalt nanoparticle toxicity and focuses on highlighting key findings from experimental animal studies and *in vitro* studies using human and animal cell lines. No epidemiologic studies focusing on the health effects of exposure to cobalt nanoparticles (CoNPs) were identified. Increased levels of Co ions in serum and testis were observed in male rats after *in vivo* exposure of 500 µg/kg bodyweight via an intra-articular injection (Wang et al. 2013). *In vivo* exposure to CoNPs at a dose of 20 mg/kg body weight via intravenous exposure in New Zealand rabbits demonstrated accumulation of CoNPs in lung, liver, and kidney tissues after a histopathological examination (Hanini et al. 2016). No other toxicokinetic studies examining the absorption, metabolism, or excretion of CoNPs were identified. *In vitro* models using human cell lines have demonstrated that CoNPs induce metabolic impairment, oxidative stress, and cytotoxicity (Alinovi et al. 2015; Alinovi et al. 2017; Bastian et al. 2009). Research on the effects of CoNPs in animals is limited but generally suggests that CoNPs are toxic in laboratory animals. Several *in vivo* and *in vitro* studies have demonstrated that CoNPs increase the production of reactive oxygen species and reactive nitrogen species, which have both been previously shown to be associated with inflammation, genotoxicity, cytotoxicity, and reproductive toxicity (Hussien and Mohamed 2018; Moche et al. 2015; Monteiller et al. 2007).

Primary target organs for CoNPs toxicity include the testicles, brain, and lungs. Male rats exposed to CoNPs at a dose of 500 μg/kg body weight via an intra-articular injection, once per week for 10 consecutive weeks, suffered from testicular damage, reduced epididymal sperm motility, viability, and concentration, and increased abnormal sperm rate (Wang et al. 2013). In male Wistar rats, significant neural damage was observed in both the hippocampus and the cortex of the temporal lobe at a dose of 2 mg/kg body weight administered intraperitoneally once per day for 20 days (Zheng et al. 2019). Zheng et al. (2019) also compared the neurotoxic potential of cobalt chloride and CoNPs and identified that the nanoparticles showed greater neurotoxic potency. Male albino rats exposed to a single oral dose of 1 g/kg body weight of CoNPs via food caused an increase in relative brain, kidney, and liver weights, along with increases in erythrocyte and hemoglobin counts (Ali 2019). No respiratory effects were observed 24 hours post treatment in male Sprague-Dawley rats exposed to a single dose of 62.5 μg CoNPs intratracheally; however, this study included only 3 rats in the treatment group (Brown et al. 2018). Transgenic mice (gpt delta) were intratracheally instilled with 50 μg CoNPs per mouse and examined on day 1, 3, 7, and 28 after exposure in a study by Wan et al. (2017). This study identified toxic effects in the respiratory system that included lung inflammation, oxidative stress, injury, and cell proliferation, which further resulted in DNA damage and DNA mutation (Wan et al. 2017). In Hansen et al. (2006), Sprague-Dawley rats underwent subcutaneous implantation of CoNPs and developed subcutaneous and intramuscular nodules. Toward the end of the study period (6 months), all treated animals developed handicapping tumors (Hansen et al. 2006).

The overall database for CoNPs in mammals is limited to a few studies in rats, mice, and rabbits. While CoNPs are becoming increasingly useful for various healthcare-related applications, the toxicity profile and toxicokinetics for these CoNPs need to be studied further. More studies need to be conducted to examine how CoNPs affect the physiology in each organ system. Exposure to CoNPs from inhalation, dermal, and oral routes, as well as via prosthetics and therapeutics needs to be studied. Since CoNPs have distinct physical and chemical properties that are different from other cobalt compounds, a focused effort should be made on developing a complete toxicological profile to better understand the health effects and toxicokinetics of these unique chemicals.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1. TOXICOKINETICS

- Absorption: Submicron size particles of a substance, such as cobalt can be almost completely absorbed through the respiratory tract, whereas larger particles may be moved after deposition in the respiratory tract by mucociliary clearance and swallowed. Inhaled cobalt absorption ranges from 52-78%. The fraction of ingested cobalt that is absorbed from the gastrointestinal tract depends on an individual's nutritional status, cobalt dose, and type of cobalt. The ingested cobalt absorption rates range from 5-97%. Absorption rates vary widely among humans. Cobalt may also be absorbed through the skin where the absorption through intact skin was <1%, while absorption through abraded skin was almost 80%.
- Distribution: Cobalt is primarily distributed to the serum, whole blood, liver, kidneys, heart, and spleen, with lower amounts reported in the skeleton, hair, lymphatic circulation, and pancreas.
- Metabolism: Cobalt is not subject to metabolism by enzymatic pathway but tends to get distributed between organ systems and excreted via urine and feces.
- Excretion: Cobalt is excreted primarily in urine and feces regardless of the route of exposure. The elimination of cobalt is often represented as a multi-compartmental model with compartments having half-lives of several hours to a week. Values for cobalt have been calculated based on urinary excretion of either stable cobalt or its radioactive isotopes, Co^{57} and Co^{60}.

3.1.1. Absorption

In general, regional deposition of cobalt in the lungs depends on both biological and physical characteristics such as particulate size, breathing patterns, and airstream velocity. Deposition of particulates greater than 2.5 µm occurs in the upper portion of the airway, whereas particulates less than 2.5 µm are deposited in the lower portion of the respiratory tract (James et al. 1994). Absorption of deposited cobalt is dependent on its solubility and location within the lung. Physiologically insoluble cobalt particles are cleared by phagocytosis and/or mucociliary transport and have a low systemic absorption (Bailey and Roy 1994; Kreyling 1990). More soluble forms of cobalt are absorbed into the bloodstream through the alveolar or bronchial walls. Particles located in the alveolar region undergo phagocytosis or dissolution and are subsequently absorbed (Kreyling 1990). Particle dissolution rates in lung fluids, in secretions, or in macrophages as well as cobalt's biochemical reactions and binding to tissue components affect the rate of absorption (Bailey and Roy 1994; Kreyling 1990).

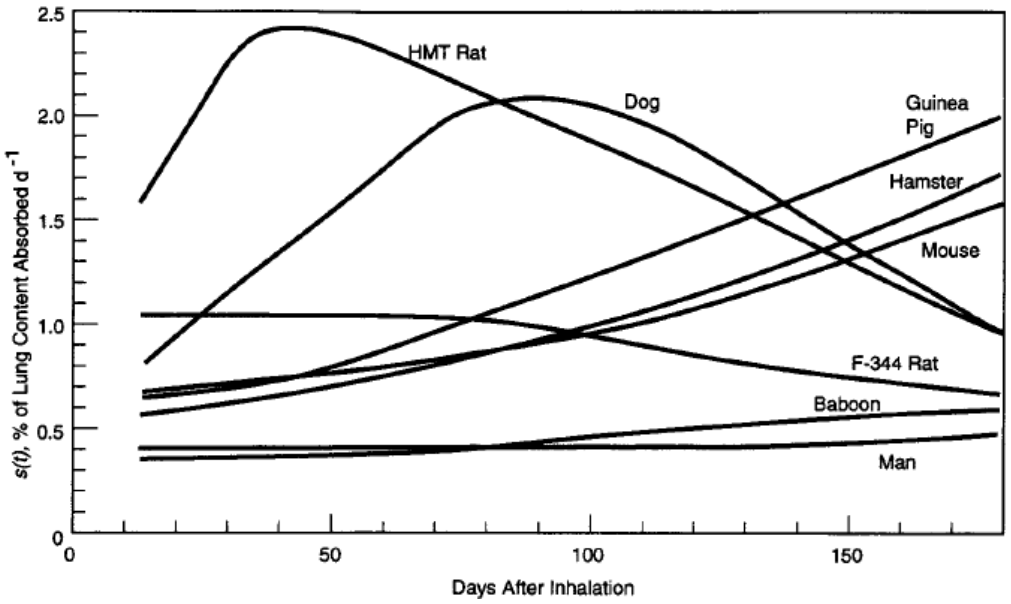
There are limited data available for either humans or animals regarding cobalt absorption following inhalation exposure. In a small study of four individuals utilizing radiolabeled (^{57}Co) cobalt oxide with geometric mean diameters of 0.8 µm and 1.7 µm, the average fractional deposition of the smaller particles was 52% and the average fractional deposition of the 1.7 µm particles was 78% (Foster et al. 1989). Urinary cobalt levels measured in workers can be an indicator of cobalt lung absorption. Lison et al. (1994) found that in workers exposed via inhalation to more soluble forms of cobalt, there was an increase in cobalt in the urine at the end of their shift, possibly indicating a rapid absorption from the lungs. However, urine measurements following exposure to cobalt oxides, a less soluble form, were lower than the amount in urine for the more soluble forms, which may be an indication of a lower absorption rate from the lungs (Lison et al. 1994). Similarly, Christensen and Poulson (1994) found higher levels of cobalt in the blood and urine of pottery plate painters when the painters used a soluble pigment compared to levels when they used a less soluble pigment.

NTP (2014) exposed female rats and mice for two weeks, three months, or two years to cobalt metal particulate aerosol via inhalation. Median diameters of the cobalt particles were measured at regular intervals during the study and were maintained at 1.86-1.92 µm for the two week inhalation study, 1.4-2.0 µm for the 3-month study, and 1.5-2.0 µm for the two-year inhalation study. Lung deposition rates were calculated. For both rats and mice, lung deposition rates generally increased with exposure. The two-week study used doses of 2.5, 5, 10, and 20 mg/m^3. The corresponding lung deposition rates for rats were: 1.46, 2.48, 3.12, 8.91 µg Co/day and for mice were: 0.57, 1.25, 1.87, 2.34 µg Co/day. For the three month and two-year studies, lung deposition rates were calculated for the following doses: 1.25, 2.5, and 5 mg/m^3. The corresponding deposition rates for rats were: 1.45, 2.13, 5.6 µg Co/day for the compartment with higher absorption rates and 0.018, 0.08, 0.29 µg Co/day for the compartment with lower absorption rates. The corresponding deposition rates for mice were: 0.87, 1.84, 1.18 µg Co/day for the fast compartment and 0.027, 0.075, and 0.22 µg Co/day for the slow compartment (NTP 2014).

In Syrian golden hamsters exposed to cobalt oxide, absorption was reported to be approximately 27% of inhaled cobalt oxide (CoO) (particle size, 1-2.5 µm) with 60% recovered in the gastrointestinal tract, which could reflect mucociliary transport and swallowing of particles (Wehner and Craig 1972). Collier et al. (1991) calculated translocation rates from lungs to blood in rats exposed to ^{57}Co labeled cobalt tetraoxide (Co_3O_4) over the duration of the study and reported that translocation rates increased with time from 0.5-1% per day initially to 1.5-4.0% 150 days post-exposure with the youngest rats exhibiting the highest rates.

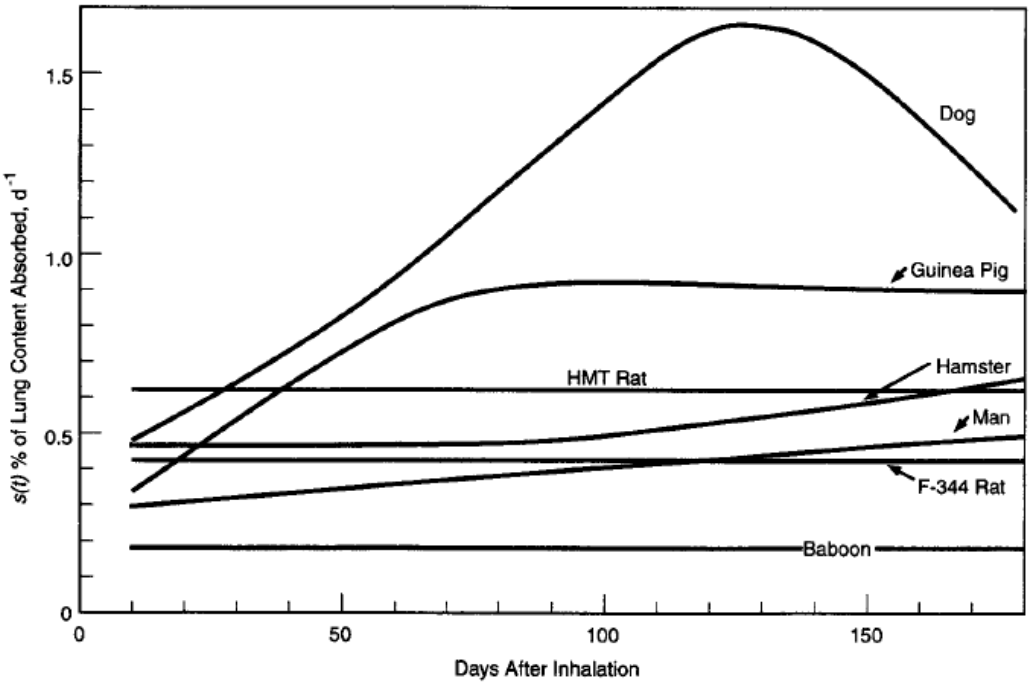
Absorption rates from the lungs into the blood were measured in two interspecies studies using $^{57}Co_3O_4$. Bailey et al (1989) measured the rate of absorption of $^{57}Co_3O_4$ at two different particle sizes (0.8 and 1.7 µm) in humans, baboons, dogs, hamsters, guinea pigs, mice, and three strains of rat (Sprague-Dawley, Fischer344, and HMT). Mice were only exposed to the 0.8 µm size particles. The fraction of cobalt translocated for the 0.8 µm particles was twice that of the 1.7 µm particles for all species except mice (Bailey et al. 1989). Dogs, baboons, and HMT rats showed the greatest differences in translocation rates. To further investigate the differences in translocation, a second study was conducted in which the three species were exposed via inhalation to a form of $^{57}Co_3O_4$ that was denser and had a smaller specific surface area than the particles in the first study. The particle size used was 0.9 µm (Kreyling et al. 1991). Initial translocation rates ranged from 0.001%/day in baboons to 0.007%/day in rats. Kreyling et al. (1991) reported that the rate-determining process for translocation to blood is the intracellular particle dissolution in the macrophage as transfer of the dissociated material to blood is fast. The translocation rates varied widely across species ranging from 0.004%/day to 0.0015%/day for the smaller particles and for the larger particles, 0.002%/day to 0.006%/day (Bailey and Roy 1994; Bailey et al. 1989). Results are summarized in Figure 3-1, Figure 3-2, and Figure 3-3.

Figure 3-1. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 0.8 µm porous Co_3O_4



Man = data for humans (male)
Source: Bailey and Roy (1994)

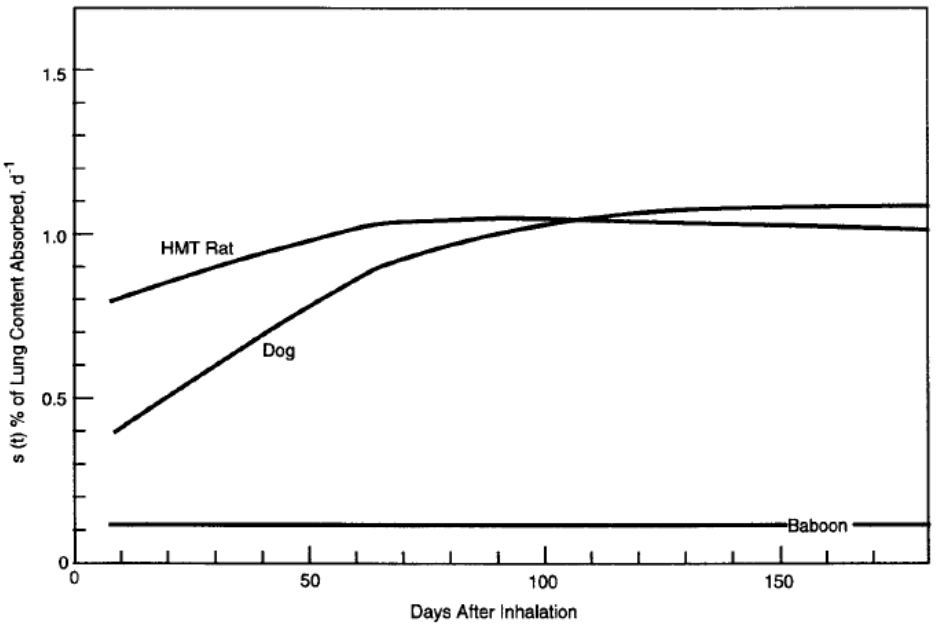
Figure 3-2. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 1.7 µm porous Co_3O_4



Man = data for humans (male)

Source: Bailey and Roy (1994)

Figure 3-3. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 0.9 µm solid Co_3O_4



Man is data for humans (male)

Source: Bailey and Roy (1994)

Absorption following oral exposure to cobalt in humans varies and is dependent on individual nutritional status, cobalt dose, and type of cobalt. Studies in humans have reported a large interindividual variability for absorption rates. The reported absorption rates range from 5% to 97% (Harp and Scoular 1952; Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). More recent estimates of absorption indicate the absorption rate for soluble forms of cobalt administered as a solid range from 10-25% and range from 20-45% for soluble forms of cobalt administered as a liquid (Tvermoes et al. 2015).

Christensen et al. (1993) measured the absorption of both soluble $CoCl_2$ and insoluble Co_3O_4 in 12 male and 11 female volunteers. Based on urinary excretion of Co, uptake of $CoCl_2$ was greater than the uptake of the insoluble Co_3O_4. Values for non-radiolabeled cobalt have been calculated based on urinary excretion of cobalt. Both overnight fasting and iron deficiency resulted in increased cobalt absorption (Smith et al. 1972; Sorbie et al. 1971; Valberg et al. 1969). Amino acids and sulfhydryl groups that bind with Co ions might reduce absorption (Paustenbach et al. 2013). Serum ferritin levels were strongly inversely correlated with blood cobalt levels in Norwegian women (Meltzer et al. 2010). Barany et al. (2005) also reported an inverse relationship between iron levels and cobalt in both adolescent girls and 15-year old boys. This result was not observed in 17-year old boys, most likely due to a better iron status. Adolescent boys had the lower blood cobalt levels overall compared to adolescent girls. Lower levels of both ferritin and total iron resulted in higher levels of cobalt in the blood. Higher activity levels in males also resulted in higher cobalt levels in the blood due to decreased iron levels (Tvermoes et al. 2014).

Cobalt and iron share a common absorptive pathway in the intestines, though cobalt absorption can take place without ferritin (Reuber et al. 1994; Schade et al. 1970; Thomson et al. 1971). The duodenum and proximal jejunum are the primary sites for cobalt ion absorption where absorption is mediated by the divalent metal transporter (DMT-1) (Knopfel et al. 2005; Danzeisen et al. 2020). Since cobalt and iron share similar characteristics, it is thought that both may compete for uptake by DMT-1. DMT-1 is involved in transporting iron into the duodenum and is upregulated by iron deficiency or by increased demand for iron (Garrick et al. 2006; Meltzer et al. 2010; Paustenbach et al. 2013). Another protein, Nramp1, may also facilitate uptake of cobalt, iron, and manganese (Forbes and Gros 2003).

Studies of gastrointestinal cobalt absorption in humans have shown differences in absorption rates based on sex with females generally having higher absorption rates likely due to higher rates of iron deficiency in women (Looker et al. 1997).

Christensen et al. (1993) reported higher levels of blood and urinary cobalt in the female volunteers compared to the male volunteers following oral administration of cobalt. After 31 days of cobalt supplementation, blood levels of cobalt were two times higher in females than in males (Finley et al. 2013). Tvermoes et al. (2014) extended the cobalt supplementation to 90 days and reported that the male volunteers had lower blood levels than females. The total amount of cobalt in an adult as vitamin B_{12} via ingestion is about 0.25 mg, of which 50–90% in contained in the liver (IARC 1991).

Absorption studies in rats report differences in absorption based on solubility with 13-34% of the more soluble forms of cobalt being absorbed compared to 1-3% of insoluble forms being absorbed (Ayala-Fierro et al. 1999; Bailey et al. 1989; Barnaby et al. 1968; Collier et al. 1989; Hollins and McCullough 1971; Kirchgessner et al. 1994; Patrick et al. 1989; Schade et al. 1970; Taylor 1962). Ayala-Fierro et al. (1999) also report an absorptive half-life of 0.9 hours for orally administered cobalt chloride in male Fisher rats. Water-soluble cobalt forms exhibit greater absorption than non-water-soluble forms (Deka et al. 1981; Firriolo et al. 1999; Inaba et al. 1980; Kinoshita and Fujita 1972; Kreyling et al. 1986). Absorption was not affected by particle size of cobalt administered to baboons, guinea pigs, HMT rats, F-344 rats, hamsters, or CBA/H mice (Bailey et al. 1989).

Danzeisen et al. (2020) measured the bioavailability of cobalt chloride ($CoCl_2$), cobalt tetraoxide (Co_3O_4), cobalt sulfide (CoS), and lithium cobalt oxide ($CoLiO_2$) in male and female rats. As reported in human studies, sex differences in bioavailability were reported for $CoCl_2$ with females (12%) showing a higher bioavailability than males (7%), although these results were not statistically significant (Danzeisen et al. 2020). The bioavailability of the other cobalt compounds was less than 0.5%, suggesting that these compounds are not well absorbed. The reported $CoCl_2$ absorption of 12% is lower than that reported in humans (Tvermoes et al. 2014). The differences between rat and human studies may be due to study design. For example, the rat study used a one-time bolus dose that was one to two orders of magnitude higher than the doses used in the human studies and the exposure duration was longer in the human studies (Danzeisen et al. 2020; Tvermoes et al. 2014).

Administration of $CoCl_2$ (labeled with radioactive ^{58}Co) and complexed with histidine, lysine, glycylglycine, ethylenediaminetetraacetic acid (EDTA), casein, or glycine resulted in decreased gastrointestinal absorption of cobalt in rats, whereas significantly greater absorption occurred when radiolabeled $CoCl_2$ was administered in cows' milk. Cobalt(II) glycine complex was absorbed in greater quantities than a cobalt(III) glycine complex (Taylor 1962). Taylor et al. (1962) performed this study to better elucidate the mechanism by which absorption occurs in the gastrointestinal tract.

Similar to humans, iron deficiency led to increased absorption of cobalt in rats; whereas simultaneous administration of cobalt and iron reduced the amount of cobalt absorbed (Reuber et al. 1994; Schade et al. 1970). Increasing oral doses of cobalt resulted in decreased fractional absorption (Houk et al. 1946; Kirchgessner et al. 1994; Taylor 1962). In young rats and guinea pigs (60 days old and younger), reported absorption is 3- to 15-fold greater than in adult (200 days of age) animals (Naylor and Harrison 1995).

Species differences in absorption are reported for more soluble cobalt compounds. Absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; Van Bruwaene et al. 1984). Danzeisen et al. (2020) evaluated the solubility of various cobalt compounds in both simulated gastric and intestinal fluid and reported that the solubilities varied by 100-fold in gastric fluid and more than 1000-fold in intestinal fluid with the more soluble compounds being more bioaccessible.

Studies evaluating absorption through dermal exposure are limited. Klassen et al. (2017) also reported a significant correlation with cobalt on the skin and uptake into blood and that dermal exposure may contribute as much to uptake as inhalation exposure. A doubling of cobalt levels on skin resulted in a 3-14% increase in blood cobalt levels (Klasson et al. 2017). Kettelarij et al. (2018b) also reported an association between dermal exposure and cobalt levels in urine. A doubling of cobalt on the skin resulted in median urinary cobalt increase of 70% pre-shift and 32% post shift. The higher pre-shift levels may reflect ongoing absorption from the previous day's exposure. Kettelarij et al. (2018) collected urine samples over the course of 24 hours (4-11 samples per worker) and collected skin samples pre- and post-shift compared to Wahlquist et al. (2020) who collected urine samples pre- and post-shift and collected skin samples once. In an experiment to measure absorption through the skin, four subjects held their right hands for 90 min in a box filled either with freshly mixed powder (5–15% cobalt) or with waste dry powder. Both conditions resulted in an increase of urinary cobalt by an order of magnitude post exposure and continuing for 48–60 hours (Scansetti et al. 1994).

Cobalt absorption through skin was studied using an *in vitro* system that used human abdominal skin obtained from autopsies or medical waste. Using cobalt powder applied in human sweat, the reported steady state percutaneous permeation was 0.0123 ± 0.0054 μg/cm^2/hr with a lag time of 1.55±0.71 hr with much of the cobalt remaining in the skin (Leggett 2008).

Animal studies suggest that dermal absorption of cobalt depends on whether the skin is intact or damaged. Absorption through intact skin is comparatively low, while absorption through damaged skin is much higher (Inaba and Suzuki-Yasumoto 1979; Lacy et al. 1996). Inaba and Suzuki-Yasumoto (1979)

examined the absorption of $2.2x10^{-5}$ mg cobalt-60 (^{60}Co)/kg as $CoCl_2$ in 1.4N HCl through 1 cm^2 of intact or abraded skin of guinea pigs. Absorption measured three hours post exposure through intact skin was <1%, while absorption through abraded skin was almost 80%. A study in hamsters also reported a low amount of absorption of cobalt through unabraded skin (Lacy et al. 1996).

3.1.2 Distribution

As a component of vitamin B_{12}, cobalt is an essential element and is found throughout the body. Cobalt is distributed to the serum, whole blood, liver, kidneys, heart, and spleen, with lower amounts reported in the skeleton, hair, lymphatic circulation, and pancreas (Collecchi et al. 1986; Forbes et al. 1954; Hewitt 1988; Ishihara et al. 1987; Muramatsu and Parr 1988; Teraoka 1981; Yamagata et al. 1962; Yukawa et al. 1980). The total body content of cobalt is estimated at 1.1–1.5 mg (ICRP 1979; Yamagata et al. 1962), with approximately 0.11 mg in the liver (ICRP 1979). Approximately 85% of the total cobalt body burden in adults is in the form of the vitamin B_{12} organometallic complex (Paustenbach et al. 2013). The amount of cobalt available to partition into and accumulate in tissues is dependent on the concentration of free cobalt ions in serum. At serum cobalt concentrations up to 3,000 mg/L, it is estimated that 8.3-8.5% exists as free cobalt ions; the rest is bound to serum proteins, primarily albumin (Paustenbach et al. 2013). Two protein carriers, albumin and α_2-macroglobulin bind to cobalt in the blood and serum (Paustenbach et al. 2013). Cobalt(II) ions can bind to lipoproteins and haptoglobin and cobalt(III) has been reported to bind to transferrin, resulting in a decrease in iron transferrin binding (Paustenbach et al. 2013). The transport/binding mechanisms for cobalt ions in blood and tissues may involve competitive interactions with receptor binding affecting feedback mechanisms that involve other divalent cations like iron and calcium. The transport binding mechanisms are not well understood (Paustenbach et al. 2013).

Autopsy results from workers exposed to cobalt via inhalation found increased cobalt levels in tissues. Significant increases in cobalt in the lung were found in copper smelter and metal workers and coal miners occupationally exposed to cobalt (Gerhardsson et al. 1984; Hewitt 1988; Hillerdal and Hartung 1983; Teraoka 1981). Gerhardsson et al. (1984) reported a median lung concentration in deceased smelter workers of 15 ppb, which is twice that of the control group; however, there were no significant differences in cobalt levels in the kidneys or liver. Hewitt (1988) reported a median lung concentration of cobalt of 0.007 µg/g wet tissue in Swedish smelter workers. In an airplane painter, increased cobalt levels were also found in the lymph nodes (0.76 ppm), lung (1.4 ppm), liver (0.46 ppm), spleen (0.45 ppm), and kidneys (0.35 ppm) (Teraoka 1981).

The tissue distribution of cobalt in animals and humans are similar. In dogs exposed to either ^{60}CoO or $^{60}Co_3O_4$ via inhalation and following translocation from the lung, the highest cobalt concentrations were

recorded in the liver, kidney, and skeleton, with ^{60}CoO having higher concentrations than $^{60}Co_3O_4$ (Barnes et al. 1976). CoO is more soluble then Co_3O_4; only 10% of the initial lung burden remained in the lung compared to 85% for $^{60}Co_3O_4$ eight days after inhalation exposure (Barnes et al. 1976). Brune et al. (1980) exposed rats to cobalt particles via inhalation for eight hours per day for up to 107 days, cobalt levels accumulated in the lungs and were almost 500 times that of controls. Dust particles remaining in the lungs were primarily found in the macrophages. After the lungs, the kidneys and liver had the next highest cobalt levels (Brune et al. 1980). Tissue distribution in rats following exposure to ^{57}Co labeled Co_3O_4 was found mainly in the thoracic tissues 182 days post exposure. Seven days post exposure the majority of the extra thoracic cobalt tissue distribution was found in the GI tract, pelt, and carcass (Collier et al. 1991). Both Patrick et al. (1989) and Talbot and Morgan (1989) reported similar results in rats and mice, respectively, with most of the cobalt remaining in the lungs and very little distributing to other organs. Kreyling et al. (1986) exposed dogs to various forms of cobalt oxides wherein the lungs retained much of the cobalt followed by the bones, muscle, and skin. The stomach, liver, and kidneys contained less cobalt (Kreyling et al. 1986).

In Syrian golden hamsters, the carcass (23%) and the GI tract (60%) had the most cobalt 24 hours post-exposure to CoO (Wehner and Craig 1972). In swine, the kidney cortex and spleen had higher cobalt levels than controls (Kerfoot 1974).

NTP (2014) reported the following distribution order for cobalt tissue concentrations (cobalt as µg Co/g tissue) in F344/N rats (in decreasing order): lung, liver, kidney, femur, heart, serum, and blood. The tissue cobalt burden (µg Co/tissue) distribution was similar except that the liver accumulated more cobalt than lung, and the heart accumulated more cobalt than the femur. In general, both the order for tissue concentrations and burdens were similar in mice.

There are limited data regarding distribution of cobalt following oral exposure in humans. However, the available studies show cobalt is distributed by serum and blood (Finley et al. 2013; Tvermoes et al. 2014). Following oral administration of cobalt in human volunteers for 31 days, Finley et al. (2013) reported that the rate of uptake for serum cobalt levels to whole blood cobalt was 1.3 µg/L for every 1.0 µg/L of cobalt in whole blood. Tvermoes et al. (2014) also reported higher serum cobalt levels than whole blood cobalt levels from a 90-day dosing study in human volunteers. Both Finley et al. (2013) and Tvermoes et al. (2014) report that women had higher concentrations in blood and serum than men. Steady-state concentrations of cobalt in whole blood and red blood cells were reached within 14-24 days following a 31-day supplementation with cobalt (Finley et al. 2013). Steady-state conditions were achieved after 20 days in men and 35 days in women following a 90-day supplementation of cobalt (Tvermoes et al. 2014).

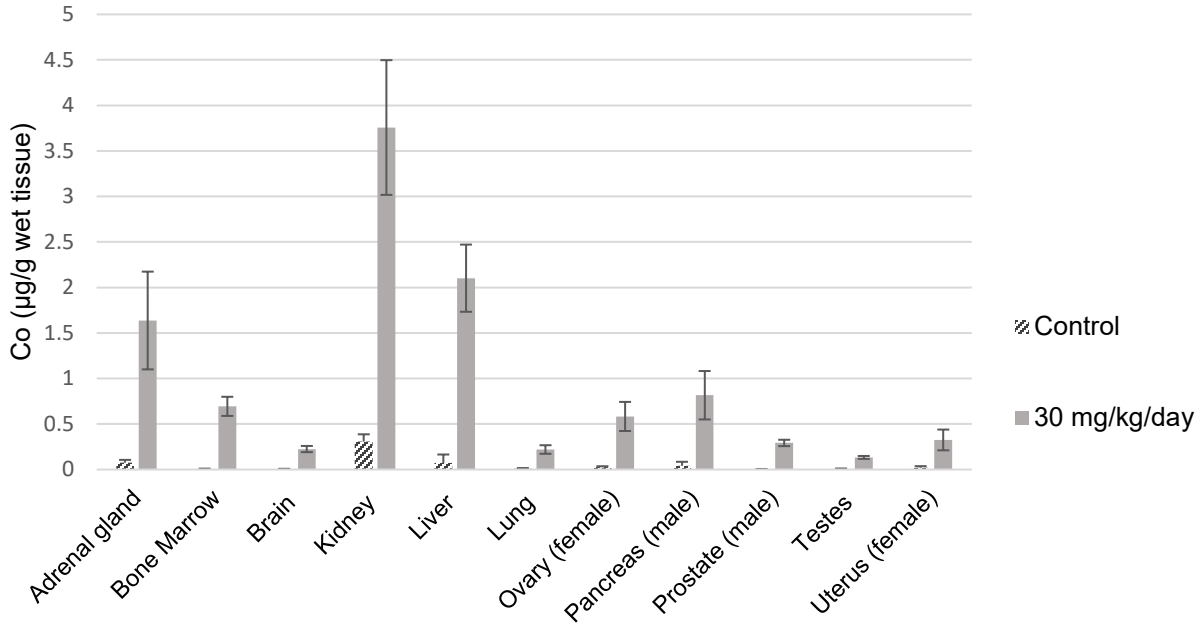
The time course data of cobalt levels in blood and serum suggest that cobalt may be sequestered in red blood cells resulting in slower clearance (Finley et al. 2013; Tvermoes et al. 2014). Protein bound cobalt comprised 95% of the total serum cobalt during dosing. Kargar et al. (2013) reported that approximately 96% of serum cobalt was bound to large molecular proteins in a 90-day study of human volunteers that ingested approximately 1 mg cobalt/day of a dietary cobalt supplement. The authors also reported an increase in percent of cobalt bound from 95% to 99% during the post-dosing time frame. The authors suggest that the increase in the fraction of bound cobalt was due to the movement of bound cobalt from extravascular to intravascular space because of the depletion of cobalt in the intravascular space by excretion and red blood cell uptake (Kargar et al. 2013).

Studies in animals show that cobalt is found primarily in the liver with smaller amounts in the kidneys, heart, stomach, and intestines following oral exposure of cobalt that resulted in gastrointestinal absorption (Ayala-Fierro et al. 1999; Greenberg et al. 1943; Persson et al. 1992; Simesen 1939; Thomas et al. 1976). In a study examining the distribution of orally administered radiolabeled cobalt ($^{60}CoCl_2$) in rats, Barnaby et al. (1968) reported that after one day, the liver contained the highest level of cobalt (4% of the radioactivity administered) with less than 1% in all other organs. However, after 132 days, the highest levels of cobalt were reported in the muscle and skeleton, both less than 1%, and the amount of cobalt in the liver had dropped to 0.016% (Barnaby et al. 1968). Following a single oral dose of cobalt naphthenate, the highest levels were found in the liver followed by the kidney and heart; negligible amounts were found in the spleen or testes (Firriolo et al. 1999). Szakmary et al. (2001) reported a dose-dependent increase in cobalt levels in fetal blood and amniotic fluid following oral exposure to cobalt in pregnant rats. Clyne et al. (1988) measured the amount of cobalt in the myocardium, soleus muscle, and serum in rats orally administered $CoSO_4$ in the diet for eight weeks. Cobalt levels in the myocardium, soleus muscle, and serum were higher in the exposed group compared to controls. While the highest cobalt levels were in the myocardium, followed by the soleus muscle, and then serum, cobalt levels in serum were 100-fold higher than controls, the myocardium levels were 30-fold higher, and the soleus muscle levels were 26-fold higher. Pehrsson et al. (1991) also reported a 30-fold increase in cobalt levels in the myocardium of rats orally exposed to cobalt in the diet. Bourg et al. (1985) reported higher cobalt levels in the blood, brain, and testis of rats exposed to cobalt in the diet.

Danzeisen et al. (2020) showed that in a 90-day exposure to 7.44 mg Co/kg-BW/day, distribution of cobalt in the tissues was primarily to the liver and kidney. The exposed rats had an approximate 100-fold increase in cobalt in the bone marrow compared to controls (Danzeisen et al. 2020). Danzeisen et al. (2020) carried out a toxicity test where rats were repeatedly administered cobalt via oral gavage daily for 90 days. Distribution of cobalt in tissues is shown in Figure 3-4. Cobalt levels were highest in the liver

and kidneys. In general, there was a 20-fold increase in tissue cobalt compared to controls; however, cobalt levels in bone marrow were 100-fold higher than controls (Danzeisen et al. 2020).

Figure 3-4. Cobalt Levels in rat tissue after 90-day oral exposure to 30 mg/kg bw/day $CoCl_2$ (7.44 mg Co/kg bw/day) compared to controls (means ± SD)[a]



Source: Danzeisen et al. (2020)

Skalny et al. (2021) administered $CoCl_2$ in drinking water to pregnant mice from three days prior to gestation through lactation. At weaning (day 25), the offspring were removed and exposed to $CoCl_2$ in drinking water until postnatal day 30. Cobalt tissue concentrations were measured on days 18, 25, and 30 in kidneys, liver, spleen, skeletal muscle, and serum. Cobalt distribution in tissues followed a dose dependent course. Serum levels were 140-fold, 194-fold, and 300-fold higher than controls on days 18, 25, and 30, respectively. Skeletal muscle levels followed the same pattern, increasing with age. However, for the liver, kidney, and spleen the maximal difference between exposed mice and controls occurred on day 25.

No studies were identified regarding distribution in humans or animals after dermal exposure to cobalt.

Smith et al. (1972) administered intravenous cobalt, as ^{60}Co, to 23 men and one woman and performed whole body scans up to 1,018 days post exposure. Results indicate that 10-30% of the cobalt was found in the liver. Jansen et al. (1996) administered $^{55}CoCl_2$ intravenously to two healthy adult human males. Scans show that 50% of the cobalt accumulated in the liver, while 40% was found in the bladder.

Similar results have been reported in animals. Houeto et al. (2018) administered $CoCl_2$ or hydroxocobalamin (HOCo) or saline (control) intraperitoneally daily for three weeks. Cobalt was higher in tissues for both $CoCl_2$ and HOCo compared to control and cobalt tissue concentrations were higher for $CoCl_2$ compared to HOCo. The kidney and spleen had the highest cobalt concentrations for the HOCo exposed rats. For the $CoCl_2$ exposed rats the tissues with the highest concentrations were the liver and kidney (Houeto et al. 2018). Two hours after intravenous injection of $^{57}CoCl_2$ in rats, cobalt was found in the liver (22.8% of the dose), kidneys (10.2%), and intestines (3.16%) (Gregus and Klaassen 1986). Similar results (29% liver, 10% kidneys, 4.6% intestines) were found following intracardiac injection of cobalt nitrate in rats (Patrick et al. 1989) or intravenous injection of $^{55}CoCl_2$ in rats (Jansen et al. 1996). After intravenous injection of $^{60}CoCl_2$ in rats, the greatest concentrations were found in the liver and kidney; however, 100 days after injection the highest concentrations were found in the spleen, heart, and bone (Thomas et al. 1976). Barnaby et al. (1968) reported similar results following intraperitoneal injection of $^{60}CoCl_2$ in rats. Following intramuscular injection of cobalt mesoporphyrin in rats, the liver and blood had the highest cobalt concentrations, followed by kidney, lung, spleen, adrenal glands, and heart at 7 days post-injection and later (Feng et al. 1998). Four weeks after subcutaneous administration of cobalt protoporphyrin, the highest concentrations of cobalt occurred in the kidney, followed by spleen, liver, lung, thymus, and gonads (Rosenberg 1993).

3.1.3 Metabolism

Metabolism of cobalt consists of formation of complexes with a variety of protein and nonprotein ligands. Cobalt is not subject to direct metabolism by enzymatic pathways but tends to predominantly get distributed in organ systems as discussed in the previous section (Section 3.1.2) or tends be excreted as is detailed in section 3.1.4. (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989; Van Bruwaene et al. 1984).

3.1.4 Excretion

In excretion following inhalation exposure, the mucociliary escalator is the main clearance mechanism for insoluble particles deposited in the conducting zone (trachea and primary bronchi), whereas soluble particles are cleared by diffusional and pinocytotic processes from this region. In the alveolar region, insoluble particles are removed by phagocytosis and transport to the mucociliary escalator. Soluble forms in the alveolar region are cleared by diffusional and pinocytotic processes (Oberdörster 1993).

No data are available on the clearance of soluble cobalt particles in humans. Following exposure of humans to physiologically insoluble cobalt compounds such as cobalt metal or cobalt oxides, clearance

from the body appears to follow three-phase kinetics. The first phase, mucociliary clearance of particles deposited in the tracheobronchial region, has a half-time of 2–44 hours (Apostoli et al. 1998; Mosconi et al. 1994a). The second phase, which involves a macrophage mediated clearance from the lungs has a halftime of 10-78 days (Beleznay and Osvay 1994; Mosconi et al. 1994a). The third clearance phase, representing long-term clearance from the lungs, has a half-time on the order of years (Bailey et al. 1989; Beleznay and Osvay 1994; Mosconi et al. 1994a; Newton and Rundo 1971).

Following a controlled aerosol exposure in humans, about 40% of the initial lung burden of inhaled ^{57}CoO was retained for a period of 6 months after exposure (Foster et al. 1989). Six months after exposure, a cumulative elimination of 33% of the initial lung burden was found in the urine and 28% was found in the feces (Foster et al. 1989). The ratio of peak absorption rate to average mechanical clearance rate (Table 3-1) was about 5 to 1. The peak translocation and average mechanical clearance of cobalt from the lungs for different species are reported in Table 3-1. Humans, baboons, and dogs had the lowest mechanical clearance rates among the different species and humans and baboons had the lowest translocation rates for 0.8 µm particles. Cobalt elimination is affected by time, e.g. urinary excretion increases with time, and by particle size with more cobalt mechanically removed via the mucociliary escalator when the aerosol consists of larger particles (Bailey et al. 1989; Foster et al. 1989).

Elimination half-lives in rats and mice exposed for two weeks to cobalt ranged from 9-11 days in blood (rats), 4-7 days in blood (mice), approximately 3 days in serum (rats), 3-4 days in serum (mice), 4-6 days in lungs (rats), and 6-7 days in lungs (mice). In rats exposed for three months to cobalt, the pulmonary clearance followed a two-phase elimination. The first, a rapid phase, had a half-life of 2-3 days and the second, slow phase, had a half-life between 19 and 23 days. For two-year exposures in rats, dose-dependent rapid clearance phase half-lives were between 1.5 days and 2.9 days, and the slow clearance phase half-lives were between 83 and 789 days for respective doses of 1.25 and either 2.5 or 5 mg/m^{3}indicating that steady state was achieved for the two highest doses. Between 95% and 99% of the cobalt was eliminated in the rapid phase with 1-5% eliminated in the slow phase. For mice exposed to cobalt for two weeks, the half-lives decreased as the dose increased. Like rats exposed for three months, the pulmonary clearance exhibited a two-phase elimination. For mice exposed for two-years to 1.25, 2.5, and 5 mg/m^3, the rapid phase half-lives were 1.2, 1.1, and 5.2 days, respectively, indicating a slightly longer half-life in animals exposed at the highest dose. The total slow phase lung cobalt clearances ranged from 3.1% to 17.6%, while the total rapid phase lung cobalt clearances ranged from 96.9% to 82.4% with increasing exposure concentration (NTP 2014).

Table 3-1. Peak Translocation and Average Mechanical Clearance Rates (%) After Inhalation of Cobalt Oxide for 180 days [a,b]

	Percent of lung content cleared per day for 180 days				
	Translocation at peak				Average mechanical
Species (strain)	0.8 µm	Peak day	1.7 µm	Peak day	Clearance (%)[c]
Human	0.45	180	0.5	180	0.1
Baboon	0.6	180	0.2	d	0.1
Beagle dog	2.1	85	1.7	180	0.03
Guinea pig	2.1	180	1	75	0.3
Rat (HMT)	2.4	40	0.6	d	0.9
Rat (F-344)	1.1	10	0.4	d	1
Hamster	1.8	180	0.7	180	0.8
Mouse	1.7	180	No data	No data	1.05

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer
[c]Clearance rates were virtually identical in both particle size groups
[d]Constant value over 180 days

The rate of urinary excretion appears to correlate with the rate of translocation of cobalt from the lungs to the blood and the rate of fecal clearance appears to correlate with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract following inhalation exposure (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kerfoot 1974; Kreyling et al. 1986; Kreyling et al. 1989; Palmes et al. 1959; Patrick et al. 1989; Talbot and Morgan 1989). The solubility of cobalt affects the rate of clearance in animals with more soluble forms, such as CoO, clearing faster than insoluble forms e.g. Co_3O_4 (Barnes et al. 1976; Kreyling et al. 1984).

Urinary excretion was the primary route of cobalt elimination after a single inhalation exposure (Palmes et al. 1959) or after 3 months of exposure (Kerfoot 1974; Palmes et al. 1959) in rats and swine. In several species of animals, most of the inhaled Co_3O_4 (labeled with ^{57}Co) following a single exposure was cleared from the lungs by 6 months after exposure (Table 3-2) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Kreyling et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989).

Table 3-2. Initial (Day 3) Lung Deposits of Cobalt Oxide and Summary of Lung Retention at 90 and 180 Days[a,b]

	Mean initial ^{57}Co activity in lung L(3)[c] (kBq)		Lung retention L(90)[d]/L(3) (%)		Lung retention L(180)[e]/L(3) (%)	
Species (strain)	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm
Human	53	42	64	75	45	56
Baboon	2,100	1,700	55	55	26	37
Beagle dog	1,150	1,450	27	45	5.5	12
Guinea pig (Harwell)	8.4	1.4	49	46	8.3	15
Rat (HMT, 1985)	10.8	4.7	5.2	20	1.3	8
Rat (HMT, 1986)	3.2	0.7	5.3	18	1.2	9.2

Table 3-2. Initial (Day 3) Lung Deposits of Cobalt Oxide and Summary of Lung Retention at 90 and 180 Days[a,b]

	Mean initial ^{57}Co activity in lung L(3)[c] (kBq)		Lung retention L(90)[d]/L(3) (%)		Lung retention L(180)[e]/L(3) (%)	
Species (strain)	0.8 μm	1.7 μm	0.8 μm	1.7 μm	0.8 μm	1.7 μm
Rat (F344, SPF)	8.8	4.4	14	25	4.7	9.2
Rat (Sprague-Dawley)	0.9	0.1	8	39	1	15
Syrian hamster	4	1.2	21	35	3.4	12
Mouse (CBA/H)	1.8	No data	15	No data	2.8	No data

[a]Derived from Bailey et al. (1989)
[b]Cobalt-57 used as tracer
[c] Lung deposits at Day 3
[d] Lung deposits at Day 90
[e] Lung deposits at Day 180

Excretion of unabsorbed cobalt following oral exposure in humans is primarily through the feces; whereas absorbed cobalt is primarily excreted in the urine with a small amount excreted in the feces. Sorbie et al. (1971) reported that within 24 h of oral administration of radioactive $^{57}CoCl_2$ or $^{60}CoCl_2$, 18% (9-23%) of the administered dose was excreted via the urine in volunteers with normal iron levels. The amount of cobalt excreted in volunteers with iron deficiency increased to 31% (23-42%). Valberg et al. (1969) also reported similar differences in excretion between iron sufficient and iron deficient volunteers. Paley et al. (1958) reported an approximately 10-fold difference in cobalt levels in the urine and feces with the feces having the higher amount. Post dosing distribution showed a different pattern with serum cobalt concentrations falling faster than whole blood cobalt levels and with whole blood cobalt levels exceeding the serum cobalt levels (Finley et al. 2013). Finley et al. (2013) reported a 66% decrease in serum cobalt levels and a 52% decrease in blood cobalt levels one- week post-dosing. Elimination of cobalt in blood and serum follows a two-phase exponential decay curve with an initial rapid phase followed by a slower second phase. The fast phase elimination half-life was three days, with 61% of cobalt concentration at the end of dosing found in the whole blood, while 77% was found in the serum. For the slow phase, the half-life was 16 days for serum and 39 days for whole blood, with 23% of the cobalt found in serum and 39% found in whole blood (Finley et al. 2013).

Blood cobalt levels one- and two-weeks post oral dosing decreased by 63% and 69%, respectively, in healthy male volunteers who received 0.4 mg cobalt per day for 15 days, indicating that much of the cobalt is rapidly eliminated from the blood post dosing (Tvermoes et al. 2013).

Tvermoes et al. (Tvermoes et al. 2014) also reported that elimination of cobalt from whole blood and serum followed a two-phase exponential decay curve, with a fast initial phase followed by slower second

phase, following ingestion of 1 mg/day cobalt for 90 days (Table 3-3). Elimination from red blood cells was linear with time and correlated with the red blood cell life span of 120 days (Tvermoes et al. 2014). Serum cobalt concentrations were correlated with urine cobalt concentrations for both men and women; however, women retained more cobalt than men. Renal clearance differences between men and women likely reflect the different glomerular filtration rates between men (120 ml/min) and women (99 ml/min) and the differences in urine production volume between men (2900 ml) and women (1800 ml). The ratio of urine to serum cobalt concentrations for men and women throughout dosing was 3.4 and 3.3, respectively. Urinary excretion of cobalt appears to be mediated by a saturable reabsorption process (Tvermoes et al. 2014).

Table 3-3. Retention of Cobalt ($CoCl_2$) in Whole Blood and Serum in Humans after Oral Dosing

	First Phase		Second Phase			
	Fraction eliminated[a]	Elimination Rate Constant (per day)	Half-life (days)	Fraction eliminated	Elimination Rate Constant (per day)	Half-life (days)
Whole blood	0.52	0.62	2.8	0.48	0.020	36
Serum	0.76	0.58	3.08	0.24	0.037	22

Data from Tvermoes et al. (2014)
[a] Over a period of 22-36 days

Animal studies demonstrate that soluble cobalt is excreted through the urine and insoluble cobalt through the feces. The cumulative urinary and fecal elimination in several species following oral administration of Co_3O_4 (with a ^{57}Co tracer) is reported in Table 3-4 (Bailey et al. 1989). No significant differences in elimination of Co_3O_4 were found among several species of animals and more than 96% was quickly eliminated in the feces (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). For the more soluble cobalt(II) chloride, reported fecal elimination levels ranged from 70 to 83% of the administered dose for rats, with urinary excretion accounting for most of the remainder of the dose (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Hollins and McCullough 1971). In lactating dairy cows, about 97% of an oral dose of cobalt chloride was recovered in the feces by day 70 post-exposure, while the urine and milk contained 0.26% and 0.012% of the dose, respectively (Van Bruwaene et al. 1984). Following a single exposure in beagle dogs, 90% of the more insoluble, Co_3O_4, was eliminated in the feces and 5% in the urine, whereas 70% of the more soluble cobalt nitrate was excreted in the feces and 25% in the urine (Kreyling et al. 1986).

Table 3-4. Summary of Retention and Excretion After Intragastric Administration of Cobalt Oxide (Co_3O_4) Particles (Mean Percentage of Recovered Activity at 7 Days Post Administration)[a,b]

Species (strain)	Cumulative Fecal Excretion (%)		Whole Body Retention (%)		Cumulative urinary excretion (%)		Absorption(%)	
	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm	0.8 µm	1.7 µm
Baboon	97.8	98.4	0.12	0.2	2	1.4	2.6	1.9
Guinea pig	98.7	97.6	0.16	0.66	1.1	1.9	1.3	2.3
Rat (HMT)	96.3	99.4	0.09	0.02	2.8	0.6	3.9	1
Rat (F344)	99.6	99.7	0.04	0.03	0.4	0.3	0.4	0.3
Hamster	96	96.3	0.5	0.18	3.5	3.5	5.1	5.1
Mouse (CBA/H)	99.1	No data	0.3	No data	0.6	No data	0.8	No data

[a]Derived from Bailey et al. 1989
[b]Cobalt-57 used as tracer

Following oral exposure, iron-deficient rats eliminated less of a given dose in the feces than normal rats, while co-administration of iron compounds resulted in an increased fecal excretion of cobalt compounds (Reuber et al. 1994).

Danzeisen et al. (2020) reported plasma toxicokinetic parameters for four different cobalt compounds administered by oral gavage. The results are presented in Table 3-5. Danzeisen et al. (2020) reported a 30% difference among compounds and between sexes in C_{Max}, the elimination constant varied by 12.5% but remained relatively constant at 0.04 (1/h), and the half-life averaged 14.8 hours with a 12.4% variation.

Table 3-5. Pharmacokinetic Parameters for Orally Administered Cobalt in Rats[a]

Test item	Dose level		Sex	C_{Max}	$t_{1/2}$ (h)	K_{el} (1/h)	$AUC_{0-t\ last}$/cobalt dose [(h mg/l)/(mg/kg)]
	mg test item/kg	mg Co/kg					
$CoCl_2.6H_2O$	10	2.48	M	2.51	14.2	0.0489	20
			F	2.61	13.7	0.0508	13.7
Co_3O_4	300	214	M	2.08	17.3	0.0402	0.18
			F	1.1	16.1	0.043	0.12
CoS	300	194	M	2.01	16.8	0.0413	0.1
			F	2.01	14.9	0.0464	0.1
$CoLiO_2$	300	180	M	3.45	13	0.0535	0.37
			F	2.88	12.2	0.0568	0.29

[a] Data from supplemental table S2 Danzeisen et al. (2020)

Table 3-6. Urinary Cobalt Levels in Rats Following Oral Exposure to Cobalt[a]

Substance	Sex	Substance (mg/kg bw)	Co (mg/kg bw)	Cobalt concentration in urine					
				Day 1		Day 2		Day 3	
				Co (ug/L)	SD (%)	Co (µg/L)	SD (%)	Co (µg/L)	SD (%)
$CoCl_2.(H_2O)6$	M	10	2.48	9791	26	834	82	239	25
	F	10	2.48	4974	35	411	64	247	69
Co_3O_4	M	300	220	6344	47	379	56	307	149
	F	300	220	5158	25	572	17	172	96

[a] Data from supplemental table S2 Danzeisen et al. (2020)

Table 3-7. Cobalt Levels in Rat Feces Following Oral Exposure to Cobalt [a]

Substance	Sex	Substance (mg/kg bw)	Co (mg/kg bw)	Cobalt concentration in feces					
				Day 1		Day 2		Day 3	
				Co (µg/g)	SD (%)	Co (µg/g)	SD (%)	Co (µg/g)	SD (%)
$CoCl_2(H_2O)6$	M	10	2.48	41.11	N/C[b]	3.91	1.01	1.69	0.59
	F	10	2.48	47.55	N/C[b]	2.77	2.53	0.35	0.45
Co_3O_4	M	300	220	5502.63	2142.22	258.5	333.8	23.33	49
	F	300	220	5335.27	1203.64	233.6	188.3	6.59	13

N/C = not calculated

[a] Data from supplemental table S3 Danzeisen et al. (2020)

[b] SD for $CoCl_2 \cdot (6H_2O)$ not calculated, as samples for group were pooled due to a laboratory error

Urinary excretion of cobalt increased from 18.1 nmol (pre-exposure) to 38.5 nmol 24-hours after exposure in five subjects who were dermally exposed for one hour by keeping their hands in a solution containing 1600 mg Co/L. The maximum amount of cobalt excreted occurred four to six hours after exposure in two subjects and in two other subjects, the urinary excretion rate increased monotonically up to 24 hours following exposure. No increase in urinary cobalt was reported for one subject (Leggett 2008).

Lacy et al. (1996) reported that much of the absorbed dose of $CoCl_2$ was excreted in urine 48 hours after a single dermal exposure in Syrian hamsters. No other studies were identified regarding excretion in animals after dermal exposure to cobalt.

In humans with metal-on-metal hip replacements, urinary cobalt levels were three-fold higher than concentrations in plasma. Cobalt clearance increased from 1.3 mL/min in the preoperative group to 3.7

mL/min in the follow-up group; with increasing daily output, the renal clearance in the postoperative group increased from 1.9 to 7.1 mL/min (Daniel et al. 2010). Smith et al. (1972) reported that 24 hours after intravenous administration of $^{60}CoCl_2$, 22% of the administered dose was excreted in the urine, 1.8% of the administered dose was excreted in the feces, and more than 90% was removed from plasma within 30 minutes. The urinary to fecal ratio was 6.7:1. Retention times for two of the subjects followed over the course of 1000 days show the following halftimes and corresponding percent leaving the body: 0.5 days (44%); 6 days (32%); 60 days (13%); and 800 days (11%). The liver retained 20% of the total body burden on average from a few days post administration through 1000 days post injection (Smith et al. 1972).

Paley et al. (1958) reported that 48 hours after intravenous administration that 56-73% of the dose was excreted in urine and Kent and McCance (1941) reported that 57% was excreted in two weeks. The average urinary excretion of ^{57}Co in 13 healthy human subjects (nine males and four females) during the first 24 hours after intravenous injection of cobalt glycinate was 34%, with no gender differences reported. The urinary to fecal excretion ratio of 6:1 was measured in one subject over the course of three days (Leggett 2008).

Following intravenous injection of cobalt nitrate ($Co(NO_3)_2$) in various species of animals, more than half was excreted within the first day and approximately 80% was excreted in the urine within 21 days (Table 3-8) (Andre et al. 1989; Bailey et al. 1989; Collier et al. 1989; Patrick et al. 1989; Talbot and Morgan 1989). Other investigators have also found that urine is the primary route of cobalt excretion following intravenous administration with approximately 5-30% excreted in the feces (Ayala-Fierro et al. 1999; Barnaby et al. 1968; Gregus and Klaassen 1986; Kreyling et al. 1986; Onkelinx 1976; Thomas et al. 1976). Excretion of cobalt (2–7% of the injected dose) in the bile was also reported in dogs and rats (Cikrt and Tichy 1981; Gregus and Klaassen 1986; Sheline et al. 1946). Urinary excretion following intraperitoneal injection is the major route of elimination, with fecal excretion accounting for much of the remaining dose (Barnaby et al. 1968; Hollins and McCullough 1971; Talbot and Morgan 1989). However, longer term clearance may be more balanced between urinary and fecal excretion (Hollins and McCullough 1971). Urinary excretion was also the predominant route following subcutaneous injection of $CoCl_2$ and $Co(NO_3)_2$ and both were excreted rapidly from the body (Rosenberg 1993; Talbot and Morgan 1989).

Table 3-8. Summary of Retention and Excretion of Cobalt Following Injection of Cobalt Nitrate $Co(NO_3)_2$ Solution (Mean Percent Recovery)[a,b]

	Whole body retention on day			Cumulative urinary excretion on day			Cumulative fecal excretion on day		
Species (Strain)	1	7	21	1	7	21	1	7	21
Baboon	-	-	-	57	74	80	5	17	20
Beagle dog	-	-	-	71	86	87	3.4	4.4	4.9
Guinea pig	34	8	3.5	64	82	85	2.2	10	12
Rat (HMT)	18	4.2	1.9	64	72	74	18	24	24
Rat (F-344)	-	-	2.9	-	-	80	-	-	18
Hamster	27	4.3	1.9	55	68	69	17	28	29
Mouse	23	2.9	1.1	59	71	72	18	26	27

- No data
[a]Derived from Bailey et al. 1989
[b] Cobalt-57 used as tracer

The chemical form of the cobalt compound may affect its rate of elimination. Subcutaneous injection of cobalt protoporphyrin, a substance where the cobalt atom is chelated within the porphyrin ring, resulted in a slower clearance from plasma ($t_{½}$ = 3 days) in rats than cobalt chloride, where greater than 95% was measured in plasma 30 minutes after injection. Approximately 20% of the cobalt from cobalt protoporphyrin remained in plasma 14 days after injection (Rosenberg 1993). Intramuscular injection of cobalt mesoporphyrin resulted primarily in fecal excretion, with high systemic retention (Feng et al. 1998).

Nishimura et al. (1978) intravenously injected $^{60}CoCl_2$ and ^{58}Cocyanocobalamin into rats. After 21 days post administration of $^{60}CoCl_2$, both the liver and kidney contained 26.4% and 13.1% of the body burden, respectively, with most of the isotope activity excreted in the urine. Comparatively, the body burden of ^{58}Co-cyanocobalamin in the kidneys was 43.8% with 12% in the liver. Most of the isotope activity was in the feces. Cumulative excretion over nine days was different for the two forms of cobalt. Cumulative excretion rates for cobalt chloride were 80% and 9% of the dose for urine and feces, respectively. Cumulative excretion rates for cobalt cyanocobalamin were 5% and 14% for urine and feces, respectively (Nishimura et al. 1978).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are biologically based tissue dosimetry models. They are increasingly used in risk assessments,

primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Models that evaluate kinetics of inhalation and oral exposures for cobalt have been developed and enhanced by ICRP (1979, 1993, 2016), Leggett (2008), and Unice et al. (2020; 2014; 2012).

The ICRP developed two models: one for inhalation that is not specific to cobalt, and a biokinetic model for oral exposure that is specific to cobalt. The inhalation model, Human Respiratory Tract Model for Radiological Protection, contains respiratory tract deposition and clearance compartmental models for inhalation exposure that can be applied to particulate aerosols of cobalt compounds (ICRP 1995). The oral exposure model is a 3-compartment model of the kinetics of ingested cobalt in humans that is applicable to infants, children, adolescents, and adults.

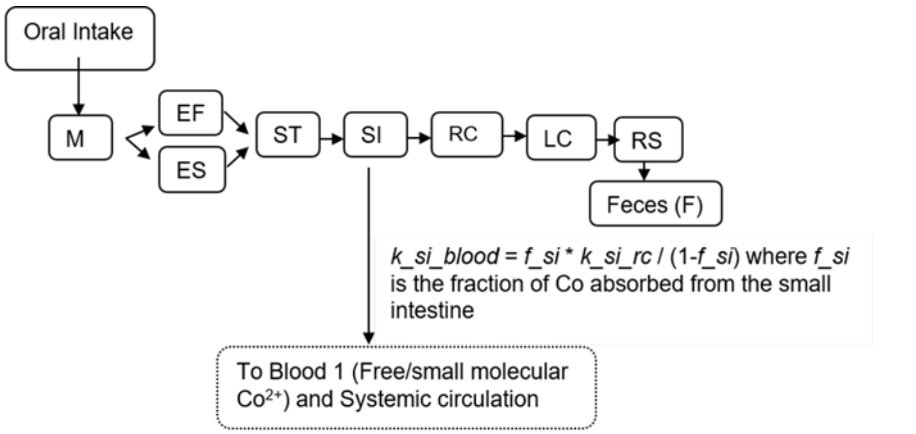
The ICRP model specific to cobalt (ICRP 1995) has several underlying assumptions. Absorption of ingested cobalt is assumed to be 60% in infants up to 3 months of age, 30% from 3 months to 15 years of age, and 10% after age 15 years. Absorbed cobalt is assumed to distribute as follows: 50% is excreted (urine and feces combined in a 6:1 ratio), 5% is transferred to the liver, and 45% is transferred to other tissues. Elimination from tissue compartments is described by three first order rate constants representing slow, medium, and fast elimination pools with half-times of 800, 60, and 6 days, respectively. The elimination half-times are assumed to be independent of age (ICRP 1979, 1993). However, the model does not account for the impact of different tissue transfer rates, the impact of bound versus free cobalt, or the impact of active transport mechanisms on how cobalt moves throughout the body over time (Paustenbach et al. 2013).

Leggett (2008) developed a biokinetic model that used five compartments: blood, liver, kidney, skeleton, and other soft tissues. The model assumed first order kinetics, and to provide a more physiologically realistic description, uses transfer coefficients to account for movement between blood and tissue compartments and from blood to excretion pathways. Using the Leggett model, Unice et al. (2012) incorporated an alimentary tract model which used a central tendency estimate for gastrointestinal absorption of 25%, with a minimum of 10% and a maximum of 35% based on available data for men and women, assumed that cobalt was ingested in a soluble form, and incorporated total blood volume and urinary excretion rates to better calculate cobalt levels in blood and urine. The model output for blood and urine was compared to the results of a Danish study of 23 subjects who ingested a soluble form of cobalt.

The model predictions were in concordance with the test population (Unice et al. 2012). In addition, Tvermoes et al (2013) conducted a study that compared the measured cobalt levels in whole blood of twenty healthy male volunteers who ingested cobalt to the model predictions of whole blood concentrations. The mean measured values were within 5% of the model's concentration range when bounded by a 15% to 35% absorption rate (Tvermoes et al. 2013).

Unice et al (2014) updated their model to reflect new toxicokinetic data involving cobalt albumin binding, uptake and storage of cobalt in red blood cells, saturable renal reabsorption of Co^{2+}, and the effect of glomerular filtration rates and free Co^{2+} on cobalt excretion. The changes incorporated were: increasing the fraction of serum protein bound cobalt from 95% during dosing to 99% post dosing; adding a post dosing linear decrease in cobalt red blood cell concentration; adjusting renal clearance to fit with glomerular filtration rates and free cobalt concentration; and adding compartments to account for serum albumin bound cobalt, exchange rates between albumin bound cobalt between intravascular and extravascular fluids, and individual red blood cell compartments representing each day in the lifetime of a red blood cell (120 days). Unice et al (2014) compared the model output to several data sets including: healthy human volunteers, whole body retention studies, dialysis patients, anephric (with non-functioning kidneys) patients, and a cobalt poisoning incident. The model compared well with all external datasets. Tvermoes et al. (2015) used this model to estimate cobalt concentrations in tissues at varying doses. Figure 3-5 and Figure 3-6 depict the model design.

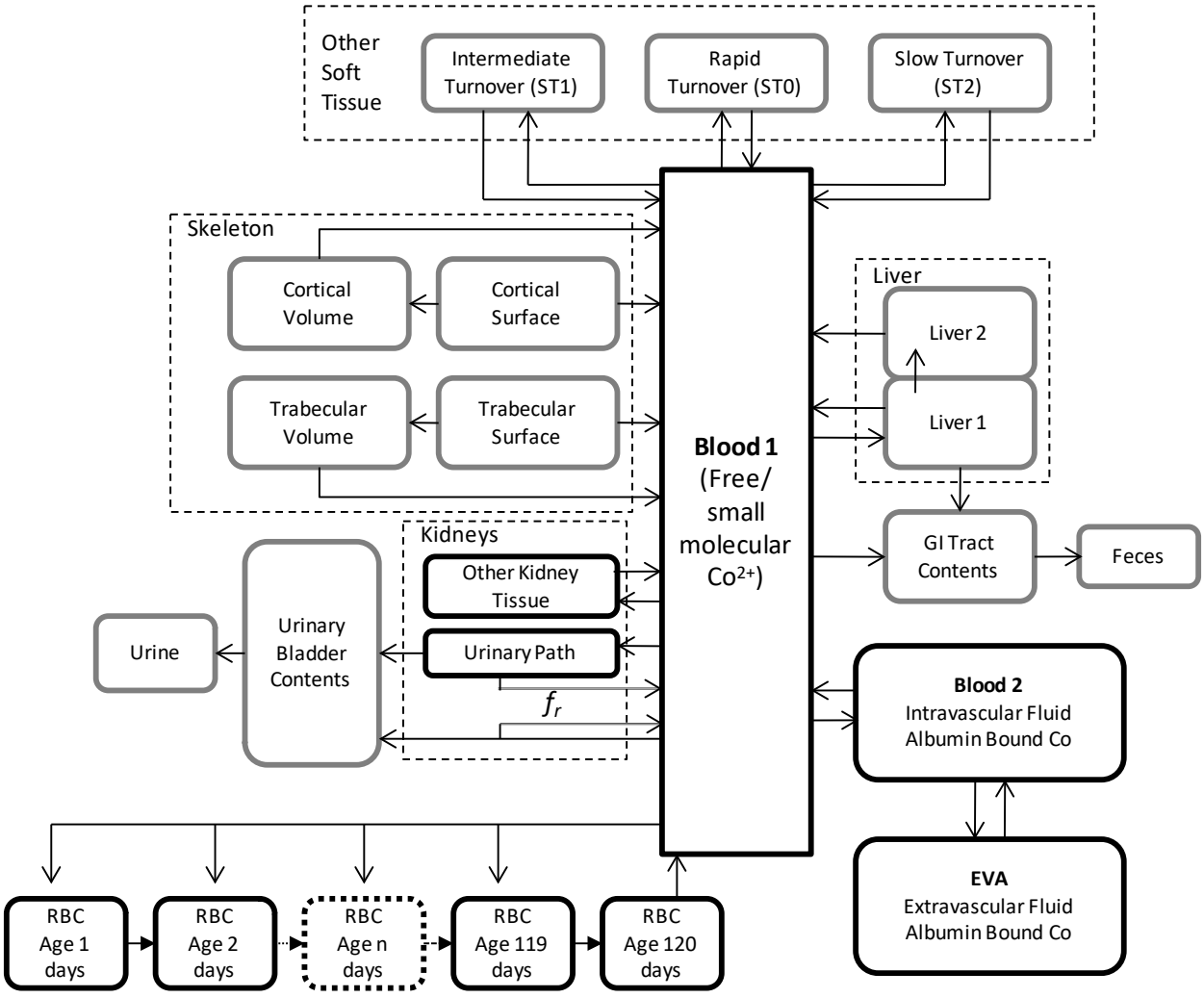
Figure 3-5. Alimentary Tract Model and Transfer Coefficients (ICRP 2016)



Where: M = mouth; EF = esophagus fast; ES = esophagus slow; ST = stomach, SI = small intestine; RS = rectosigmoid; LC = left colon; RC = rectosigmoid colon; F= feces

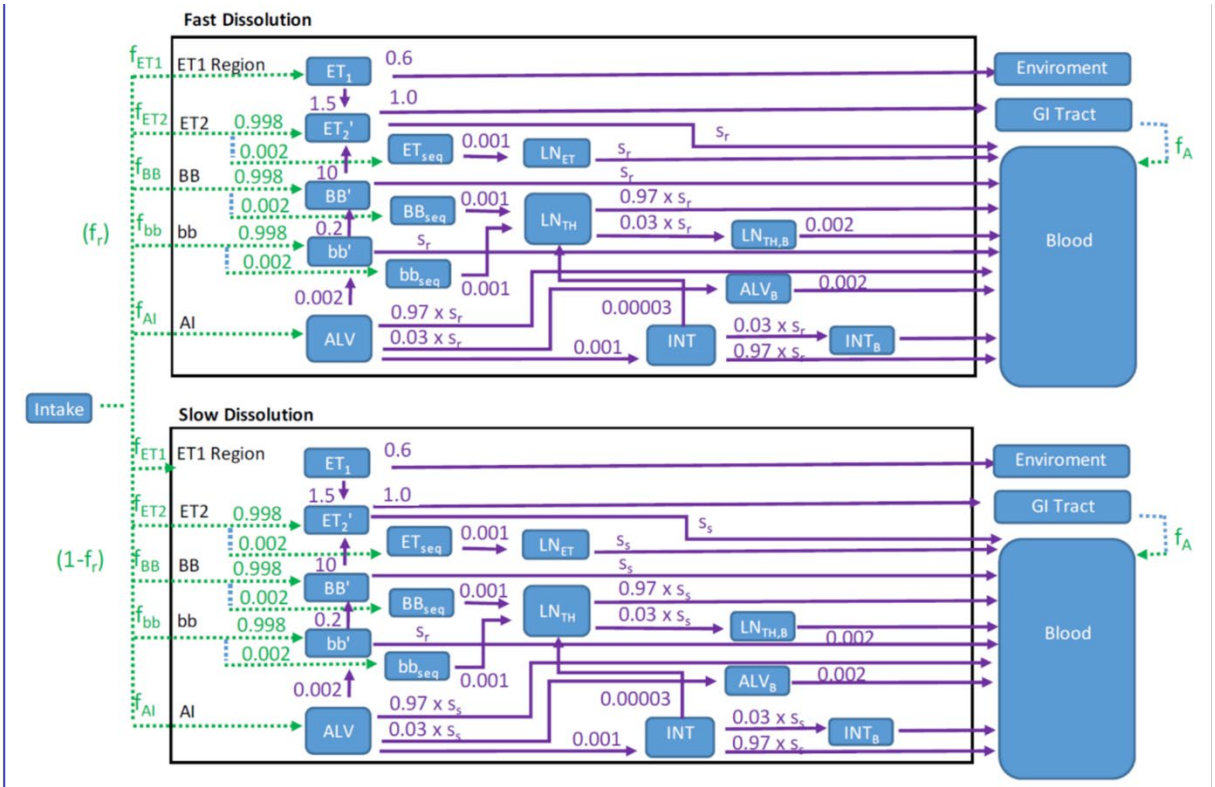
Source: ICRP 2016

Figure 3-6. Detailed Systemic Model



From Unice et al (2014) supplemental data

Figure 3-7. Updated Model Inhalation



Compartments and regions

ID (1994)	Symbol (2015)	Region or compartment
1,2,3	ALV, AI	Alveoli (ALV), Alveolar-Interstitial (AI)
1,2,3	INT	Interstitium
4,5	bb, bb'	Bronchioles
6	bb_{seq}	Sequestered in bronchioles
7,8	BB, BB'	Bronchi
9	BB_{seq}	Sequestered in bronchi
10	LN_{TH}	Lymph nodes in thoracic region
11	ET_2, ET_2'	Posterior nasal passage, larynx and pharynx
12	ET_{seq}	Sequestered in extrathoracic tissue
13	LN_{ET}	Lymphatic system in extrathoracic region
14	ET_1	Anterior nasal
15	GI	GI tract
16	Environment	environment (e.g. tissue paper)

From Unice et al. (2020)

Unice et al. (2020) further updated their cobalt models to include an inhalation pathway based on the ICRP Human Respiratory Tract Model (HRTM) (Figure 3-7). Their modified ICRP HRTM accounts for particle-size dependent deposition in the extra thoracic region, both the bronchial and bronchiolar airways, and the alveolar–interstitial region of the lungs. A default particle density of 3 g/cm^3 was used. Other assumptions for most forms of cobalt included: moderate respiratory absorption rates (ICRP 'Type

M'), with a rapid fraction of 0.2, a rapid dissolution half-life of 17 hours, a slow dissolution half-life of 137 days, and absorption fraction from the alimentary tract of 0.02. The new human alimentary tract model (HATM) was used together with the human respiratory tract model in Unice et al. (2020) (HRTM; ICRP, 1994a,b). Modeling of other chemical forms of cobalt, e.g., cobalt oxides, used the following assumptions: slow absorption rates (ICRP 'Type S'), with a rapid fraction of 0.01, rapid dissolution half-life of 17 hours, slow dissolution half-life of 19 years, and absorption fraction from the alimentary tract of 0.001. To account for species differences in regional lung deposition, animal doses were modeled using human equivalent concentrations. The modeled data and measured data showed good agreement, within a factor of two, for blood, liver, testes, and tissue concentrations. When the model was run using occupational inhalation exposure scenarios, the results showed that the systemic body burden was higher for ingestion than for inhalation (Unice et al. 2020).

3.1.6 Animal-to-Human Extrapolations

Retention and clearance of physiologically insoluble ^{57}Co particles varies widely across species, illustrating the potential difficulty of extrapolating the results of animal lung retention experiments to humans even qualitatively (Bailey et al. 1989). Conversely, differences in absorption of physiologically insoluble cobalt oxide following oral exposure do not appear to exist between species (humans were not included in the study) (Bailey et al. 1989). Absorption of soluble cobalt compounds is greater in rats (13–34%) than in dairy cows (1–2%) and guinea pigs (4–5%) following oral exposure (Ayala-Fierro et al. 1999; Bailey et al. 1989; Barnaby et al. 1968; Hollins and McCullough 1971; Kirchgessner et al. 1994; Naylor and Harrison 1995; Schade et al. 1970; Taylor 1962; Van Bruwaene et al. 1984). Current PBPK model assumptions for cobalt are based on human data (Unice et al. 2020).

3.2. CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to cobalt are discussed in Section 5.7, Populations with Potentially High Exposures.

Age-Related Exposure and Pharmacokinetic Differences. No studies that examined pharmacokinetic differences between adults and children were identified. Animal studies have suggested several differences in pharmacokinetic behavior of cobalt compounds between children and adults. Following inhalation exposure to Co_3O_4, deposition tended to increase with age (Collier et al. 1991). The youngest animals exposed (3 weeks postnatal) had significantly lower fractional retention 182 days postexposure compared to 13-, 21-, and 46-week-old animals. There were no significant differences in fractional retention among the older animals until 281 days post exposure where there were significant differences among all age groups. The authors attributed this to a faster rate of translocation of cobalt from the lung to the blood, which could enhance subsequent excretion. The youngest animals had a significantly faster translocation rate which was not further explained by the study authors. There were no significant differences in mechanical clearance rates of ^{57}Co labelled Co_3O_4 in animals of different ages (Collier et al. 1991). Naylor and Harrison (1995) reported that in rats and guinea pigs, fractional absorption of cobalt following oral exposure was highest one day after birth, remained elevated in rats, but not guinea pigs, during the suckling stage and diminished rapidly with time thereafter.

In animal studies where soluble cobalt compounds were intravenously injected, cobalt was shown to cross the placenta and enter the fetus. Twenty-four hours after intravenous injection of cobalt chloride in rats, 0.14% of the dose was found in the fetus, 0.19% in the chorioallantoic placenta, and 0.22% in the yolk sac (Zylicz et al. 1975). The amount of cobalt crossing the placenta following intravenous injection was greater in later gestational stages, although less than 1% of the maternal dose reached the fetus (Nishimura et al. 1978; Zylicz and Zabloina 1976; Zylicz et al. 1975). The form of cobalt may also be important relative to bioavailability to the fetus. Nishimura et al (1978) reported that the fetal uptake of cobalt, following intravenous administration of either cyanocobalamin or cobalt chloride to the mother, was increased for cyanocobalamin (5% of the maternal dose) compared to cobalt chloride (less than 1% of the maternal dose).

Cobalt is detected in human breast milk at concentrations in the parts per billion (ppb) range in the inorganic form (Byczkowski et al. 1994). Animal studies report low amounts of cobalt in the breast milk. Milk obtained 70 days post exposure from lactating dairy cows contained 0.012% of the exposure dose (Van Bruwaene et al. 1984). One to two percent of cobalt given intravenously to mother rats as cyanocobalamin was transferred to offspring via the breast milk (Nishimura et al. 1978).

Health Effects from Exposure to Cobalt. Available data have not clearly defined whether children are at greater risk from exposure to stable cobalt than adults. Data on effects of cobalt in children following inhalation exposures are lacking. Jacobziner and Raybin (1961) reported two cases of children who had accidentally ingested unknown amounts of cobalt chloride. In one case a 19-month-old male ingested acetylsalicylic acid followed by stomach lavage and was asymptomatic; the following day he ingested cobalt chloride, developed poisoning symptoms (bluish skin and lips, swollen lips and tongue, restless, then drowsiness), and received stomach lavage, but died approximately 6.5 hours after the ingestion. However, a 3-year-old male who swallowed a mixture of cobalt and chloride from a chemistry set (compounds not specified) showed no symptoms before or after stomach lavage (Jacobziner and Raybin 1961).

Enlarged thyroid glands have been reported in children given cobalt chloride for treatment of anemia. However, the thyroid glands returned to normal size upon cessation of treatment (Chamberlain 1961; Little and Sunico 1958; Sederholm et al. 1968; Washburn and Kaplan 1964). Patch testing of children aged 4–14 years revealed that 13 out of 45 girls and 3 out of 26 boys reacted to cobalt chloride with contact dermatitis (Romaguera and Vilaplana 1998). A review of the literature suggests that the effects of cobalt may not be the same for all humans. Individuals, including children, who do not have functioning kidneys, or suffer from sepsis, or have sickle-cell disease could have higher levels of free cobalt in organ tissues due to either decreased serum albumin levels or an increase in serum ischemia-modified albumin, that might result in a stronger response to cobalt at doses that would not adversely affect healthy individuals (Paustenbach et al. 2013). Jin et al. (2018) analyzed NHANES data 2003-2012 for an association between urinary mineral cation concentrations and estimated glomerular filtration rate and reported that a decrease in renal function (decrease in filtration rate) was associated with a decrease in cobalt in urine.

Individuals who are sensitized to cobalt could be at risk for developing cobalt induced asthma (Shirakawa et al. 1988; Shirakawa et al. 1989). Sensitization to cobalt in hard metal workers results in cobalt specific increases in serum antibodies (IgE and IgA) resulting in the development of hard metal asthma (Bencko et al. 1983; Shirakawa et al. 1988; Shirakawa et al. 1989). Two studies by Potolicchio et al (1999; 1997) suggest that the presence of a polymorphism (for glutamate 69 in the β chain) in the HLA-DP gene might increase susceptibility to hard metal lung disease. Following oral exposure, individuals with iron deficiency could also have an increased risk, as both human and animal studies have shown an increased absorption of cobalt compounds in iron-deficient animals and humans (Barany et al. 2005; Meltzer et al. 2010; Reuber et al. 1994; Schade et al. 1970; Sorbie et al. 1971; Valberg et al. 1969).

A significant increase in the number of skeletons with delayed ossification was reported in the offspring of mice intravenously injected with approximately 1.2 mg cobalt/kg at day 8 of gestation, but not when injected on day 3 (Wide 1984). Other studies, however, have not shown developmental effects of stable cobalt compounds, or have shown effects only at maternally toxic doses (Domingo et al. 1985b; Paternian and Domingo 1988; Seidenberg et al. 1986).

3.3. BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to cobalt are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by cobalt are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Levels of cobalt in the blood, feces, and urine can be used to indicate exposure to this chemical. Most of the data for this response come from occupational studies. Non-occupational studies are available; however, although they provide cobalt levels in urine and/or blood, information regarding external

exposure dose is not available. Typical background levels (geometric mean) of urinary cobalt in humans range from 0.32 to 0.42 µg/L and blood cobalt was 0.151 µg/L (Hoet et al. 2013). Cobalt has been measured in the blood after supplementation of inorganic cobalt (Finley et al. 2013; Tvermoes et al. 2013; Tvermoes et al. 2014).

Goldoni et al. (2004) measured cobalt in the exhaled breath of hard metal workers and found cobalt in the exhaled breath from 11.9 to 741 nanomoles/liter with levels higher at the end of the shift. Conversely, another study reported that exhaled breath concentrations of cobalt were not correlated to workplace air concentrations, which may limit its usefulness as a biomarker (Broding et al. 2009).

Wahlquist et al. (2020) examined the relationships between exposure to inhalable cobalt particulates in the air to blood and urine in hard metal workers. Exposure to cobalt in the air was correlated with both cobalt in blood and urine, whereas dermal exposure was correlated with blood but not urine. Klassen et al. (2017) reported similar results; blood cobalt levels were significantly correlated with inhalable cobalt in air or cobalt on the skin from occupational exposure. Kettelarij et al. (2018b) did report an association between skin exposure and levels of cobalt in the urine. A 32% increase in urinary cobalt levels post worker shift were reported after a doubling of cobalt deposit dusts on the skin, indicating that urine may be a good biomarker of dermal exposure. However, it could also reflect inhalation exposures. Hutter et al. (2016) reported urinary cobalt levels of 200 µg/L at an exposure of 1 mg/m^3 cobalt in air. They also indicated that urinary cobalt was higher in smokers than nonsmokers.

Earlier studies report associations between cobalt exposure and cobalt levels in blood and urine (Alexandersson 1988; Ichikawa et al. 1985; Lison et al. 1994; Nemery et al. 1992; Scansetti et al. 1985). Occupational exposure to 0.1 mg/m^3 cobalt resulted in blood levels of cobalt ranging from 0.57 to 0.79 µg/dL, and urinary levels from 59 to 78 µg/L (Ichikawa et al. 1985). Timing of biomarker measurement may be important. Apostoli et al. (1994) reported that for workers in hard metal manufacturing, urinary cobalt increases rapidly post exposure, peaking 2-4 hours after the work day ended, and decreasing thereafter over time. Correlations between recent worker exposure and cobalt levels in the blood or urine are more consistent for exposure to soluble cobalt compounds, than for less soluble compounds (Lison et al. 1994).

3.3.2 Biomarkers of Effect

No cobalt-specific biomarkers of effects resulting from cobalt toxicity were identified. Diminished respiratory function and polycythemia are the most notable signs of cobalt toxicity. Diminished respiratory function in humans includes decreased values for the FEV1 and FVC lung parameters, in particular a decrease in FEV1/FVC ratio, plus increased cough, dyspnea, and sputum. The FEV1 and

FVC measures correlated with urinary cobalt concentrations (Gennart and Lauwerys 1990; Kusaka et al. 1986a).

Animal studies demonstrate that exposure to cobalt caused an increase in lung inflammation and necrosis (NTP 1991, 1998, 2014). Polycythemia (as reported by the study authors) along with changes in hemoglobin and hematocrit were also observed in animal studies after inhalation exposure (NTP 1991, 1998, 2014). Oral exposure to cobalt caused polycythemia (as reported by the study authors) in humans (see Section 2.7) (Davis and Fields 1958). Finley et al. (2012b) examined the human and animal toxicology and reported that the blood cobalt levels exceeded 300 μg/L. In another study by the same authors, polycythemia (as reported by the study authors) and reduced iodide uptake were reported (Finley et al. 2012a). Additionally, monitoring of cobalt specific changes in serum antibodies (IgE and IgA) could indicate sensitization to cobalt occurred (Bencko et al. 1983; Shirakawa et al. 1988; Shirakawa et al. 1989). More research is needed in this area to identify biomarkers of effect after exposure to cobalt as changes in respiratory functions, development of polycythemia, and changes in serum antibodies are not unique to cobalt induced toxicity.

3.4. INTERACTIONS WITH OTHER CHEMICALS

Animal studies suggest that exposure to cobalt affects metal ion metabolism. Zaksas et al. (2013) administered $CoCl_2$ to mice and measured the effect of cobalt on several mineral ions in plasma. Cobalt increased the plasma levels of iron, magnesium, aluminum, and silicon, while reducing the amount of boron. Since cobalt binds to plasma transferrin, which also binds iron, the potential exists for cobalt to affect iron transport or metabolism. Cobalt can adversely affect the metabolism of other essential minerals by competing for binding sites, altering signal transduction, and affecting protein biosynthesis (Zaksas et al. 2013). Skalny et al. (2021) evaluated the effect of $CoCl_2$ exposure on tissue distribution of metal ions in immature mice (see Section 3.12 for details on the experiment). A dose dependent effect by $CoCl_2$ on tissue levels of copper, iron, manganese, and zinc was reported. The authors suggest that exposure to cobalt alters essential mineral metabolism. Moshtagie et al. (2004) evaluated the competition between cobalt and iron in binding to human serum transferrin. Iron binding to human serum transferrin was reduced by 20% when cobalt ions were present, and iron uptake was reduced by 30%, indicating competition for binding.

Studies suggest an adverse impact of cobalt ions on calcium ions. Soluble cobalt can block inorganic calcium uptake channels, limiting calcium influx into cells. This effect may be linked to a reduction of steroidogenesis in mouse Leydig cells (Henquin et al. 1983; Moger 1983; Yamatani et al. 1998). Cobalt can alter calcium influx for mice into liver cells following exposure to glucagon (Yamatani et al. 1998)

and pancreatic β cells (Henquin and Lambert 1975) and for rats into isolated pancreatic islet cells (Henquin and Lambert 1975). Cobalt might also affect neuromuscular transmission through antagonism with calcium ions (Weakly 1973).

An *in vivo* study designed to determine the effects on RNA expression patterns using human bronchial epithelial cells exposed to cobalt, lead, and cadmium concurrently reported four specific alterations in RNA expression patterns associated with: cell cycle regulation; oxidative stress response; glutathione metabolism and steroidogenesis; and xenobiotic metabolism (Glahn et al. 2008).

Cobalt in combination with bleomycin is used in cancer treatment as a therapeutic agent (Goodwin and Meares 1976; Hansen et al. 1976; Kapstad 1978, 1979). When used in combination, the anti-tumor effects are amplified. The bleomycin cobalt ion combination acts by binding to and cleaving the DNA in tumor cells (Kakinuma and Orii 1982).

Cobalt chelators have been tested in rats to evaluate their mitigation potential in reducing the toxic effects of cobalt. In rats previously exposed to cobalt, treatment with Glutathione, N-acetyl-L-cysteine (NAC) and diethylenetriaminepentaacetic acid (DTPA) increased the urinary excretion of cobalt. Other chelators, EDTA, NAC, and 2,3-dimercaptosuccinic acid (DMSA) increased fecal cobalt excretion. NAC was reported to increase both urinary and fecal excretion of cobalt (Baker and Czarnecki-Maulden 1987; Domingo et al. 1983; Llobet et al. 1988). The amino acid cysteine also reportedly reduced the toxicity of cobalt in chicks (Baker and Czarnecki-Maulden 1987).

An interrelationship between cobalt and nickel sensitization has been reported in individuals exposed to the two metals. The dermatological impact is greater in individuals sensitized to both metals (Rystedt and Fisher 1983; Veien et al. 1987). One animal study using guinea pigs showed some interaction between nickel and cobalt (Wahlberg and Liden 2000). Studies of cultured alveolar type II cells showed a synergistic (greater than additive) response with co-exposure to cobalt and nickel chlorides (Cross et al. 2001). Bonefeld et al. (2015) reported that mice dermally exposed to a mixture of nickel and cobalt had increased immune response to both metals in combination than to either metal alone.

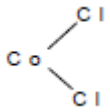
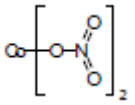
Hard metal dusts, consisting of 5–10% cobalt with the balance being tungsten carbide, were considerably more toxic than cobalt or tungsten carbide particles alone (Harding 1950). The increase in toxicity could be the result of the oxidation of cobalt metal to ionic cobalt, which results in increased solubility of cobalt and leads to the generation of active oxygen species (Lasfargues et al. 1995; Lison et al. 1996; Lison et al. 1995).

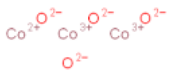
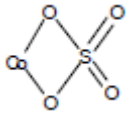
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1. CHEMICAL IDENTITY

Cobalt is a naturally occurring element in the earth's crust. It occurs in several minerals, often with nickel, silver, lead, copper, and iron ores (Haynes 2015). It is a member of Group 9 of the periodic table along with rhenium, iridium, and meitnerium, and adjacent to iron and nickel. There is only one stable isotope of cobalt, ^{59}Co. The rest of the 31 known isotopes of cobalt are not naturally occurring. Most of the radioactive forms have masses from 47-58 and 60-77. The radioactive properties of these are maintained in the US by the National Nuclear Data Center. ^{60}Co, the most common radioisotope, is formed by the neutron activation of stable ^{59}Co, has a 5.27 year half-life, and emits beta particles (99.77 keV 99.88%) and gamma radiation (1173 keV 99.85%, 1332 keV 99.98%) (NNDC 2021). It is used as a source of high energy gamma radiation in cancer therapy (e.g., in a gamma knife), food irradiation, and industrial radiography of welds. It along with primarily ^{57}Co and ^{58}Co are waste byproducts of nuclear reactor operations. Cobalt isotopes have half-lives that are specific to the isotope, and most are less than 24 hours (NNDC 2021). The isotopes of cobalt have the same chemical and physical properties, so they interact the same with biological systems. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for cobalt and selected cobalt compounds.

Table 4-1. Chemical Identity of Cobalt and Selected Cobalt Compounds

Characteristic	Cobalt	Cobalt(II) Chloride	Cobalt(II) Nitrate
Synonym(s) and Registered trade name(s)	CI 77320; Kobalt; NCI-C60311; Aquacat; Cobalt-59; Super Cobalt	Cobaltous chloride; Cobalt dichloride; Cobalt muriate; Cobaltous dichloride; Kobalt chloride	Cobaltous nitrate; Cobalt bis(nitrate); Cobalt dinitrate; Cobalt (2+) nitrate; cobalt nitrate
Chemical formula	Co	$CoCl_2$	$Co(NO_3)_2$
Chemical structure	Co		
CAS registry number	7440-48-4	7646-79-9 (anhydrous)	10141-05-6 (anhydrous)

Characteristic	Cobalt(II) Oxide	Cobalt Tetraoxide	Cobalt(II) Sulfate
Synonym(s) and Registered trade name(s)	Cobalt monoxide; Cobalt Black; Zaffre; Oxocobalt; Cobaltous Oxide; Monocobalt oxide; CI Pigment Black 13	Cobalt oxide; UNII-USK772NS56; Cobaltosic oxide; Cobalt oxide black; Tricobalt tetroxide; Cobalto-cobaltic oxide; Cobaltic-cobaltous oxide; Cobalto-cobaltic tetroxide; Cobalt(II, III) oxide	Cobaltous sulfate; Cobalt(II) sulphate; Cobalt(II) sulfate (1:1); Cobalt(2+) sulfate; Cobalt sulfate; Sulfuric acid, cobalt(2+) salt (1:1)
Chemical formula	CoO	Co_3O_4	$CoSO_4$
Chemical structure	O=Co		
CAS registry number	1307-96-6	1308-06-1	10124-43-3 (anhydrous)

Characteristic	Cobalt(II) Sulfide	Cobalt Arsenide
Synonym(s) and Registered trade name(s)	Cobalt sulfide; sulfanylidenecobalt; cobalt sulphide; cobalto monosulfide; cobalt (2+) sulfide; cobaltous sulfide	Arsanylidynecobalt; cobalt monoarsenide; cobalt(III) arsenide
Chemical formula	CoS	CoAs
Chemical structure	S=Co	Co≡As
CAS registry number	1317-42-6	27016-73-5

CAS = Chemical Abstracts Service
Source: (HSDB 2017a, 2017b, 2017c, 2017d); (PubChem 2021a, 2021b, 2021c, 2021d, 2021e)

4.2. PHYSICAL AND CHEMICAL PROPERTIES

Cobalt is a magnetic, brittle, hard, gray metal that is resistant to oxidation (Haynes 2015). Cobalt's physical and chemical properties make it ideal for a variety of applications. Alloys containing cobalt can maintain their strength at high temperatures, making them useful in gas turbine engines, chemical and petroleum plants, and power plants (USGS 2011). Cobalt and cobalt compounds are nonvolatile and are emitted to the atmosphere in particulate form. Soluble chloride released to waterways is expected to sorb to particles. Cobalt is also an essential trace element found in Vitamin B_{12}.

Table 4-2 lists important physical and chemical properties of cobalt and cobalt compounds.

Table 4-2. Physical and Chemical Properties of Cobalt and Selected Cobalt Compounds

Property	Cobalt	Cobalt(II) Chloride	Cobalt(II) Nitrate
Molecular weight	58.933[a]	129.8[a]	182.9[a]
Color	Gray, silvery bluish-white[a,b]	Blue[a]	Pale red[a]
Physical state	Solid[c]	Solid	Solid[g]
Melting point	1,495°C[a]	737 °C[a]	Decomposes at 100-105 °C[g]
Boiling point	2,927°C[a]	1049 °C[a]	No data
Density at 20°C/4°C	8.9 g/cm^3[a]	3.36 g/cm^3[a]	2.49 g/cm^3[a]
Odor	Odorless[c]	Slight sharp odor[f]	Odorless[g]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water	No data	Soluble in water[f]	Soluble in water[g]
Organic solvent(s)	Soluble in dilute acids; readily soluble in dilute nitric acid[a,d]	Soluble in alcohols, acetone, ether, glycerol, and pyridine[f]	No data
Partition coefficients:			
Log K_{OW}	No data	No data	No data
Log K_{OC}	No data	No data	No data
Vapor pressure:			
At 726 mmHg and 85°C	2.09×10^{-10} mmHg[a]	No data	No data
Approximately	0 mmHg[c]	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	1 ppm = 2.4 mg/m^3[e]	No data	No data
Explosive limits	No data	Reacts violently with alkali metals such as potassium or sodium causing fire and explosion hazard[f]	No data

Table 4-2. Physical and Chemical Properties of Cobalt and Selected Cobalt Compounds

Property	Cobalt(II) Oxide	Cobalt Tetraoxide	Cobalt(II) Sulfate
Molecular weight	74.932[a]	240.8[a]	155[a]
Color	Gray[a]	Black[a]	Red[a]
Physical state	Solid[a]	Solid[a]	Solid[h]
Melting point	1,830°C[a]	Decomposes at 900°C[a]	>700 °C[a]
Boiling point	No data	No data	No data
Density at 20°C/4°C	4.63 g/cm^{3}[a]	6.11 g/cm^{3}[a]	3.71 g/cm^{3}[a]
Odor	No data	No data	Odorless[i]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water	Insoluble in water[a]	Insoluble in water[a]	330 g/L at 20 °C[h]
Organic solvent(s)	Soluble in acid solutions[a]	Soluble in acid solutions and alkaline solutions[a]	1.04 g/11 mL methanol at 18 °C[h]
Partition coefficients:			
Log K_{OW}	No data	No data	No data
Log K_{OC}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Cobalt and Selected Cobalt Compounds

Property	Cobalt(II) Sulfide	Cobalt Arsenide
Molecular weight	90.998[a]	133.855[a]
Color	Black[a]	No data
Physical state	Solid[a]	Solid[a]
Melting point	1,117°C[a]	1,180°C[a]
Boiling point	No data	No data
Density at 20°C/4°C	5.45 g/cm^{3}[a]	8.22 g/cm^{3}[a]
Odor	No data	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Taste threshold	No data	No data
Solubility:		
Water	Insoluble in water[a]	No data
Organic solvent(s)	Soluble in acid solutions[a]	No data
Partition coefficients:		
Log K_{OW}	No data	No data
Log K_{OC}	No data	No data
Vapor pressure	No data	No data
Henry's law constant	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors	No data	No data
Explosive limits	No data	No data

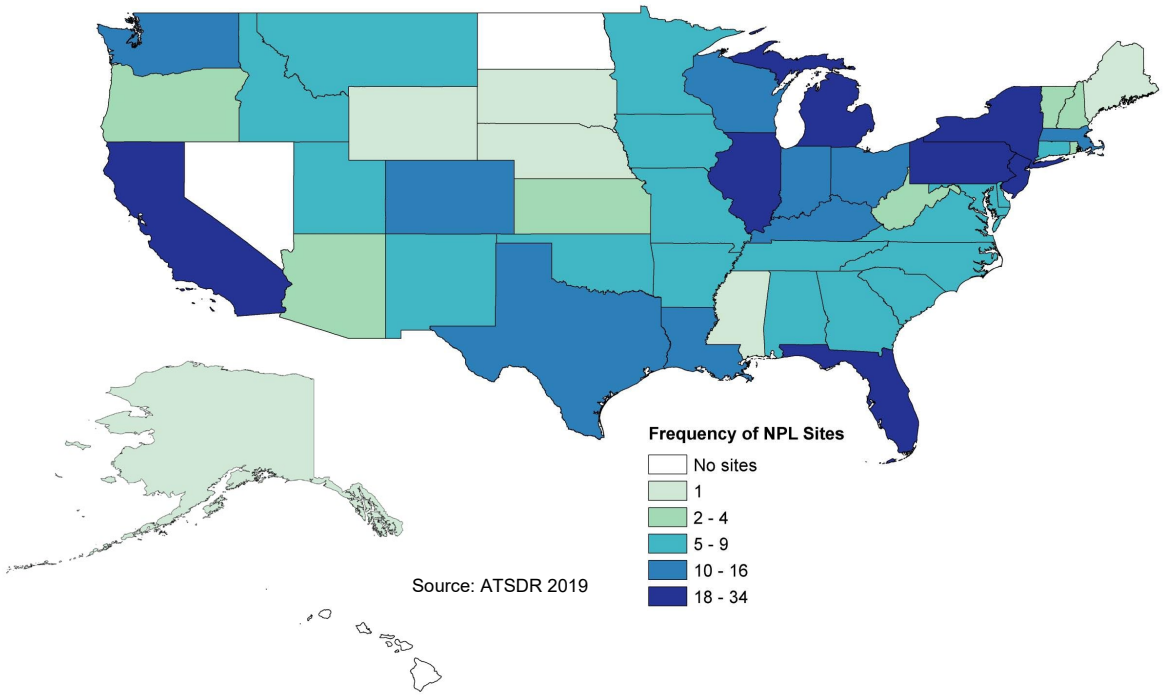
[a] (Haynes 2015)
[b] Browning 1996
[c] (NIOSH 2019)
[d] O'Neil 2013
[e] (EPA 2000)
[f] (HSDB 2017c)
[g] (HSDB 2017d)
[h] (HSDB 2017a)
[I] (PubChem 2021d)

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1. OVERVIEW

Cobalt has been identified in at least 425 of the 1,867 hazardous waste sites that have been proposed for inclusion on the Environmental Protection Agency (EPA) National Priorities List (NPL) (ATSDR 2019). However, the number of sites evaluated for cobalt is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 420 are located within the United States, 1 is located in the Virgin Islands, 3 are located in Puerto Rico, and 1 is located in Guam (not shown).

Figure 5-1. Number of NPL Sites with Cobalt Contamination



- In the U.S. cobalt is produced from deposits as a by-product of other metals. Cobalt is used in several commercial, industrial, and military applications. The leading use is in rechargeable batteries, followed by superalloys, and other uses include magnets and tools.
- Natural sources that release cobalt include wind-blown continental dust, seawater spray, volcanoes, forest fires, and continental and marine biogenic emissions. Anthropogenic sources include the burning of fossil fuels and sewage sludge, phosphate fertilizers, mining and smelting

of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds.

- Cobalt is released to the atmosphere in particulate form. It may settle to the ground by wet or dry deposition. Cobalt released into waterways may sorb to particles and settle into the sediment or be absorbed directly into the sediment.
- Cobalt levels monitored in ambient air are generally less than 0.002 μg/m^3 (EPA 2020). Cobalt naturally occurs in the earth's crust. Concentrations of cobalt in surface water and groundwater in the United States are generally low.
- The general population may be exposed to cobalt through inhalation of ambient air and ingestion of food and drinking water. The general population may also be exposed to cobalt transferred to users of consumer goods, like leather products and jewelry; from the wearing down of implanted medical devices and prosthetics, and by using drilling and grinding tools that contain cobalt.
- Workers in the hard metal industry (tool production, grinding, etc.) and industries such as coal mining, metal mining, smelting, and refining, cobalt dye painters, and cobalt chemical production are exposed to higher levels of cobalt via airborne dust and direct contact. Populations living near these industrial sites are also exposed to higher levels of cobalt.

Cobalt occurs naturally in the earth's crust, and therefore, in soil. Low levels of cobalt also occur naturally in seawater and in some surface water and groundwater (Smith and Carson 1981). However, elevated levels of cobalt in soil and water may result from anthropogenic activities such as the mining and processing of cobalt-bearing ores, the application of cobalt-containing sludge or phosphate fertilizers to soil, the disposal of cobalt-containing wastes, and atmospheric deposition from activities such as the burning of fossil fuels and smelting and refining of metals (Smith and Carson 1981). Cobalt is released into the atmosphere from both anthropogenic and natural sources. However, emissions from natural sources are estimated to slightly exceed those from manufactured sources. Natural sources include windblown soil, seawater spray, volcanic eruptions, and forest fires. Primary anthropogenic sources include fossil fuel and waste combustion, vehicular and aircraft exhausts, processing of cobalt and cobalt containing alloys, copper and nickel smelting and refining, and the manufacture and use of cobalt chemicals and fertilizers derived from phosphate rocks (Barceloux 1999; Lantzy and Mackenzie 1979; Nriagu 1989; Smith and Carson 1981).

Cobalt compounds are non-volatile, and cobalt will be emitted to the atmosphere only in particulate form. Its transport in air depends on its form, particle size and density, and meteorological conditions. Cobalt so released will return to land or surface water as wet or dry deposition. Coarse particles, those with aerodynamic diameters >2 μm (such as those obtained during ore processing), may deposit within 10 km

from the point of emission; finer particles (such as are obtained from thermal processes) may travel longer distances. It is generally assumed that anthropogenic cobalt originating from combustion sources exists primarily as the oxide; arsenides or sulfides may be released during mining and ore processing (Schroeder et al. 1987). Frequently, sediment and soil are the ultimate sinks for cobalt; however, this process is dynamic, and cobalt can be released into the water depending upon conditions. Soluble cobalt compounds released into waterways will sorb to particles and may settle into the sediment or be sorbed directly by sediment. It may precipitate out as carbonates and hydroxides or with mineral oxides. It may also sorb to or complex with humic acid substances in the water. These processes are sensitive to environmental factors such as pH and the proportion of dissolved cobalt will be higher at low pH. Cobalt can also be transported in dissolved form or as suspended sediment by rivers to lakes and the sea or by ocean currents. The proportion of cobalt transported in each form is highly variable (Smith and Carson 1981). In deep sediment where water is anoxic and hydrogen sulfide is present, some mobilization of cobalt from sediment may occur, probably due to the formation of bisulfides and polysulfides (Bargagli 2000; Brugmann 1988; Finney and Huh 1989; Glooschenko et al. 1981; Knauer et al. 1982; Nriagu and Coker 1980; Shine et al. 1995; Smith and Carson 1981; Szefer et al. 1996; Windom et al. 1989). Cobalt adsorbs rapidly and strongly to soil and sediment in which it is retained by metal oxides, crystalline minerals, and natural organic matter. The mobility of cobalt-containing sediment depends on the nature of the soil or sediment; mobility increases with decreasing pH and redox potential (Eh) and in the presence of chelating/complexing agents (Brooks et al. 1998; Buchter et al. 1989; King 1988; McLaren et al. 1986; Schnitzer 1969; Smith and Carson 1981; Swanson 1984). While cobalt may be taken up from soil by plants, the translocation of cobalt from roots to above-ground parts of plants is not significant in most soils. The bioaccumulation factors (dry weight basis) for cobalt in marine fish and freshwater fish are ~100–4,000 and <10–1,000, respectively; accumulation is largely in the viscera and on the skin, as opposed to the edible parts of the fish. Cobalt does not biomagnify up the food chain (Barceloux 1999; Evans et al. 1988; Freitas et al. 1988; Smith and Carson 1981).

Atmospheric cobalt is associated with particulate matter. Mean cobalt levels in air at unpolluted sites are generally <1–2 ng/m^3. In several open-ocean environments, geometric mean concentrations ranged from 0.0004 to 0.08 ng/m^3 (Chester et al. 1991). However, in source areas, cobalt levels may exceed 10 ng/m^3; the highest average cobalt concentration recorded was 48 ng/m^3 at the site of a nickel refinery in Wales (Hamilton 1994; Smith and Carson 1981).

The concentrations of cobalt in surface and groundwater in the United States are generally low: <1 µg/L in pristine areas and 1–10 µg/L in populated areas (Hamilton 1994; Smith and Carson 1981). However, cobalt levels may be considerably higher in mining or agricultural areas. Cobalt levels in most drinking

water is <1–2 µg/L, although levels as high as 107 µg/L have been recorded (Greathouse and Craun 1978; Meranger et al. 1981; Smith and Carson 1981).

The average concentrations of cobalt in the earth's crust are 20–25 mg/kg (Abbasi et al. 1989; Greathouse and Craun 1978; Merian 1985; Smith and Carson 1981). Most soils contain 1–40 mg cobalt/kg; the average cobalt concentration in U.S. soils is 7.2 mg/kg (Smith and Carson 1981). Soils near ore deposits, phosphate rocks, or ore smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain high concentrations of cobalt; concentrations up to 800 mg/kg have been detected in such areas (Kloke et al. 1984; Smith and Carson 1981).

The level of cobalt in most foods is low. However, food is the largest source of exposure to cobalt in the general population. The estimated average daily dietary intake of cobalt in Canada was 11 µg/day. Food groups contributing most heavily to this intake were bakery goods and cereals (29.8%) and vegetables (21.9%) (Dabeka and McKenzie 1995). No estimates of the average dietary input of cobalt in the United States were located. People living near mining and smelting facilities or metal shops where cobalt is used in grinding tools may be exposed to higher levels of cobalt in air or soil. Similarly, people living near hazardous waste sites may be exposed to higher levels of cobalt in these media. However, much of the cobalt in soil may not be in a form that is available for uptake by the body. People who work in the hard metal industry, metal mining, smelting, and refining or other industries that produce or use cobalt and cobalt compounds may be exposed to substantially higher levels of cobalt, mainly from dusts or aerosols in air. Populations living near these sites may also be exposed to higher than background levels of cobalt. Workers in other occupations who come into contact with metal tools and devices, like dental technicians, may also be at higher risk of exposure.

5.2. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Cobalt is the third most abundant element in the earth’s crust, averaging approximately 17.3 ppm (Dehaine et al. 2021). Pure cobalt does not exist in nature. Cobalt is found in many minerals with nickel, silver, lead, copper, and iron such as carrollite ($Cu(Co,Ni)_2S_4$), pentlandite ($(Fe,Ni,Co)_9S_8$), linnaeite (Co_3S_4), siegenite ((Co,Ni)3S4), skutterudite ($(Co,Fe,Ni)As_{2-3}$), safflorite ($(Co,Fe)As_2$), cobaltite (CoAsS), glaucodot ((Co,Fe,)AsS), erythrite ($Co_3(AsO_4)_2 \cdot 8H2O$), heterogenite (CoO(OH)), and asbolane ($(Ni,Co)_{2-x}Mn(o,OH)_4 \cdot nH_2O$) (USGS 2017). The largest cobalt reserves are in the Congo (Kinshasa), Australia, Cuba, the Philippines, and Russia (USGS 2020). There is an estimated 1 million tons of cobalt resources in the United States; most of the U.S. cobalt deposits are in Minnesota, but other important

deposits are in Alaska, California, Idaho, Michigan, Missouri, Montana, Oregon, and Pennsylvania (USGS 2020). Cobalt production from these deposits, except those in Idaho and Missouri, would be as a byproduct of another metal (USGS 2020). Most of the world's cobalt resources are produced as a byproduct of copper mining, and cobalt is also produced as a byproduct of nickel mining (USGS 2017). The U.S. supply of cobalt is comprised mostly of imports and scrap (secondary production) (USGS 2020). In 2019, an estimated 2,700 metric tons of cobalt were recycled from scrap, while 500 metric tons were mined (USGS 2020). Cobalt is also found in meteorites and deep-sea nodules.

Cobalt is mined using a combination of conventional underground and open pit methods (Farjana et al. 2019). The production of pure metal from these ores depends on the type of the ore, energy availability, environmental concerns, market demand, and overall project economics (USGS 2017). Sulfide ores and stratiform sediment-hosted Cu-Co deposits are first ground and crushed, then concentrated by froth flotation and refined (De Cuyper 1988). The concentrate is then processed by leaching, roasting and then leaching, or smelting and then leaching (USGS 2017). Individual metals are separated from the resulting solution using hydrometallurgical, electrometallurgical, vapometallurgical, and pyrometallurgical methods such as chemical precipitation, electrowinning, hydrogen reduction, ion exchange, and solvent extraction (Farjana et al. 2019; USGS 2017).

Table 5-1 lists facilities in each state that manufacture, process, or use cobalt or cobalt compounds, the intended use, and the range of maximum amounts of these substances that are stored on site. In 2019, there were 331 reporting facilities that produced, processed, or used cobalt and 380 that produced, processed, or used cobalt compounds in the United States. The data listed in Table 5-1 are derived from the Toxics Chemicals Release Inventory (TRI) (TRI19 2020). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use Cobalt or Cobalt Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	10000	99999	1, 5, 12, 13, 14
AL	22	0	999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
AR	8	1000	99999	1, 3, 5, 7, 8, 12,
AZ	12	1000	999999	1, 2, 5, 7, 8, 9, 10, 11, 12, 13, 14
CA	30	1000	999999	1, 2, 3, 6, 7, 8, 9, 10, 12, 13, 14
CO	4	1000	99999	1, 10, 11, 12, 13, 14
CT	12	100	999999	8, 11, 12
DE	1	1000	9999	8
FL	9	100	999999	1, 2, 3, 5, 8, 9, 10, 12, 14

Table 5-1. Facilities that Produce, Process, or Use Cobalt or Cobalt Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
GA	14	1000	999999	1, 2, 3, 4, 5, 6, 7, 8, 12, 13, 14
IA	10	10000	999999	7, 8
ID	3	100	99999	1, 2, 3, 4, 5, 7, 9, 12, 13, 14
IL	30	1000	9999999	1, 5, 7, 8, 10, 12, 13,
IN	42	0	999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	16	0	9999999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 14
KY	21	100	999999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13,
LA	24	0	999999	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14
MA	11	100	999999	7, 8, 9, 11, 12
ME	3	0	99999	1, 5, 8
MI	35	0	999999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
MN	10	100	999999	1, 2, 5, 8, 9, 10, 12, 13
MO	8	0	999999	1, 5, 8, 12, 14
MS	10	1000	999999	1, 2, 3, 5, 7, 8, 9, 10, 13, 14
MT	2	10000	99999	1, 3, 4, 5, 6, 12, 13, 14
NC	31	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14
ND	3	100	99999	1, 5, 12, 13, 14
NE	4	1000	9999	1, 3, 4, 5, 7, 8, 9, 12, 13
NH	2	10000	99999	2, 3, 8, 11
NJ	9	100000	999999	2, 3, 4, 7, 8, 9, 10, 11, 12
NM	4	100	99999	1, 3, 4, 5, 9, 11, 12, 13
NV	12	0	9999999	1, 3, 4, 5, 7, 8, 12, 13, 14
NY	12	1000	9999999	2, 3, 7, 8, 9, 12, 14
OH	60	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	18	1000	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14
OR	6	1000	999999	1, 2, 3, 7, 8, 12
PA	62	0	9999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
PR	2	1000	99999	8
RI	1	10000	99999	7
SC	25	100	999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
SD	2	1000	9999	8
TN	26	100	999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
TX	46	0	999999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	3	100	99999	1, 3, 4, 8, 9, 10, 12, 13
VA	5	10000	999999	2, 3, 4, 6, 7, 8
WA	3	10000	999999	1, 2, 3, 4, 7, 10, 11, 14
WI	22	0	999999	1, 5, 7, 8, 10, 12
WV	10	100	999999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Cobalt or Cobalt Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WY	3	1000	99999	1, 5, 10, 12, 13

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: (TRI19 2020); Data are from 2019

5.2.2. Import/Export

According to USGS (2020) an estimated 13,600 metric tons of cobalt were imported into the United States in 2019. Annual imports ranged from 11,400 to 12,800 between 2015 and 2018 (USGS 2020). Between 2015 and 2018, Norway, Japan, China, and Canada supplied 17%, 13%, 11%, and 11% of cobalt, respectively (USGS 2020). Imports for 2016 by form included (form, metric tons cobalt content): metal, 10,800; oxides and hydroxides, 1,410; acetates, 30; carbonates, 263; chlorides, 8; and sulfates 377 (USGS 2019).

Cobalt exports in the United States ranged from 3,830 to 6,960 metric tons between 2015 and 2019; exports in 2019 are estimated to be 4,000 metric tons (USGS 2020).

5.2.3 Use

In 2019 the estimated apparent consumption of cobalt in the U.S. was 12,400 metric tons (USGS 2020). Due to cobalt's hardness, ferromagnetic properties, and resistance to oxidation, it can be added to steels to produce alloys for applications requiring metals with high tensile strength, heat and corrosion resistance, and high magnetic strength. It is used in many commercial, industrial, and military applications, and is often used in medical devices and prosthetics.

The leading use of cobalt globally is in rechargeable battery electrodes, while another major use is in superalloys (USGS 2020). Other uses for cobalt include cemented carbides and diamond tools, controlled-expansion, and corrosion- and wear-resistant alloys, high-speed and strong yet ductile steels, and magnets. Chemical uses for cobalt include animal feed additives, catalysts in the chemical and petroleum industries, drying agents, dyes and pigments, glass decolorizers, ground coats for porcelain enamels,

humidity indicators, magnetic recording media, rubber adhesion promoters for steel-belted radial tires, and vitamin B_{12} (USGS 2019). Cobalt is present as an accelerator in polyester resins, which are found in coating, lacquers, and finishes (Anavekar and Nixon 2006; Cahill and Andersen 2010). Some artist pastels contain cobalt as a pigment (Brock and Stopford 2003). In 2019, 46% of cobalt consumed in the U.S. was used in superalloys (mainly for aircraft gas turbine engines), 9% in cemented carbides for cutting and wear-resistant applications, 14% in various metallic applications, and 31% in various chemical applications (USGS 2020).

5.2.4 Disposal

There is a paucity of data on the methods of disposal of cobalt and its compounds. Due to the lack of natural sources of economically extractable ores in the United States, cobalt is mostly imported or produced from scrap material in the United States, and it is considered a strategic mineral. It is economical to recycle certain cobalt wastes rather than to dispose of them. Recycling of superalloy scrap is an important method for the recovery of cobalt. Cobalt recycled from purchased scrap accounted for about 29% of reported consumption in 2019 (USGS 2020). According to TRI (TRI19 2020), 3.09 and 15 million pounds of cobalt were recycled onsite and offsite, respectively, in 2019. For cobalt compounds, 0.7 million pounds were recycled onsite and 3.04 million pounds were recycled offsite in 2019. Waste water containing cobalt can be treated before disposal, for instance, by precipitation of carbonate or hydroxide of cobalt or by passage through an ion-exchange resin (Clifford et al. 1986).

In August 1998, EPA issued a final rule listing spent hydrotreated and hydrorefined catalysts as hazardous waste under the Resource Conservation and Recovery Act (EPA 1998). Listing under this act requires that releases of these substances will be subject to certain management and treatment standards and emergency notification requirements. Information regarding effluent guidelines and standards for cobalt may be found in Title 40 of the Code of Federal Regulations, Parts 421.230, 421.310, and 471.30.

5.3. RELEASES TO THE ENVIRONMENT

According to the Toxic Chemical Release Inventory (TRI), in 2019, total releases of cobalt to the environment (including air, water, soil, and underground injection) from 331 reporting facilities that produced, processed, or used cobalt were 445,819 pounds (TRI19 2020). Total releases of cobalt compounds from 380 reporting facilities were 4,620,079 pounds (TRI19 2020). Table 5-2 and Table 5-3 list the amounts released from these facilities grouped by state. Industrial sectors producing, processing, or using cobalt that contributed the greatest environmental releases in 2019 were metal mining and hazardous waste with 120,000 and 111,103 pounds, respectively. Industrial sectors producing, processing,

or using cobalt compounds that contributed the greatest environmental releases in 2019 were hazardous waste and metal mining with 1,235,185 and 1,228,152, pounds, respectively.

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt

		Reported amounts released in pounds per year[b]							
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
AL	8	164	66	0	24,023	38,000	24,230	38,024	62,253
AZ	2	56	0	0	78,000	0	78,056	0	78,056
AR	3	503	28	0	45	0	503	73	576
CA	18	125	23	0	62,720	1,539	58,182	6,225	64,407
CO	2	0	0	0	42,000	0	42,000	0	42,000
CT	11	576	275	0	501	1,005	587	1,770	2,357
FL	2	219	3	0	103	303	219	409	628
GA	6	475	63	0	360	3	477	424	900
ID	1	0	0	0	0	0	0	0	0
IL	12	480	7	0	33	28	481	67	548
IN	27	1,927	197	0	1,620	0	1,932	1,812	3,744
IA	6	42	0	0	0	0	42	0	42
KS	11	379	0	0	215	9	384	219	603
KY	6	12	3	0	1,920	59	14	1,980	1,994
LA	3	0	40	11,400	0	0	11,440	0	11,440
ME	2	40	0	0	0	357	40	357	397

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt

		Reported amounts released in pounds per year[b]							
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
MA	11	74	27	0	2,547	3,809	88	6,369	6,457
MI	18	2,088	157	0	5,758	90	2,113	5,980	8,093
MN	5	2	0	0	0	0	2	0	2
MS	4	1	190	0	128	0	191	128	319
MO	5	268	0	0	5	0	273	0	273
NE	1	78	0	0	270	0	78	270	348
NV	5	1,102	3	0	28,953	0	29,913	145	30,058
NH	2	3	1	0	2,064	0	3	2,065	2,068
NJ	8	255	8	0	30,374	45	255	30,427	30,682
NY	11	288	24	0	29	2,367	293	2,415	2,708
NC	16	67	10	0	116	113	69	236	305
OH	29	171	192	0	22,361	15,023	5,729	32,017	37,747
OK	8	0	0	0	0	0	0	0	0
OR	4	335	25	0	3,496	148	342	3,662	4,004
PA	29	348	24	0	2,254	25,670	357	27,939	28,296
SC	9	102	40	0	6,440	0	119	6,463	6,582
SD	1	0	0	0	0	0	0	0	0
TN	9	885	64	0	866	0	1,351	464	1,816
TX	10	98	19	0	6,473	2	107	6,486	6,592
UT	1	10	5	0	5	0	10	10	20
VA	3	9	5	0	31	49	9	85	95
WV	1	240	47	0	0	0	240	47	287
WI	19	133	1,923	0	7,013	49	133	8,985	9,118
PR	2	0	0	0	5	0	0	5	5
Total	331	11,553	3,470	11,400	330,728	88,668	260,261	185,559	445,819

The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt

		Reported amounts released in pounds per year[b]							
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site

[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection
Source: TRI19 2020; Data are from 2019

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt Compounds

		Reported amounts released in pounds per year[b]							
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
AL	14	3,244	21,214	0	47,586	361	30,455	41,949	72,405
AK	1	1	7	0	14,000	0	14,008	0	14,008
AZ	10	526	255	0	331,754	152	330,630	2,057	332,687
AR	5	77	7	0	58,401	627	55,034	4,078	59,112
CA	13	84	32	0	46,295	1,163	44,545	3,030	47,574
CO	2	10	4	0	0	0	14	0	14
CT	1	750	0	0	0	0	750	0	750
DE	1	0	0	0	0	6	0	6	6
FL	7	125	0	0	11,796	0	11,921	0	11,921
GA	8	113	994	0	24,762	0	12,813	13,056	25,868
ID	2	1	0	0	231	0	228	4	232
IL	18	413	725	0	192,134	1,984	193,098	2,158	195,256
IN	15	880	173	0	143,261	1,058	124,570	20,802	145,372
IA	4	276	0	0	0	0	276	0	276
KS	5	23	7	0	22,502	803	32	23,303	23,335
KY	15	248	689	0	109,321	2,702	104,325	8,635	112,960
LA	21	1,282	6,534	31	244,993	5,849	213,425	45,264	258,689
ME	1	13	0	0	366	0	13	366	379
MI	17	606	105	0	513,839	5	491,880	22,675	514,555
MN	5	253	29	0	77	393	282	470	752
MS	6	30	303	45,873	3,092	406	47,060	2,644	49,704
MO	3	112	0	0	10,173	0	10,285	0	10,285
MT	2	64	0	0	20,603	22	20,667	22	20,689

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt Compounds

		Reported amounts released in pounds per year[b]							
							Total Release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site
NE	3	21	0	0	2,768	0	1,371	1,418	2,789
NV	8	17,221	19	0	669,232	0	648,148	38,324	686,472
NJ	1	0	0	0	318	507	0	825	825
NM	4	35	0	0	70,624	14,018	70,659	14,018	84,677
NY	1	0	0	0	0	37	0	37	37
NC	15	265	72	0	204,306	228	109,688	95,182	204,870
ND	3	1,101	6	0	51,025	0	43,646	8,486	52,132
OH	31	2,075	824	14,060	155,138	9,244	130,008	51,333	181,341
OK	10	169	14	0	46,935	1,510	38,404	10,224	48,628
OR	2	0	160	0	14	53	0	227	227
PA	33	5,641	3,078	0	86,070	5,809	47,443	53,156	100,598
RI	1	0	0	0	0	0	0	0	0
SC	16	146	39,953	0	26,069	4,884	51,974	19,077	71,051
SD	1	0	0	0	0	0	0	0	0
TN	17	308	6,935	0	136,300	485	119,891	24,137	144,028
TX	36	7,572	4,577	3,542	836,180	47,356	841,979	57,248	899,227
UT	2	258	0	0	15,500	0	15,758	0	15,759
VA	2	12	0	0	0	567	12	567	579
WA	3	32	17	0	2,106	0	49	2,106	2,155
WV	9	866	26	0	212,704	24	160,095	53,525	213,620
WI	3	70	1	0	703	0	165	609	774
WY	3	586	0	0	11,176	1,700	11,762	1,700	13,462
Total	380	45,507	86,761	63,506	4,322,354	101,951	3,997,360	622,718	4,620,079

The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt Compounds

	Reported amounts released in pounds per year[b]								
								Total Release	
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On and off-site

RF = reporting facilities; UI = underground injection

Source: TRI19 2020; Data are from 2019

5.3.1 Air

Estimated releases of 11,553 pounds (~5.2 metric tons) of cobalt to the atmosphere from 331 domestic manufacturing and processing facilities in 2019 accounted for about 2.6% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). The releases of cobalt which refers to CAS 7440-48-4 are summarized in Table 5-2. Estimated releases of 45,507 pounds (~20.6 metric tons) of cobalt compounds to the atmosphere from 380 domestic manufacturing and processing facilities in 2019 accounted for about 98% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). Cobalt compounds refer to any unique chemical substance that contains cobalt (EPA 2005). These releases are summarized in Table 5-3.

The sources of cobalt in the atmosphere are both natural and anthropogenic (Barceloux 1999). Natural sources include wind-blown continental dust, seawater spray, volcanoes, forest fires, and continental and marine biogenic emissions. The worldwide emission of cobalt from natural sources has been estimated to range from 13 to 15 million pounds/year (Lantzy and Mackenzie 1979; Nriagu 1989). The global atmospheric emission of cobalt from anthropogenic sources is an estimated 9.7 million pounds/year. Therefore, natural sources contribute slightly more to cobalt emissions in the atmosphere than anthropogenic sources (Lantzy and Mackenzie 1979). The primary anthropogenic sources of cobalt in the atmosphere are the burning of fossil fuels and sewage sludge, phosphate fertilizers, mining and smelting of cobalt-containing ores, processing of cobalt-containing alloys, and industries that use or process cobalt compounds. Small amounts of cobalt are found in coal, crude oils, and oil shales. Therefore, burning of these fossil fuels for power generation will emit cobalt into the atmosphere. The cobalt contents of the fly ash and flue gases of a coal-burning power plant are approximately 25 mg/kg and 100–700 mg/m^3, respectively. Gasoline contains <0.1 mg cobalt/kg, but catalytic converters may contain cobalt; therefore, emissions from vehicular exhaust are also a source of atmospheric cobalt (Abbasi et al. 1989; Holcombe et al. 1985; Ondov et al. 1982; Smith and Carson 1981). Cobalt metal has been detected in tobacco from

U.S. cigarettes at mean values of 0.44 to 1.11 µg/g dry tobacco (Fresquez et al. 2013). Therefore, smoking is a potential source of atmospheric cobalt that could impact indoor air quality.

Cobalt has been identified in air samples collected at 3 of the 425 current or former NPL hazardous waste sites where it was detected in some environmental media (i.e., air, soil, sediment, or water) (ATSDR 2019).

5.3.2 Water

Estimated releases of 3,470 pounds (~1.6 metric tons) of cobalt to surface water from 331 domestic manufacturing and processing facilities in 2019, accounted for about 0.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An additional 728 pounds (~0.3 metric tons) were released to publicly owned treatment works (POTWs) (TRI19 2020). These releases are summarized in Table 5-2.

Estimated releases of 86,761 pounds (~39 metric tons) of cobalt compounds to surface water from 380 domestic manufacturing and processing facilities in 2019, accounted for about 1.9% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An additional 6,154 pounds (~2.8 metric tons) were released to publicly owned treatment works (POTWs) (TRI19 2020). These releases are summarized in Table 5-3.

Compounds of cobalt occur naturally in seawater and in some surface, spring, and groundwater (Smith and Carson 1981). Cobalt is also released into water from anthropogenic sources. While there has been no mine production of cobalt in the United States in recent years, cobalt is a byproduct or coproduct of the refining of other mined metals such as copper and nickel. Historic mining operations that processed cobalt containing ores may continue to release cobalt into surface water and groundwater. Wastewater from the recovery of cobalt from imported matte or scrap metal, refining of copper and nickel, or during the manufacture of cobalt chemicals are sources of cobalt in water (Smith and Carson 1981). Process water and effluent from coal gasification and residue from solvent-refined coal contain cobalt. The accidental discharge of activated sludge and sewage may be important sources of cobalamins in waterways, together with bioconcentration by benthic organisms (Smith and Carson 1981). The discharge of wastewater by user industries, such as paint and pigment manufacture, also contributes to the release of cobalt into water. In one case, manufacturers of nickel-cadmium batteries operating between 1953 and 1979 discharged cobalt from a battery factory to the Hudson River in Foundry Cove, New York, of which 1.2 metric tons are estimated to be present in the eastern cove (Knutson et al. 1987). Atmospheric deposition is an additional source of cobalt in water. Lake Huron receives an estimated 76% of its cobalt input from natural sources and 24% from anthropogenic sources. The corresponding estimated values for Lake

Superior are 85.4 and 14.6% (Smith and Carson 1981). In these Great Lakes, it therefore appears that natural inputs of cobalt far exceed anthropogenic ones.

Cobalt has been identified in water at 66 sites, respectively, of the 426 NPL hazardous waste sites, where it was detected in some environmental media (i.e., air, soil, sediment, or water) (ATSDR 2019).

5.3.3. Soil

Estimated releases of 330,728 pounds (~150 metric tons) of cobalt to soils from 331 domestic manufacturing and processing facilities in 2019, accounted for about 74% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An additional 11,400 pounds (~5.2 metric tons), constituting about 2.6% of the total environmental emissions, were released via underground injection (TRI19 2020). These releases are summarized in Table 5-2. Estimated releases of 4.3 million pounds (~1,950 metric tons) of cobalt compounds to soils from 380 domestic manufacturing and processing facilities in 2019, accounted for about 94% of the estimated total environmental releases from facilities required to report to the TRI (TRI19 2020). An additional 63,506 pounds (~29 metric tons), constituting about 1.4% of the total environmental emissions, were released via underground injection (TRI19 2020). These releases are summarized in Table 5-3.

Cobalt occurs naturally in the earth's crust and, therefore, in soil. However, elevated levels of cobalt in soil may result from anthropogenic activities such as the mining and processing of cobalt-bearing ores, the application of cobalt-containing sludge or phosphate fertilizers to soil, the disposal of cobalt containing wastes, and atmospheric deposition from activities such as burning of fossil fuels, smelting, and metal refining (Smith and Carson 1981).

Cobalt has been identified in soil at 97 of the 425 NPL hazardous waste sites, where it was detected in some environmental media (i.e., air, soil, sediment, or water) (ATSDR 2019).

5.4. ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Cobalt compounds are nonvolatile, and thus, cobalt is emitted to the atmosphere in particulate form. The transport of cobalt in air depends on its particle size and density, and meteorological conditions. It can be returned to land or surface water by rain, or it may settle to the ground by dry deposition. In areas that are not arid, wet deposition may exceed dry deposition (Arimoto et al. 1985; Erlandsson et al. 1983). Coarse particles, with aerodynamic diameters >2 μm (such as those obtained during ore processing) may deposit within 10 km from the point of emission; finer particles may travel longer distances. It is the

larger particles that may be responsible for elevated local concentrations around emission sources. The mass median diameter for cobalt particles emitted from a power generator with a stack emission controlled by an electrostatic precipitator or scrubber ranged from <2 to 12 μm. The mass median diameter of cobalt in the ambient atmosphere is about 2.6 μm (Milford and Davidson 1985). Golomb et al. (1997) report average total (wet+dry) deposition rates of cobalt to Massachusetts Bay during the period of September 15, 1992 to September 16, 1993. The total deposition rate was 58 $\mu g/m^2$-year, of which 47 $\mu g/m^2$-year was dry deposition and 12 $\mu g/m^2$-year was wet deposition. Total cobalt deposition flux at a site in the Rhone delta in southern France in 1988–1989 was 0.42±0.23 kg/km^2-year with 0.15 kg/km^2-year in the form of wet deposition (Guieu et al. 1991).

Water. As with most metals, sediment and soil are frequently the final repository for cobalt released into the environment, although the process is dynamic, and cobalt can be released into the water depending upon conditions. Cobalt released into waterways may sorb to particles and settle into the sediment or be sorbed directly into the sediment. However, complexation of cobalt to dissolved organic substances can significantly reduce sorption to sediment particles (Albrecht 2003). Studies by Jackman et al. (2001) suggest that interparticle migration of cobalt can influence the transport of metal ions, including cobalt, in sediments. For example, migration of a metal ion from a highly mobile sediment particle, such as clay, to less mobile gravels will slow the transport of that metal. Cobalt can also be transported in dissolved form or as suspended sediment by rivers to lakes and the sea or by ocean currents. Sediment in areas of active sedimentation would receive a large portion of the suspended sediment. In the case of the Peach Bottom Atomic Power Station where ^{60}Co was released into the Conowingo Reservoir, an impoundment of the lower Susquehanna River, <20% of the radionuclide was trapped in the reservoir sediment (<2% of that would remain after >30 years due to radioactive decay), and the rest was thought to have been transported downstream and into the Chesapeake Bay (McLean and Summers 1990). Environmental samples of publicly-relevant surface and drinking water, fish, sediment, air particulates, milk, and food products in the Chesapeake Bay area do not detect ^{60}Co (Exelon 2019). It is often assumed that the primary mode of transport of heavy metals in aquatic systems is as suspended solids (Beijer and Jernelov 1986). However, in the case of cobalt, the percent that is transported by suspended solids is highly variable. Examples of the percentage of cobalt transported in suspended solids include (water body, percent): Main River (Germany), 33.4–42.2%; Susquehanna River (near its source in New York), 9%; New Hope River (North Carolina), 92%; Yukon River, >98%; Danube River (1961–1970), 27.4– 85.9%; Columbia River (^{60}Co, downstream of the Hanford site), 95–98%; Strait of Juan de Fuca (Puget Sound, Washington), 11–15%; North Sea, 34%; and Lake Washington (Washington), 0% (Smith and Carson 1981). In the oxic zones of many surface waters, dissolved cobalt levels decrease with increasing depth. This may be due to cobalt's

continuous input into surface water from discharges or to increased adsorption and precipitation of the soluble forms with increasing depth. The fact that cobalt concentration profiles in deep water follow manganese and aluminum profiles strongly suggests that dissolved cobalt is precipitated in the adsorbed state with oxides of iron and manganese and with crystalline sediments such as aluminosilicate and goethite. A part of the cobalt may also precipitate out as carbonate and hydroxide in water. The higher concentration of organic pollutants in polluted water probably results in the formation of higher concentrations of soluble organic complexes. In a deep sediment where the water was anoxic and contained hydrogen sulfide, some mobilization of cobalt was observed, probably due to the formation of bisulfide and polysulfide complexes (Bargagli 2000; Brugmann 1988; Finney and Huh 1989; Glooschenko et al. 1981; Knauer et al. 1982; Nriagu and Coker 1980; Shine et al. 1995; Smith and Carson 1981; Szefer et al. 1996; Windom et al. 1989).

Sediment and Soil. Cobalt strongly binds to humic substances naturally present in aquatic environments. Humic acids can be modified by UV light and bacterial decomposition, which may change their binding characteristics over time. The lability of the complexes is strongly influenced by pH, the nature of the humic material, and the metal-to-humic substance ratio. The lability of cobalt-humate complexes decreases with time ("aging effect") (Burba et al. 1994). The "aging effect" indicates that after a period of time (~12 hours), complexes that were initially formed are transformed into stronger ones from which the metal ion is less readily dislodged. In the Scheldt Estuary and the Irish Sea, between 45 and 100% of dissolved cobalt was found to occur in these very strong complexes (Zhang et al. 1990).

The distribution coefficient of cobalt may vary considerably in the same sediment in response to conditions affecting the pH, redox conditions, ionic strength, and amount of dissolved organic matter (Mahara and Kudo 1981). Uptake of ^{60}Co from the water by sediment increased rapidly as the pH was increased from 5 to 7–7.5 and then slightly decreased (Benes et al. 1989). Therefore, pH would be an important factor affecting the migration of cobalt in surface water.

The mobility of cobalt in soil is inversely related to how strongly it is adsorbed by soil constituents. Cobalt may be retained by mineral oxides such as iron and manganese oxide, crystalline materials such as aluminosilicate and goethite, and natural organic substances in soil. Sorption of cobalt to soil occurs rapidly (within 1–2 hours). Soil-derived oxide materials were found to adsorb greater amounts of cobalt than other materials examined, although substantial amounts were also adsorbed by organic materials. Clay minerals sorbed relatively smaller amounts of cobalt (McLaren et al. 1986). In addition, little cobalt was desorbed from soil oxides while substantial amounts desorbed from humic acids and montmorillonate. In clay soil, adsorption may be due to ion exchange at the cationic sites on clay with either simple ionic cobalt or hydrolyzed ionic species such as $CoOH^+$. Adsorption of cobalt onto iron and

manganese increases with increasing pH (Brooks et al. 1998). In addition, as pH increases, insoluble hydroxides or carbonates may form, which would also reduce cobalt mobility. Conversely, sorption onto mobile colloids would enhance its mobility. In most soils, cobalt is more mobile than lead, chromium (II), zinc, and nickel, but less mobile than cadmium (Baes and Sharp 1983; King 1988; Mahara and Kudo 1981; Smith and Carson 1981). In several studies, the K_d of cobalt in a variety of soils ranged from 0.2 to 3,800. In 11 U.S. soils, the mean Freundlich K_F and n values were 37 L/kg and 0.754, respectively; K_F values ranged from 2.6 to 363 L/kg and correlated with soil pH and CEC (Buchter et al. 1989). In 13 soils from the southeastern United States whose soil pH ranged from 3.9 to 6.5, cobalt sorption ranged from 15 to 93%; soil pH accounted for 84–95% of the variation in sorption (King 1988).

Organic complexing agents such as ethylenediaminetetraacetic acid (EDTA), which are used for decontamination operations at nuclear facilities, greatly enhance the mobility of cobalt in soil. Other organic complexing agents, such as those obtained from plant decay, may also increase cobalt mobility in soil. However, both types of complexes decrease cobalt uptake by plants (Killey et al. 1984; McLaren et al. 1986; Toste et al. 1984). Addition of sewage sludge to soil also increases the mobility of cobalt, perhaps due to organic complexation of cobalt (Gerritse et al. 1982; Williams et al. 1985). Leaching of cobalt has been observed from municipal and low-level radioactive waste sites (Cyr et al. 1987; Czyscinski et al. 1981; Friedman and Kelmers 1988). The mobility of cobalt was assessed in two soils from the Cabriolet and Little Feller event sites at the Nevada Test site as a function of various parameters such as pH, ionic strength, cobalt concentrations, soil solids concentrations, and particle size distribution (DOE 1996). Cobalt was quantitatively sorbed on these soils (at least 90% sorbed) when the pH was above 7 and the solid concentration was at least 20 g/L. The experiments suggest that binding is principally on amphoteric surface-hydroxyl surfaces. Since the pH of these soils is around 8, cobalt would bind strongly under normal environmental conditions. Migration would be severely retarded under all but the most extreme conditions, e.g., pH of 4 or below and high ionic strength soil solutions (approximately 0.1 M). In addition, unrealistically large quantities of water would be needed to displace cobalt from the upper layers of the soil profile.

Other Media. Cobalt may be taken up from soil by plants. Surface deposition of cobalt on leaves of plants from airborne particles may also occur. Elevated levels of cobalt have been found in the roots of sugar beets and potato tubers in soils with high cobalt concentrations (e.g., fly ash-amended soil) due to absorption of cobalt from soil. However, the translocation of cobalt from roots to above-ground parts of plants is not significant in most soils, as indicated by the lack of cobalt in seeds of barley, oats, and wheat grown in high-cobalt soil (Mermut et al. 1996; Smith and Carson 1981). Mermut et al. (1996) found 0.01–0.02 mg/kg in 10 samples of durum wheat grain from different areas of Saskatchewan where surface soil

cobalt levels ranged from 3.7 to 16.4 mg/kg. The enrichment ratio, defined as the concentration in a plant grown in amended soil (fly ash) over the concentration in unamended soil, was about 1. Other authors have determined the transfer coefficient (concentration in plant/concentration in soil) for cobalt to be 0.01–0.3.

Concentration factors have also been reported for various other aquatic organisms. Freshwater mollusks have concentration factors of 100–14,000 (~1–300 in soft tissue). Much of the cobalt taken up by mollusks and crustacea from water or sediment is adsorbed to the shell or exoskeleton; very little cobalt is generally accumulated in the edible parts (Amiard and Amiard-Triquet 1979; Smith and Carson 1981).

5.4.2 Transformation and Degradation

Air. There is a paucity of data in the literature regarding the chemical forms of cobalt in air and their transformations in the atmosphere. It is generally assumed that anthropogenic cobalt originating from combustion sources exists primarily as the oxide and most commonly as cobalt(II) oxide as a result of interactions with oxidants in the atmosphere (Schroeder et al. 1987). In addition, cobalt may be released into the atmosphere as its arsenide or sulfide during ore extraction processes. It is not clear if these species are transformed in the atmosphere. Should a relatively insoluble species such as the oxide be transformed into a more soluble form such as the sulfate, one would expect greater quantities to be washed out of the atmosphere in rain.

Water. Many factors control the speciation and fate of cobalt in natural waters and sediments. These include the presence of organic ligands (e.g., humic acids, EDTA), the presence and concentration of anions (Cl^-, OH^-, CO_3^{-2}, HCO_3^-, SO_4^{-2}), pH, and redox potential (Eh). Modeling the chemical speciation of a metal in water depends upon the environmental factors assumed and the stability constants of the various complexes. Mantoura et al. (1978) predicted the equilibrium levels of Co^{2+} species in fresh water to follow the order: free $Co^{+2} \geq CoCO_3 > CoHCO_3^+ >> CoSO_4 \geq$ Co•humic acid. However, the mole percent of various cobalt species in a Welsh lake was found to be free Co^{+2}, 76%; $CoCO_3$, 9.8%; $CoHCO_3^+$, 9.6%; humate complexes, 4.0%; and CoSO4, 0.4%. The rank order of species concentration in seawater was estimated to be: $CoCO_3$>free Co^{+2}>$CoSO_4 \geq CoHCO_3^+$ (Mantoura et al. 1978). In another model, the speciation of cobalt was completely different with $CoCl^+$>free Co^{+2}>$CoCO_3$>$CoSO_4$ (Smith and Carson 1981).

Tipping et al. (1998) estimated the equilibrium speciation of cobalt in riverine, estuarine, and marine surface water of the Humber system (England). In all but seawater, cobalt complexed with carbonate (HCO_3^- and CO_3^{2-}) and constituted about 70% of dissolved cobalt, while the free Co^{2+} ion was the major

species representing ~25% of the total, which is much lower than the 61% predicted by Mantoura et al. (1978). As the alkalinity of the water increases, the proportion of cobalt complexed with carbonate increases at the expense of free Co^{2+}. The proportion, but not the concentration, of cobalt that exists as the free ion and the carbonate complexes in river water is independent of the level of fulvic acid in the water. In seawater, the carbonate species and the free aqua species assume roughly equal importance. The proportion of dissolved cobalt complexed with fulvic acid decreased with increasing salinity. About 20% of cobalt in seawater was estimated to be present as complexes with sulfate.

In a bioconcentration study in which $CoCl_2$ was initially added to the seawater, at month's end, the cationic form of cobalt was progressively converted into anionic and neutral forms, possibly as a result of complexation with organic ligands (Carvalho 1987). Addition of humic acid to natural waters may merely increase the concentration of colloidal dispersed metal rather than form truly soluble humic complexes. In water that contains high organic wastes such as was the case in the Rhone River in France, cobalt was almost completely complexed. A study determined that the distribution of ^{60}Co in the Rhone River sampled at Arles, France was 45% in the particulate phase, 30% in the dissolved phase, and 25% in the colloidal phase (Eyrolle and Charmasson 2001). Cobalt forms complexes with EDTA that are very stable environmentally. EDTA is often used in agriculture, food and drug processing, photography, and textile and paper manufacturing, and therefore, it is a likely constituent of industrial discharges. Acidity and redox potential have an effect on the behavior of cobalt in water. The adsorption of cobalt by particulate matter decreases with decreasing pH, since the increasing H^+ concentration competes with metal binding sites. This may lead to increased concentrations of dissolved cobalt at low pH. The effect of Eh (redox potential) on the speciation of cobalt has been shown by the increase in the concentration of dissolved cobalt by orders of magnitude with increasing depth in certain parts of Baltic waters. The increase in the concentration of dissolved cobalt may be due to the formation of soluble bisulfide and polysulfide complexes in the anoxic zones. The residence time of soluble cobalt in seawater has been estimated to range from <1 to 52 years (Brugmann 1988; Knauer et al. 1982; Smith and Carson 1981). Vitamin B_{12}, which contains cobalt, is synthesized by 58 species of seven genuses of bacteria as well as blue-green algae and actinomycetes (mold-like bacteria). Consequently, vitamin B_{12} levels in marine water range from very low levels in some open ocean water to much higher levels in some coastal waters. Freshwater environments have comparable levels of vitamin B_{12}.

The high level of cobalamins in coastal water appears to be related to the occurrence of macrophytes in these areas with their high concentrations of vitamin B_{12}. Cobalamins are released into the water when the organisms die (Smith and Carson 1981). Alkaline thermal groundwater in granitic areas have been studied as possible waste disposal sites for radioactive waste (Alaux-Negrel et al. 1993). Water in these areas is

characterized by high pH, low CO_2 partial pressure, and generally low redox potential; sulfide concentrations are in the range of 10^{-4} to 10^{-3} mol/L. The solubility of cobalt is controlled by the solubility of CoS (log K_1 and log K_2 being 5.7 and 8.7 at 25°C) and therefore, levels of cobalt are very low, 10^{-8}–10^{-10} mol/L. The ^{60}Co (III) picolinate complex that is released into water by some nuclear reactors does not break down immediately on release into seawater, but rather can coexist with the ^{60}Co (II) forms for lengthy periods in the environment (Leonard et al. 1993a, 1993b). Studies indicate that several processes occur to the Co(III) organic complexes, including reduction to the inorganic form, sorption of both species to particulate matter, and transformations of the uncomplexed species. This applies to both stable and radioactive cobalt compounds.

Sediment and Soil. The speciation of cobalt in soil or sediment depends on the nature of the soil or sediment, concentration of chelating/complexing agents, pH, and redox potential (Eh) of the soil. Dissolved cobalt may be absorbed by ion exchange and other mechanisms, or may form complexes with fulvic acids, humic acid, or other organic ligands in soil. The humic and fulvic complexes of cobalt are not very stable compared with those of copper, lead, iron, and nickel. The speciation of cobalt in sediment from nine sites in the Red Sea, a sea that is unique in that it has no permanent streams flowing into it, was assessed using a sequential extraction technique (Hanna 1992). The mean percentages contained in the various fractions were exchangeable, 5.5%; carbonate, 5%; Fe/Mn oxides, 24%; organic, 30.4%; sulfides, 13%; and lithogenous, 22%. While the mean concentration of cobalt in the sediment increased from 0.003 to 0.006 ppb between 1934 and 1984, its distribution among the different phases did not change appreciably. The reduction of soil Eh, which may occur when soil is flooded or in deeper layers of soil that are oxygen-depleted, may change the speciation of cobalt. This may result in the reduction of soil iron and manganese and the subsequent release of adsorbed cobalt from the mineral oxides. Similarly, a decrease in soil pH may result in the solubilization of precipitated cobalt and desorption of sorbed cobalt, resulting in increased cobalt mobility (Smith and Carson 1981). Co^{2+} may also be oxidized to Co^{3+} by manganese oxides, a common component of soils and aquifer material, with subsequent surface precipitation (Brusseau and Zachara 1993). This process may affect transport of cobalt in the subsurface environment. EDTA complexes of cobalt are very stable and are likely to form in soils containing EDTA. EDTA is widely used as a decontaminating agent at nuclear facilities. Although cobalt-EDTA complexes are adsorbed by some soils, the mobility of cobalt in soil may increase as a result of complex formation (Schnitzer 1969; Smith and Carson 1981; Swanson 1984). ^{60}Co that is disposed of in shallow land trenches have sometimes been found to migrate more rapidly than expected from the disposal sites. Organic chelating agents are frequently present at these sites and would possibly increase the solubility and transport of the radionuclide.

Bacterial action can affect the mobility of a substance by mediating reactions or by participating in reactions that lower the pH. Another way of influencing mobility is by degrading complexing agents used in cleaning reactors (e.g., citric acid), thereby releasing the element. However, experiments on the fate and transport of cobalt released upon the biodegradation of the complexing ligand indicate that results are not always predictable; the means of ligand removal and the geochemical environment are important factors that must be considered (Brooks et al. 1998).

5.5. LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to cobalt depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of cobalt in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on cobalt levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable**.** Table 5-4 shows the limit of detections typically achieved by analytical analysis in environmental media.

Table 5-4. Lowest Limit of Detection for Cobalt Based on Standards[a]

Media	Detection limit	Reference
Water	0.02 µg/L	(USGS 2006)
Marine water	0.02 µg/L	(EPA 1997)
Ambient air	0.12 ng/m^3 (fine element) 1.08 ng/m^3 (coarse element)	(EPA 1999)
Soil and sediment	0.004 µg/g	(USGS 2006)
Urine	0.023 µg/L	(CDC 2018)
Blood	0.06 µg/L	(CDC 2017)
Biota	0.004 µg/g	(USGS 2006)

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Stable cobalt has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 425 of 1,867 current or former NPL hazardous waste sites (ATSDR 2019). Presented in Table 5-5 is a summary of the range of concentrations detected in environmental media at NPL sites.

Table 5-5. Cobalt Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (mg/L)	0.042	0.064	12.7	124	66
Soil (mg/kg)	15	17.1	5.71	199	97
Air (mg/m^3)	5.17 x 10^{-5}	2.62 x 10^{-5}	11.3	4	3

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019).Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Atmospheric cobalt is associated with particulate matter. Cobalt in the air, including cobalt compounds, is monitored by EPA, and recorded in the Air Quality System. Data from 2016-2020 is summarized in Table 5-6. Mean cobalt levels in ambient air are generally less than 0.002 µg/m^3 (EPA 2020).

Table 5-6. Percentile Distribution of Annual Mean Cobalt (TSP) Concentrations (µg/m^3) Measured in Ambient Air Locations Across the United States

Year	Number of U.S. locations	25th	50th	75th	95th	Maximum
2016	33	0.00018	0.0010	0.0010	0.0011	0.0011
2017	35	0.00014	0.00045	0.0015	0.0018	0.0022
2018	32	0.00019	0.00058	0.00085	0.0011	0.0014
2019	33	0.00012	0.00020	0.00079	0.0011	0.0014
2020	4	0.000025	0.000033	0.000061	0.00013	0.00014

TSP = total suspended particles
Source: EPA 2020

At the South Pole, cobalt levels of 0.00049±0.00015 ng/m^3 were recorded in 1974–1975 (Maenhaut et al. 1979). Geometric mean cobalt levels in several open-ocean environments ranged from 0.0004 to 0.08 ng/m^3 (Chester et al. 1991). The average annual PM-10 (particles with diameters ≤10 µm) cobalt concentration at Nahant, Massachusetts (near Boston) in 1992–1993 was 1.7 ng/m^3 (Golomb et al. 1997). Half of the cobalt was contained in fine particles (<2.5 µm) and half in coarse particles (2.5–10 µm). The mean cobalt level in southern Norway in 1985–1986 (n=346) was 0.10 ng/m^3 with 35% of the samples falling below the detection limit of 0.04 ng/m^3 (Amundsen et al. 1992). Atmospheric cobalt levels in industrial settings may exceed 10 ng/m^3. The highest recorded average cobalt concentration in air was 48 ng/m^3 in Clydach, Wales at the site where nickel and cobalt were refined (Smith and Carson 1981). These

data show the contribution of anthropogenic sources in increasing the level of cobalt in the ambient air. Typical occupational cobalt levels are $1.0x10^4$– $1.7x10^6$ ng/m^3 (Barceloux 1999; IARC 1991).

5.5.2 Water

The concentrations of cobalt in surface water and groundwater in the United States are generally low, <1 µg/L in pristine areas and 1–10 µg/L in populated areas (Hamilton 1994; Smith and Carson 1981). However, cobalt levels may be considerably higher in mining or agricultural areas. Levels as high as 4,500 µg/L were reported in Mineral Creek, Arizona, near a copper mine and smelter; levels of 6,500 µg/L were reported in the Little St. Francis River, which receives effluent from cobalt mining and milling operations (Smith and Carson 1981). Mining at Blackbird Mine in Idaho, a large deposit of cobalt in North America, occurred from the early 1900s to 1982. Cobalt concentration in surface water and groundwater samples collected in 1992 from area creeks near this mine were reported to range from <1 to 625,000 µg/L, and from not detected to 315,000 µg/L, respectively (ATSDR 1995). Eckel and Jacob (1988) analyzed U.S. Geological Survey (USGS) data for 6,805 ambient surface water stations and estimated the geometric mean and median dissolved cobalt concentration as 2.9 and 2.0 µg/L, respectively. Mean cobalt levels reported in seawater range from 0.078 µg/L in the Caribbean Sea to 0.39 µg/L in the Indian Ocean (Hamilton 1994). Vitamin B_{12} is synthesized by bacteria, macrophytes, blue-green algae, and actinomycetes, and cobalt levels in oceans often correlate with biological productivity. In the Baltic Sea, dissolved cobalt levels that are 1.0 ng/L near the surface, increase to 71.0 ng/L at a depth of 200 m (Brugmann 1988). The rise in dissolved cobalt is coincident with the onset of anoxic conditions and the presence of hydrogen sulfide, indicating that soluble bisulfide and polysulfide complexes may be present.

EPA analyzed cobalt in drinking water for the Third Unregulated Contaminant Monitoring Rule. Of 62,982 results, 833 were above the Minimum Reporting Level (1 µg/L) and 3 were above the reference concentration (70 µg/L) (EPA 2017). In Canadian finished drinking water, the median and maximum levels of cobalt were <2.0 and 6.0 µg/L (Meranger et al. 1981). Meranger et al. (1981) tested source water and drinking water in 71 municipalities across Canada and concluded that, in general, both surface water and groundwater used for drinking water supplies contain negligible amounts of cobalt. Greathouse and Craun (1978) analyzed 3,834 grab samples of household tap water from 35 geographical areas in the United States for 28 trace elements. Cobalt was found in 9.8% of the samples at concentrations ranging from 2.6 to 107 µg/L. It is not clear whether these higher levels could indicate that cobalt was picked up in the distribution system. In the earlier National Community Water Supply Study (2,500 samples), 62% of the samples contained <1 µg Co/L; the average and maximum cobalt concentrations were 2.2 and 19 µg/L, respectively (Smith and Carson 1981). Cobalt was not detected (detection limit 8 µg/L) in a 1982–

1983 survey of drinking water in Norway that covered 384 waterworks serving 70.9% of the Norwegian population (Flaten 1991).

The mean concentrations of cobalt in rain is around 0.03–1.7 µg/L, with levels generally ranging from 0.002 µg/L at Enewetak Atoll to about 2.9 µg/L in the Swansea Valley, Wales (Arimoto et al. 1985; Dasch and Wolff 1989; Hansson et al. 1988; Heaton et al. 1990; Helmers and Schrems 1995; Nimmo and Chester 1993; Nimmo and Fones 1997; Smith and Carson 1981). The highest recorded level of cobalt in precipitation was 68.9 µg/L in the vicinity of a nickel smelter in Monchegorsk in the Russian Arctic (Reimann et al. 1997). An analysis of rain in the Mediterranean and urban and coastal sites in northwest England showed that about 33–44% of the cobalt occurred as very stable dissolved organic complexes (Nimmo and Chester 1993; Nimmo and Fones 1997).

5.5.3 Sediment and Soil

Cobalt is the 33rd most abundant element in the earth's crust. Its average concentrations in the earth's crust and in igneous rocks are 20–25 and 18 mg/kg, respectively (Abbasi et al. 1989; Merian 1985; Smith and Carson 1981). Trace metals in soils may originate from parent rock or from anthropogenic sources, primarily fertilizers, pesticides, and herbicides. Most soils contain 1–40 mg cobalt/kg. The average cobalt concentration in U.S. soils is 7.2 mg/kg (Smith and Carson 1981). Soils containing <0.5–3 mg cobalt/kg are considered cobalt-deficient because plants growing on them have insufficient cobalt (<0.08–0.1 mg/kg) to meet the dietary requirements of cattle and sheep. Cobalt-deficient soils include the humus podzols of the southeastern United States, and the podzols, brown podzolic soils, and humus groundwater podzols in the northeastern parts of the United States. Podzols are generally coarse textured soils. The cobalt content of surface soils from 13 sites in the brown and dark brown soil zones of southwestern Saskatchewan ranged from 3.7 to 16.0 mg/kg and only in one case was the soil cobalt appreciably elevated above the corresponding parent material (Mermut et al. 1996). Fertilizers used in this agricultural area contained 0.12–102 mg Co/kg, with a median of 5.7 mg/kg.

Mean cobalt concentrations in surface soil from nine sites on two active volcanic islands off of Sicily ranged from 5.1 to 59.0 mg/kg (Bargagli et al. 1991). Soils near ore deposits, phosphate rocks, or ore smelting facilities, and soils contaminated by airport traffic, highway traffic, or other industrial pollution may contain much higher concentrations of cobalt; concentrations up to 800 mg/kg have been detected in such areas (Kloke et al. 1984; Smith and Carson 1981). Cobalt concentrations from 28 samples collected from surface deposits in the Big Deer and Blackbird Creek drainage basins in Idaho near the Blackbird Mine ranged from 26.5 to 7,410 mg/kg (ATSDR 1995). At a metal forge where metal alloys were ground for decades, cobalt concentrations were higher in soil, baghouse dust, and surface dust than in background

samples (Suh et al. 2019). Concentrations were 8,000 mg/kg in baghouse dust, 44.6-4503 mg/kg in surface dust, and 32.1-185 mg/kg in soil (Suh et al. 2019). The background concentration in soil was 11.2-15.6 mg/kg (Suh et al. 2019).

Soils around the large copper-nickel smelters in Sudbury, Ontario have been shown to contain high levels of cobalt. Fifty kilometers from the smelters, cobalt levels in surface soil were 19 mg/kg. These levels increased to 48 mg/kg at 19 km, 33 mg/kg at 10 km, and 42–154 mg/kg between 0.8 and 1.3 km from the smelter (Smith and Carson 1981). Soils around a cemented tungsten carbide tool grinding factory contained cobalt levels as high as 12,700 mg/kg, almost 2,000 times the average in U.S. soils (Abraham and Hunt 1995). However, neighborhood soils between 30 and 160 meters from the factory only contained 12–18 mg Co/kg.

Unpolluted freshwater sediment contains about the same levels of cobalt as does cobalt-sufficient soil, generally <20 mg/kg (Smith and Carson 1981). In the Hudson River Estuary, cobalt levels in suspended sediment were an order of magnitude higher than in bottom sediment (Gibbs 1994). This can be attributed to the finer grain size of suspended sediment or local sources. Cobalt levels in core samples (surface to 42 cm deep) from the Upper St. Lawrence Estuary were independent of depth, indicating the lack of any recent significant anthropogenic releases (Coakley et al. 1994).

5.5.4 Other Media

The cobalt content of plants depends on the plant, the cobalt content of the soil, and numerous environmental factors. The mean cobalt concentration reported for terrestrial plants was 0.48 μg/g, while the mean and median levels for freshwater vascular plants were 0.48 and 0.32 μg/g, respectively (Outridge and Noller 1991). The median cobalt level in freshwater vascular plants from polluted waters was about the same as in unpolluted waters, 0.37 μg/g, although extremely high levels of cobalt, up to 860 μg/g, was reported in one species, *Myriophyllum verticillatum*, from central Ontario lakes. Grasses normally contain 0.2–0.35 μg/g of cobalt, but grasses from cobalt-deficient regions contain only 0.02–0.06 μg/g of cobalt (Hamilton 1994). Durum wheat grown in southeastern Saskatchewan contained 0.01–0.02 mg/kg dry weight (Mermut et al. 1996). In view of the cobalt content of the soil and the fact that almost half of the cobalt in fertilizers used in the area was in a readily available form, the uptake of cobalt by wheat was negligible.

Cobalt concentrations have been reported in various aquatic animals and seabirds. Eel and a freshwater fish from three Dutch polder lakes contained 2.5–25.0 and 2.50–5.63 mg cobalt/kg wet weight, respectively (Badsha and Goldspink 1988). Muscle tissue of ocean fish and rock crabs caught near dump sites off New York City, New Haven, Connecticut, and Delaware Bay contained 10–40 and 16.0 μg/kg,

respectively (Greig and Jones 1976). In a study of the levels and distribution of 14 elements in oceanic seabirds, the concentration of cobalt, an essential element, appeared to be highly regulated, with over 80% of the body burden residing in the skeleton. The mean cobalt concentration in the livers of 11 seabird species ranged from 0.048 to 0.078 μg/g dry weight, and cobalt had the lowest coefficient of variation in the different species of the elements studied (Kim et al. 1998). In another study in Antarctica, mean cobalt levels in fish and amphipods were 0.11–0.14 and 1.01 μg/g dry weight, respectively, while those in the tissue of penguin and other sea birds ranged from 0.09 to 0.11 μg/g (Szefer et al. 1993). The concentration of cobalt in the tissue of 14 bluefin tuna caught by various commercial fishing vessels off Newfoundland was essentially the same, 0.01±0.004 μg/g (Hellou et al. 1992a). Similarly, in a broad survey of contaminant levels in nine species of fish and fiddler crabs from 11 sites in the lower Savannah River, Georgia and the Savannah National Wildlife Refuge, mean cobalt levels among different species and sites were statistically indistinguishable (Winger et al. 1990). These and other studies indicate that cobalt does not biomagnify up the food chain (Smith and Carson 1981). While high levels of cobalt were found in sediment from the Tigris River in Turkey and low levels in the water, cobalt was not detected in two species of fish, *Cyprinion macrostomus* and *Garra rufa* (Gumgum et al. 1994). Cobalt was detected in two other species of fish collected between 1995 and 1996 in the upper Sakarya river basin, Turkey. Cobalt concentrations ranged from 0.038 to 0.154 μg/g dry weight for *Cyprinus caprio* and from 0.045 to 0.062 μg/g dry weight for *Barbus plebejus* (Barlas 1999).

Some female birds sequester metals into their eggs under certain conditions, a phenomenon that may jeopardize the developing embryos. The geometric mean concentrations of cobalt in tern eggs collected from coastal New Jersey in 1971 and 1982 were 0.48 and 0.50 mg/kg, respectively. Unlike the levels of seven other common metals (e.g., mercury, cadmium, copper, lead, manganese, nickel, and zinc), the level of cobalt in tern eggs (and in the environment) showed no decline over the 11-year period (Burger and Gochfeld 1988).

The level of cobalt in most Canadian foods was low; items with the highest concentrations in this study were waffles (0.076 μg/g), corn cereal (0.074 μg/g), and potato chips (0.070 μg/g) (Dabeka and McKenzie 1995). Green leafy vegetables and fresh cereals were the richest sources of cobalt (0.2–0.6 μg/g dry weight), while dairy products, refined cereals, and sugar contained the least cobalt (0.1–0.3 μg/g dry weight) (Barceloux 1999). The levels of cobalt were determined in 50 different food items, mainly meat, fish, fruit, vegetables, pulses, and cereals on the Swedish market during the years 1983–1990 (Jorhem and Sundstrom 1993). Beef liver and seeds were fairly high in cobalt and fish, fruit, and root and leafy vegetables were under 0.01 μg cobalt/g fresh weight. The cobalt levels in μg/g fresh weight were highest in alfalfa seeds, 0.86; linseed, 0.56; milk chocolate, 0.34; dark chocolate, 0.24; white poppy seeds, 0.30;

blue poppy seeds, 0.15; soya beans, 0.084; green lentils, 0.054; and beef liver, 0.043. The cobalt content of 20 brands of alcoholic and nonalcoholic beer widely consumed in Spain ranged from 0.16 to 0.56 µg/L with a median of 0.39 µg/L (Camean et al. 1998). Cobalt, which was at one time added to beer to decrease over foaming of the head in glasses continuing residual soap, has been associated with cardiomyopathies (heart disease) in heavy beer drinkers; however, reported liver effects could have been the result of heavy alcohol consumption by the study population. Cobalt is present in various consumer products including cleaners, detergents, and soaps, which have resulted in dermatitis in sensitive individuals (Kokelj et al. 1994; Vilaplana et al. 1987).

The concentration of cobalt in U.S. coal averages about 5 mg/kg, levels in crude oil and fuel oil are 0.001–10 and 0.03–0.3 mg/kg, respectively, and those in gasoline are <0.1 mg/kg (Smith and Carson 1981). Cobalt levels were below the detection limit of 0.05 ppm dry weight in all but 1 of 26 samples of composted yard waste, sewage sludge, and municipal solid waste samples nationwide in 1991. The one positive sample of composted yard waste contained 1.53 ppm of cobalt (Lisk et al. 1992).

5.6. GENERAL POPULATION EXPOSURE

Exposure of the general population to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. In general, intake from food is much greater than from drinking water, which in turn, is much greater than from air. From the monitoring data available, the mean concentration of cobalt in ambient air in the United States is less than 0.002 µg/m^3 (EPA 2020). However, levels may be orders of magnitude higher in source areas. Therefore, exposure to cobalt in air will vary substantially from non-source areas to areas with cobalt-related industries.

Similarly, the median cobalt concentration in U.S. drinking water is <2.0 µg/L; however, values as high as 107 µg/L have been reported in surveys of water supplies (Smith and Carson 1981). Therefore, exposure from drinking water may vary considerably from one location to another. In Canada, the daily cobalt intake of the average adult from drinking water is ≤2.6 µg; this could increase to 10 µg for those living in areas with the highest cobalt levels (Meranger et al. 1981).

General population exposure to cobalt from food is highly variable and normally higher than intake from drinking water. Most of the cobalt ingested is inorganic; vitamin B_{12}, which occurs almost entirely in food of animal origin, constitutes only a very small fraction of cobalt intake. The cobalt intake in food has been estimated to be 5.0–40.0 µg/day (Jenkins 1980). The daily cobalt intake, including food, water, and beverages of two men that were followed for 50 weeks was much higher, 310 and 470 µg (Smith and Carson 1981). The estimated average daily cobalt intake from the diet in Canada was 11 µg/day; the intake varied from 4 to 15 µg/day between the various age/sex groups (Barceloux 1999; Dabeka and

McKenzie 1995). The contributions of various food groups to cobalt intake in this study were (category, contribution of dietary intake): bakery goods and cereals, 29.8%; vegetables, 21.9%; beverages, 9.8%; milk and milk products, 9.4%; meat and poultry, 9.1%; soups, 6.4%; fruit and fruit juices, 5.0%; sugar and candies, 2.8%; fish, 2.7%; fats and oils, 2.2%; and miscellaneous, 1.1%. The average daily intake of cobalt in France was estimated to be 29 μg/day (Biego et al. 1998). In this study, foods were divided into nine categories. The foods accounting for the greatest contributions of cobalt intake were milk and dairy products, fish-crustaceans, and condiments-sugar oil, respectively, contributing 32, 20, and 16% to the daily intake. The U.S. Department of Agriculture (USDA) conducted a special exploratory study in 1985–1986 to determine the concentration of trace metals in tissue of health livestock and poultry randomly selected from those slaughtered. Between 0.6 and 5.9% of samples in the 11 production classes had levels of cobalt that exceeded the lowest reliable quantitation level of 0.15 ppm (0.15 mg/kg) and the mean of positive samples ranged from 0.20 to 0.23 ppm in all classes but heifer/steer, which had a level of 1.92 ppm (Coleman et al. 1992). Cobalt, which had been added to beer to decrease over foaming, was associated with cardiomyopathies (heart disease) in heavy beer drinkers; indications of liver effects could have been the result of heavy alcohol consumption. However, according to a recent Spanish study, the low levels of cobalt presently found in beer do not make a significant contribution to the total cobalt intake in heavy beer drinkers (Camean et al. 1998).

Since cobalt is used in such a wide variety of applications, the general public may come into contact with cobalt in consumer goods. In a study of cobalt release and skin deposition from short, repetitive contact with metallic items mimicking daily contact, average skin doses were 0.7-1.1 μg/cm^2 (Midander et al. 2014). Midander et al. (2014) concluded that short, repetitive contact with metallic items could be harmful. Alinaghi et al. (2019) found that leather and jewelry were clinically relevant exposure sources to 475 cobalt-allergic patients in Denmark from 2002 to 2017. Exposure sources included leather shoes, gloves, furniture, clothing, other leather items, jewelry, tools, cutting oil, mobile phones, chemicals, cement, and paints. However, the sources of most cases (84.8%) of cobalt allergy were unknown (Alinaghi et al. 2019). Bregnbak et al. (2015b) also found that leather was the most frequent exposure source causing dermatitis after non-occupational use of cobalt-containing tools. Cobalt was detected in several jewelry and clothing items in Korea, including belts, bracelets, earrings, rings, hair pins, necklaces, watches, buttons, and zippers (Cheong et al. 2014). Cases of allergic contact dermatitis in several people have been associated with leather furniture containing 800-1250 ppm cobalt (Bregnbak et al. 2017; Thyssen et al. 2013). Cobalt has been quantified at concentrations of 0.1-0.2 ppm in several household products in Italy, including heavy duty powders, hand wash powders, laundry tables, heavy

duty liquids, machine and hand wash liquids, fine wash liquids, dishwashing liquids, and liquid and powder cleaners (Basketter et al. 2003).

Laptop computers may release cobalt when in contact with skin, and release rates from an HP laptop into artificial sweat were as much as 0.87 ng/cm^2/hr from the wrist support and as much as 0.07 ng/cm^2/hr from the lid (Midander et al. 2016). Cobalt was detected in 6% of 31 laptops from 5 different brands tested (Midander et al. 2016).

Since cobalt and other heavy metals have been used on hand-painted china, a study was conducted to see whether these metals are released into food under acidic conditions. Forty-six samples of porcelain dinnerware from Europe or Asia that were manufactured before the mid-1970s and had hand-painted designs over the glaze were filled with 4% acetic acid to within 7 mm of the rim and analyzed after 24 hours (Sheets 1998). Of these, 36 samples released <0.02 µg/mL of cobalt and 10 released 0.020– 2.9 µg/mL. High levels of blood cobalt were recorded in the case of lead poisoning in an adult woman by a Greek jug, which was likely released from the underglaze dye due to degradation caused by juice (Selden et al. 2007). The Food and Drug Administration (FDA) has not established dinnerware extraction limits for cobalt.

People may also be exposed to cobalt in cosmetic products. Cobalt levels in eye shadows range from less than 0.5-253.33 µg/g, with products from China having the highest concentrations (Corazza et al. 2009); (Omolaoye et al. 2010). Sainio et al. (2000) found that eye shadows containing more than 10 µg/g of cobalt were mainly darker pigmented colors like brown, gray, and black. Face paints for both adults and children produced in China, Spain, the UK, and the U.S. were analyzed and found to contain up to 5.5 µg/g cobalt (Corazza et al. 2009). Lipstick contained concentrations up to 1.30 µg/g (Corazza et al. 2009; Liu et al. 2013; Sneyers et al. 2009). Concentrations of cobalt in skin creams ranged from 0.00013-2.2 µg (Bocca et al. 2007; Onwordi et al. 2011; Sneyers et al. 2009).

Higher urinary cobalt concentrations were related to older housing built after 1990 (Shiue and Bramley 2015). Smokers may be exposed to cobalt in mainstream smoke, but the level of exposure has not been assessed (Barceloux 1999).

Urinary cobalt has been measured in the U.S. general population during NHANES 1999-2018, blood cobalt was measured in 2015-2018, and urinary cobalt (creatinine corrected) was measured in 1999-2018 (CDC 2022). Table 5-7 shows the geometric mean and selected percentiles of urinary cobalt in the U.S. population surveyed for NHANES 2011-2012, 2013-2014, 2015-2016, and 2017-2018. Table 5-8 shows the geometric mean and selected percentiles of blood cobalt in the U.S. population from NHANES 2015-2016 and 2017-2018. Table 5-9 shows the geometric mean and selected percentiles of urinary cobalt

(creatinine corrected) in the U.S. population surveyed for NHANES 2011-2012, 2013-2014, 2015-2016, and 2017-2018.

Table 5-7. Geometric Mean and Selected Percentiles of Urinary Cobalt (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2022)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total							
	2011-2012	.326 (.309-.344)	.323 (.306-.347)	.543 (.510-.577)	.860 (.800-.979)	1.27 (1.09-1.45)	2,504
	2013-2014	.391 (.373-.411)	.408 (.382-.435)	.687 (.662-.713)	1.04 (.976-1.09)	1.35 (1.23-1.48)	2,664
	2015-2016	.414 (.394-.435)	.434 (.415-.455)	.687 (.658-.725)	1.06 (.983-1.12)	1.53 (1.34-1.71)	3,061
	2017-2018	.424 (.398-.451)	.437 (.412-.451)	.710 (.673-.756)	1.16 (1.07-1.27)	1.61 (1.37-1.83)	2,808
Age Group							
3-5 years	2015-2016	.426 (.397-.456)	.466 (.410-.512)	.739 (.662-.833)	1.08 (.947-1.25)	1.55 (1.23-2.07)	486
	2017-2018	.472 (.410-.542)	.526 (.448-.627)	.854 (.749-.917)	1.22 (1.04-1.52)	1.64 (1.34-1.78)	403
6-11 years	2011-2012	.397 (.356-.442)	.452 (.361-.510)	.704 (.616-.772)	1.00 (.846-1.38)	1.42 (1.00-1.78)	399
	2013-2014	.447 (.411-.487)	.479 (.408-.522)	.789 (.718-.877)	1.05 (.991-1.33)	1.55 (1.14-1.84)	402
	2015-2016	.534 (.494-.577)	.599 (.525-.636)	.886 (.773-.948)	1.20 (.992-1.40)	1.63 (1.20-2.05)	379
	2017-2018	.519 (.459-.586)	.559 (.474-.642)	.877 (.787-.942)	1.45 (1.18-1.83)	1.88 (1.57-2.21)	333
12-19 years	2011-2012	.416 (.358-.484)	.429 (.341-.527)	.700 (.622-.806)	1.12 (.960-1.30)	1.56 (1.16-1.96)	390
	2013-2014	.549 (.462-.653)	.602 (.491-.701)	.936 (.783-1.05)	1.43 (1.08-1.75)	1.76 (1.49-3.07)	451
	2015-2016	.571 (.527-.620)	.604 (.535-.659)	.892 (.840-1.08)	1.48 (1.32-1.74)	1.92 (1.57-2.23)	402
	2017-2018	.516 (.488-.545)	.583 (.514-.656)	.879 (.835-.948)	1.33 (1.20-1.39)	1.49 (1.39-1.65)	364
20 years and older	2011-2012	.307 (.288-.327)	.308 (.289-.328)	.491 (.457-.534)	.800 (.695-.940)	1.16 (.984-1.36)	1,715
	2013-2014	.367 (.349-.386)	.382 (.357-.410)	.647 (.614-.673)	.930 (.882-1.04)	1.23 (1.17-1.34)	1,811
	2015-2016	.385 (.364-.408)	.403 (.379-.427)	.638 (.599-.666)	.949 (.877-1.06)	1.41 (1.21-1.66)	1,794
	2017-2018	.401 (.371-.433)	.409 (.384-.438)	.650 (.619-.702)	1.08 (.981-1.20)	1.61 (1.27-1.88)	1,708
Sex							
Males	2011-2012	.317 (.299-.336)	.316 (.293-.339)	.496 (.452-.547)	.715 (.659-.798)	0.963 (.858-1.03)	1,262
	2013-2014	.380 (.355-.407)	.414 (.374-.452)	.641 (.604-.684)	.883 (.820-.951)	1.11 (1.04-1.26)	1,318
	2015-2016	.397 (.376-.420)	.434 (.405-.466)	.651 (.609-.692)	.860 (.815-.954)	1.08 (.960-1.19)	1,524
	2017-2018	.419 (.375-.468)	.427 (.388-.466)	.679 (.611-.738)	1.03 (.906-1.15)	1.47 (1.20-1.88)	1,381

Table 5-7. Geometric Mean and Selected Percentiles of Urinary Cobalt (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2022)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Females	2011-2012	.335 (.310-.361)	.340 (.308-.382)	.591 (.554-.643)	1.07 (.891-1.20)	1.49 (1.30-1.74)	1,242
	2013-2014	.402 (.374-.432)	.398 (.366-.438)	.741 (.701-.789)	1.16 (1.06-1.23)	1.5 (1.36-1.75)	1,346
	2015-2016	.432 (.397-.469)	.433 (.391-.489)	.752 (.675-.865)	1.33 (1.20-1.43)	1.82 (1.54-2.13)	1,537
	2017-2018	.428 (.391-.469)	.446 (.410-.487)	.760 (.694-.835)	1.26 (1.19-1.33)	1.61 (1.47-1.79)	1,427
Race/ethnicity							
Mexican American	2011-2012	.350 (.322-.381)	.350 (.307-.377)	.550 (.490-.598)	.891 (.721-1.18)	1.41 (1.14-2.08)	317
	2013-2014	.415 (.378-.456)	.439 (.400-.482)	.686 (.610-.766)	.918 (.866-1.09)	1.15 (1.06-1.56)	453
	2015-2016	.469 (.431-.511)	.488 (.431-.558)	.777 (.688-.852)	1.21 (1.01-1.42)	1.81 (1.32-2.14)	585
	2017-2018	.431 (.397-.468)	.437 (.410-.474)	.708 (.626-.815)	1.14 (.997-1.27)	1.39 (1.23-1.70)	435
Non-Hispanic black	2011-2012	.340 (.311-.373)	.333 (.304-.358)	.519 (.489-.576)	.909 (.790-.986)	1.44 (1.06-1.60)	669
	2013-2014	.468 (.410-.535)	.471 (.402-.561)	.796 (.691-.877)	1.26 (1.03-1.39)	1.5 (1.35-1.67)	581
	2015-2016	.461 (.422-.503)	.478 (.436-.513)	.740 (.660-.845)	1.20 (.956-1.40)	1.52 (1.34-1.85)	671
	2017-2018	.470 (.443-.499)	.476 (.430-.514)	.718 (.657-.806)	1.26 (1.04-1.55)	1.86 (1.29-2.35)	639
Non-Hispanic white	2011-2012	.320 (.295-.348)	.320 (.296-.357)	.543 (.485-.591)	.858 (.750-.995)	1.2 (1.03-1.35)	820
	2013-2014	.374 (.349-.401)	.387 (.345-.429)	.681 (.638-.723)	1.02 (.930-1.10)	1.34 (1.21-1.56)	985
	2015-2016	.402 (.374-.432)	.422 (.386-.454)	.675 (.627-.734)	1.00 (.938-1.11)	1.49 (1.24-1.71)	924
	2017-2018	.411 (.372-.454)	.428 (.391-.446)	.702 (.640-.759)	1.11 (.958-1.33)	1.57 (1.31-1.89)	918
All Hispanic	2011-2012	.338 (.321-.357)	.326 (.306-.350)	.530 (.490-.583)	.891 (.763-1.14)	1.41 (1.10-1.81)	573
	2013-2014	.412 (.384-.442)	.442 (.409-.481)	.674 (.631-.731)	.964 (.891-1.07)	1.2 (1.09-1.36)	701
	2015-2016	.440 (.417-.465)	.465 (.431-.514)	.718 (.662-.795)	1.16 (.991-1.34)	1.69 (1.34-2.03)	982
	2017-2018	.441 (.420-.463)	.451 (.427-.478)	.742 (.696-.829)	1.20 (1.07-1.30)	1.41 (1.31-1.70)	676
Asian	2011-2012	.317 (.282-.357)	.323 (.300-.355)	.519 (.445-.634)	.968 (.723-1.58)	1.78 (.980-2.31)	353
	2013-2014	.362 (.315-.416)	.354 (.312-.434)	.653 (.578-.789)	1.05 (.854-1.25)	1.57 (1.09-2.26)	292
	2015-2016	.376 (.334-.424)	.365 (.342-.438)	.610 (.533-.698)	.990 (.734-1.37)	1.44 (.990-2.31)	332
	2017-2018	.416 (.386-.449)	.462 (.399-.508)	.759 (.655-.809)	1.15 (.966-1.37)	1.64 (1.12-2.18)	365

Table 5-8. Geometric Mean and Selected Percentiles of Blood Cobalt (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2022)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)[a]				Sample size
			50th	75th	90th	95th	
Total	2015-2016	Not calculated	<LOD	<LOD	.700 (.540-.900)	1.08 (.750-1.49)	3,442
	2017-2018	Not calculated	<LOD	<LOD	.460 (<LOD-.600)	.670 (.540-.860)	3,518
Age Group							
40-59 years	2015-2016	Not calculated	<LOD	<LOD	.650 (.470-.970)	1.07 (.710-1.57)	1,719
	2017-2018	Not calculated	<LOD	<LOD	.450 (<LOD-.560)	.620 (.480-.950)	1,585
60+ years	2015-2016	Not calculated	<LOD	<LOD	.750 (.550-.940)	1.13 (.790-1.49)	1,723
	2017-2018	Not calculated	<LOD	<LOD	.490 (<LOD-.720)	.720 (.540-.990)	1,933
Sex							
Male	2015-2016	Not calculated	<LOD	<LOD	.620 (.460-.880)	1.07 (.680-1.58)	1,656
	2017-2018	Not calculated	<LOD	<LOD	.470 (<LOD-.580)	.670 (.560-.740)	1,716
Female	2015-2016	Not calculated	<LOD	<LOD	.740 (.580-.940)	1.08 (.800-1.43)	1,786
	2017-2018	Not calculated	<LOD	<LOD	.460 (<LOD-.640)	.670 (.510-.970)	1,802
Race/ethnicity							
Mexican American	2015-2016	Not calculated	<LOD	<LOD	.570 (.460-.700)	.750 (.550-1.34)	589
	2017-2018	Not calculated	<LOD	<LOD	.450 (<LOD-.580)	.660 (.490-.730)	439
Non-Hispanic Black	2015-2016	Not calculated	<LOD	<LOD	.490 (<LOD-.740)	.870 (.690-1.10)	714
	2017-2018	Not calculated	<LOD	<LOD	.410 (<LOD-.500)	.570 (.430-1.00)	817
Non-Hispanic White	2015-2016	Not calculated	<LOD	<LOD	.750 (.550-1.07)	1.20 (.790-1.57)	1,195
	2017-2018	Not calculated	<LOD	<LOD	.500 (.420-.640)	.700 (.560-.970)	1,271
All Hispanic	2015-2016	Not calculated	<LOD	<LOD	.550 (.430-.690)	.760 (.630-1.06)	1,062
	2017-2018	Not calculated	<LOD	<LOD	<LOD	.590 (.450-.730)	774
Asian	2015-2016	Not calculated	<LOD	<LOD	.800 (.600-.980)	1.03 (.820-1.44)	368
	2017-2018	Not calculated	<LOD	<LOD	.450 (.410-.490)	.600 (.490-.650)	485

[a]The limit of detection for 2015-2016 and 2017-2018 is 0.41 µg/L.
LOD = limit of detection

Table 5-9. Geometric Mean and Selected Percentiles of Urinary Cobalt (creatinine corrected) (in µg/g of creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2022)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total							
	2011-2012	.370 (.349-.391)	.347 (.330-.371)	.557 (.513-.593)	.880 (.768-1.03)	1.29 (1.12-1.46)	2,502
	2013-2014	.452 (.437-.466)	.443 (.427-.454)	.656 (.625-.688)	.969 (.920-1.03)	1.31 (1.18-1.47)	2,663
	2015-2016	.465 (.447-.484)	.444 (.421-.464)	.682 (.636-.722)	1.07 (.999-1.16)	1.39 (1.24-1.52)	3,058
	2017-2018	.462 (.437-.490)	.435 (.410-.463)	.697 (.644-.733)	1.12 (1.03-1.20)	1.55 (1.33-1.81)	2,806
Age Group							
3-5 years	2015-2016	.980 (.919-1.05)	.952 (.875-1.01)	1.35 (1.22-1.48)	1.94 (1.65-2.10)	2.45 (2.03-2.98)	485
	2017-2018	.974 (.916-1.04)	.978 (.916-1.05)	1.31 (1.24-1.41)	1.91 (1.45-2.28)	2.29 (1.91-2.81)	403
6-11 years	2011-2012	.567 (.535-.602)	.571 (.526-.611)	.778 (.713-.834)	1.19 (.974-1.30)	1.38 (1.10-1.67)	398
	2013-2014	.667 (.614-.725)	.646 (.593-.704)	.914 (.853-.986)	1.26 (1.09-1.40)	1.57 (1.24-2.13)	402
	2015-2016	.757 (.701-.817)	.732 (.658-.785)	1.03 (.957-1.11)	1.37 (1.17-1.50s)	1.7 (1.28-2.64)	379
	2017-2018	.724 (.667-.787)	.708 (.653-.755)	.966 (.873-1.04)	1.42 (1.17-1.75)	1.82 (1.29-2.69)	332
12-19 years	2011-2012	.398 (.349-.455)	.373 (.316-.441)	.585 (.454-.700)	.832 (.688-1.09)	1.26 (.830-2.77)	390
	2013-2014	.497 (.463-.534)	.480 (.446-.525)	.692 (.597-.769)	.920 (.819-1.10)	1.3 (1.09-1.61)	451
	2015-2016	.534 (.504-.565)	.508 (.455-.552)	.799 (.697-.939)	1.16 (1.05-1.42)	1.5 (1.33-1.78)	402
	2017-2018	.465 (.437-.495)	.423 (.392-.455)	.723 (.596-.780)	1.00 (.848-1.13)	1.23 (1.05-1.38)	364
20 years and older	2011-2012	.349 (.330-.369)	.327 (.300-.341)	.508 (.467-.552)	.803 (.711-.982)	1.24 (1.10-1.50)	1,714
	2013-2014	.428 (.412-.444)	.417 (.390-.441)	.607 (.580-.643)	.929 (.853-.994)	1.27 (1.10-1.46)	1,810
	2015-2016	.420 (.402-.439)	.404 (.384-.426)	.582 (.551-.616)	.900 (.809-1.03)	1.2 (1.05-1.41)	1,792
	2017-2018	.425 (.397-.454)	.397 (.367-.432)	.591 (.544-.665)	1.02 (.892-1.16)	1.46 (1.20-1.81)	1,707
Sex							
Males	2011-2012	.297 (.280-.315)	.276 (.254-.294)	.426 (.397-.456)	.637 (.564-.750)	0.865 (.748-1.17)	1,261
	2013-2014	.379 (.362-.398)	.368 (.344-.390)	.529 (.493-.560)	.758 (.689-.852)	1.02 (.871-1.29)	1,317
	2015-2016	.377 (.360-.395)	.348 (.334-.379)	.526 (.483-.550)	.839 (.746-.913)	1.08 (.966-1.18)	1,524
	2017-2018	.390 (.363-.420)	.360 (.334-.392)	.563 (.508-.593)	.924 (.799-1.08)	1.33 (1.11-1.59)	1,380
Females	2011-2012	.455 (.418-.496)	.433 (.407-.466)	.660 (.600-.729)	1.10 (.900-1.36)	1.54 (1.28-1.84)	1,241
	2013-2014	.534 (.515-.553)	.532 (.502-.549)	.774 (.733-.816)	1.12 (.991-1.27)	1.48 (1.27-1.77)	1,346
	2015-2016	.568 (.540-.598)	.533 (.511-.563)	.799 (.760-.869)	1.24 (1.16-1.40)	1.7 (1.48-1.98)	1,534
	2017-2018	.544 (.513-.577)	.498 (.468-.543)	.815 (.764-.866)	1.22 (1.14-1.36)	1.71 (1.45-1.98)	1,426

Race/ethnicity							
Mexican American	2011-2012	.394 (.357-.435)	.374 (.322-.400)	.576 (.531-.637)	1.02 (.877-1.24)	1.5 (.988-2.02)	317
	2013-2014	.474 (.449-.500)	.448 (.425-.473)	.669 (.610-.721)	.971 (.888-1.03)	1.28 (1.03-1.51)	453
	2015-2016	.512 (.479-.548)	.488 (.464-.533)	.771 (.690-.850)	1.18 (1.01-1.40)	1.5 (1.37-1.79)	584
	2017-2018	.465 (.432-.500)	.437 (.378-.497)	.708 (.662-.786)	1.14 (1.00-1.25)	1.45 (1.19-1.57)	433
Non-Hispanic black	2011-2012	.265 (.248-.282)	.244 (.222-.267)	.401 (.342-.457)	.645 (.559-.816)	1.02 (.737-1.41)	669
	2013-2014	.356 (.332-.382)	.337 (.315-.377)	.545 (.490-.624)	.841 (.754-.952)	1.08 (.930-1.22)	581
	2015-2016	.366 (.347-.386)	.342 (.328-.377)	.556 (.504-.595)	.799 (.696-.972)	1.07 (.929-1.24)	669
	2017-2018	.355 (.337-.375)	.330 (.295-.351)	.576 (.500-.611)	.885 (.798-1.02)	1.28 (.979-1.61)	639
Non-Hispanic white	2011-2012	.387 (.360-.417)	.365 (.336-.400)	.574 (.513-.615)	.860 (.749-1.09)	1.29 (1.04-1.57)	818
	2013-2014	.461 (.442-.480)	.447 (.430-.469)	.669 (.613-.703)	.987 (.912-1.13)	1.32 (1.19-1.61)	984
	2015-2016	.475 (.453-.497)	.457 (.427-.471)	.686 (.629-.746)	1.07 (.972-1.20)	1.41 (1.19-1.63)	924
	2017-2018	.476 (.439-.517)	.446 (.415-.473)	.700 (.605-.760)	1.14 (1.02-1.33)	1.64 (1.29-1.98)	918
All Hispanic	2011-2012	.379 (.351-.409)	.361 (.322-.384)	.572 (.520-.626)	.944 (.809-1.15)	1.33 (1.13-1.91)	573
	2013-2014	.460 (.444-.475)	.448 (.429-.464)	.663 (.619-.703)	.952 (.888-1.00)	1.17 (1.03-1.35)	701
	2015-2016	.497 (.468-.527)	.465 (.436-.503)	.748 (.669-.837)	1.16 (1.04-1.28)	1.46 (1.35-1.70)	981
	2017-2018	.475 (.450-.503)	.454 (.423-.498)	.719 (.671-.781)	1.13 (1.02-1.24)	1.45 (1.25-1.57)	674
Asian	2011-2012	.424 (.378-.475)	.386 (.329-.457)	.659 (.531-.785)	1.18 (.907-1.51)	1.61 (1.14-2.72)	353
	2013-2014	.567 (.516-.624)	.540 (.482-.567)	.814 (.670-.931)	1.38 (1.07-1.97)	2.09 (1.39-3.78)	292
	2015-2016	.514 (.473-.559)	.475 (.421-.548)	.736 (.624-.885)	1.30 (1.11-1.57)	1.66 (1.44-2.12)	332
	2017-2018	.544 (.504-.588)	.511 (.450-.569)	.830 (.768-.882)	1.39 (1.04-1.70)	1.86 (1.40-2.28)	365

In a study of pregnant women in Puerto Rico from 2011-2017, the mean urinary concentration of cobalt was 1.0 ng/ml and the mean blood concentration was 0.34 ng/ml (Ashrap et al. 2020). Compared to NHANES data, median concentrations of cobalt were two-fold higher (Ashrap et al. 2020). Smoking and consuming milk was associated with significantly higher urinary cobalt concentrations, while no predictors for blood cobalt were reported (Ashrap et al. 2020). In China, cobalt was detectable in 27.2% of both maternal and umbilical cord samples, and the median concentration in maternal and cord blood was below the detection limit (1.1 ng/g) (Hu et al. 2015). Cobalt concentrations in maternal serum of Polish mothers with fetuses with neonatal abnormalities was 0.52-0.61 µg/L and 0.24-0.27 µg/L in amniotic fluid (Kocylowski et al. 2019).

Junque et al. (2020) analyzed urinary cobalt in 4-year-old children in a heavily industrialized zone in Spain. Higher urinary cobalt was associated with consumption of sweets, traffic pollution, and iron deficiency anemia. Cao et al. (2014) found that children living near the largest coking plant in China had mean blood cobalt levels of 1.12 µg/dL. Mean cobalt concentrations were measured in the soil (12.0 mg/kg), dust (8.85 mg/kg), ambient air (0.03 µg/m3), drinking water (0.14 µg/m3), vegetables (0.11 mg/kg), and staple food (0.22 mg/kg) (Cao et al. 2014). Children may also be exposed to cobalt in costume jewelry, detergents, and cosmetics (Brandao and Gontijo 2012).

Dabeka and McKenzie (1995) estimated that the dietary cobalt intake by Canadian children ages 1–19 ranged from 7 to 14 µg/day. Milk constitutes a larger part of children's diets than that of adults, and infants may consume infant formula. Cobalt concentrations ranging from 0.3 to 0.8 ng/g in cow's milk were reported by Iyengar (Iyengar 1982). The levels of cobalt in human breast milk from Nigeria, Zaire, Guatemala, Hungary, Philippines, and Sweden ranged from 150 (Hungary) to 1,400 ng/g (Philippines), median 320 ng/g (Nriagu 1992). Garg et al. (1993) reported much lower cobalt levels in three samples of human breast milk in India, 2.42 ng/g, and reported a cobalt concentration of 5.07 ng/g in cow's milk in India. Dabeka (1989) determined cobalt levels in various infant formulas. Milk-based infant formulas and evaporated milk contained <1 ng/g of cobalt on a "ready-to-use" basis. Milk-based formulas with added iron contained about twice the cobalt as those with no added iron and soy-based formulas contained about 5 times more cobalt. Using literature values of cobalt in food, Dabeka also estimated that infants 0–12 months old ingest an average of 0.52 µg Co/kg-day (3.93 µg/day) from food and water and that for an infant, 0–12 months old, the total dietary cobalt intake would range from 0.42 µg/kg-day (3.39 µg/day) for a breast or milk-based formula fed infant to 1.0 µg/kg-day (7.33 µg/day) for an infant fed soy-based formula powder. In a 1967 study of the total dietary intake of some trace elements, excluding drinking water, of institutionalized children aged 9–12 in 28 U.S. cities, cobalt intake ranged from 0.297 to 1.767 mg/day with a mean value of 1.024 mg/day (Murthy et al. 1971).

5.7. POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in the hard metal industry (tool production, grinding, etc.) and industries such as coal mining, metal mining, smelting, and refining, cobalt dye painters, and cobalt chemical production are exposed to higher levels of cobalt via airborne dust and direct contact. Kennedy et al. (2017) estimates that through 2008, up to 14,348 individuals in the U.S. worked in the hard metal industry. Exposure to cobalt during the wet grinding of hard metal tools is especially high when local exhausts are not in use (Sesana et al. 1994).

Several studies of cobalt concentrations in air in the hard metal industry have been reported. The concentrations of cobalt in the air of hard metal manufacturing, welding, and grinding factories may range from 1 to 300 μg/m^3, compared to normal atmospheric levels of 0.4–2.0 ng/m^3 (Burr and Sinks 1989; Haddad and Zikovsky 1985; Koponen et al. 1982; Lichtenstein et al. 1975). The maximum OSHA permissible level is 100 μg/m^3. The concentration of cobalt in the dust of an electric welding factory was 4.2 μg/g compared to its normal dust level of 0.1–1.0 μg/g (Baumgardt et al. 1986). The higher rate of exposure to cobalt for occupational groups is also reflected in the higher cobalt content in tissues and body fluids of living and deceased workers in this group. The levels of cobalt in the urine of workers in the hard metal industry varied with the levels of cobalt concentration in the working atmosphere. At a concentration of 0.09 mg/m^3, the urinary excretion of cobalt exceeded normal values by orders of magnitude. When the cobalt concentration in the working atmosphere was 0.01 mg/m^3 or lower, urinary cobalt excretion was 4–10 times higher than normal level (Alexandersson 1988; Scansetti et al. 1985). At high exposure levels, the cobalt concentration in blood was 20 times higher than normal; in the low exposure group, it was only slightly higher than in the control group (Alexandersson 1988). An extensive survey of workers potentially exposed to cobalt in the Bergamo Province in northern Italy in 1991 identified 403 exposed workers in different production areas (Mosconi et al. 1994b). Significant cobalt exposure occurred especially for operators working in diamond abrasive production, particularly in mold filling and sintering units where occupational limits were regularly exceeded. Exposure in tool production, tool sharpening, and hard metal alloy filling is much more restrained.

In the hard metal industry in Japan, Kumagai et al. (1996) found that mean 8-hour time weighted averages (TWAs) of airborne cobalt were >50 μg/m^3 for workers involved in powder preparation (shift rotation that included varied work hours which were less than full time), powder preparation (full-time), rubber press, and shaping operations; mean atmospheric concentrations were 459, 147, 339, and 97 μg/m^3, respectively. Workers involved in the manufacture and maintenance of hard metal and Stellite^{TM} blades in Finland were exposed to breathing zone cobalt concentrations ranging from 2 to 240 μg/m^3, with a geometric mean of 17 μg/m^3 (Linnainmaa et al. 1996). The average proportion of water-soluble cobalt in airborne

cobalt was 68% (range 14–100%). Wet grinding was not sufficient to adequately control cobalt levels and coolant cobalt levels were high. In a group of 12 factories in Italy in which 48 workers who had been exposed to cobalt in operations such as sharpening with diamond grinding stones were tested; the mean concentration of cobalt in air was 21.2 and 137.7 μg/m^3 (Permissible exposure limit [PEL]-TWA 100 μg/m^3) in work places with and without dust ventilation, respectively (Imbrogno and Alborghetti 1994).

Measurements of hair, blood, and urine samples of non-exposed males, steel mill production workers, and steel mill quality control workers aged 22-55 years old showed that cobalt concentrations in biological samples of exposed workers are significantly higher than non-exposed individuals, indicating different exposure extent (Afridi et al. 2009). Horng et al. (2003) also found that mean urinary cobalt levels were significantly higher in steel plant production workers (8.18±2.73 μg/L) and quality control workers (7.39±1.26 μg/L) than in the control population (0.92±8.13 μg/L). Mean urinary cobalt increased 1.5-3 fold in workers during a shift in a digital video cassette manufacturing plant (Fujio et al. 2009). Cobalt concentrations then decreased before the next shift supporting that the results were occupationally derived. These urinary concentrations also had a significant correlation with cobalt oxide measurements in the air (Fujio et al. 2009). A study in the United States determined the concentrations of trace metals in seminal plasma in industrial workers in a petroleum refinery, smelter, and chemical plant as compared with those of hospital workers (control group). There were four groups each with 50 adult men. The mean cobalt concentrations (μg/dL), including standard errors, were determined to be 31±2 (hospital workers), 25±0.8 (metal ore smelter workers), 19±0.6 (petroleum refinery workers), and 22±1 (chemical workers) (Dawson et al. 2000). Ferdenzi et al. (1994) obtained a correlation between Friday TWA air cobalt levels and Friday end-of-shift urine levels among women in the powder sintering industry. Median urinary cobalt concentrations were 25 μg/L (range: 1– 51 μg/L) and 29 (3–159 μg/L), on Monday and Friday before the shift, respectively, and 85 μg/L (6–505 μg/L) on Friday after the shift. Imbrogno and Alborghetti (1994) evaluated the levels of occupational exposure to cobalt during dry and/or wet hard metal sharpening. The mean urine cobalt level in the workers in 12 factories was found to range from 0 to 40.3 μg/L and the maximum was 86 μg/L. The average urinary cobalt level among workers using wet/mixed sharpening methods was 4 times higher than those using dry sharpening methods; 21.38 μg/L as compared to 5 μg/L, respectively. Gallorini et al. (1994) found that the ratio of inorganic to organic cobalt in the urine of hard metal workers was 2.3 compared to 1.01 in controls; the ratio was constant over the range of urinary cobalt levels analyzed (180–1,254 μg/L). Exposure to cobalt during the wet grinding of hard metal tools (Widia tools) used in the wood industry produced exposure to cobalt above the PEL-TWA of 100 μg/m^3 (Sesana et al. 1994). However, exhausts added to reduce breathing zone concentrations near the grinding wheels were shown to substantially reduce exposure levels. In the

processing department of a small company producing carbide tip saw blades for the woodworking industry, area air sampling showed that exposure levels were low in all departments except tip grinding processes. Wet and dry tip grinding areas were assessed for total airborne cobalt and contained 55 and 21 μg/m^3 of cobalt, respectively (Stebbins et al. 1992). For the method collecting respirable particles, cobalt levels ranged from 2 to 28 μg/m^3. Wet grinding is a traditional method for controlling dust during grinding. However, some coolants may contain significant concentrations of cobalt (in this case, 61–538 mg/mL) that can contribute to exposure during grinding (Stebbins et al. 1992). Among cobalt blue dye plate painters in a porcelain factory in Denmark, the blood and urine cobalt levels were, respectively, 2–4 and 5–15 times higher than in control groups (Raffin et al. 1988). Similarly, lungs taken from deceased, occupationally exposed workers also had higher levels of cobalt than lungs from control groups. Lungs of deceased hard metal industry workers in Sweden contained 2.5–4 times higher levels of cobalt than control lungs (Gerhardsson et al. 1988). Similarly, the lungs of coal miners from England contained 6 times higher cobalt levels than control lungs (Hewitt 1988).

Kettelarij et al. (2018a) studied skin doses and exposure sources of workers in the hard metal industry, finding that the highest skin doses (median 1.51 μg/cm^2, 0.25-28 μg/cm^2,) occurred in workers handling raw materials. Skin doses in raw material workers were significantly higher than those in sintered material workers and office workers. Cobalt was measured on many different types of surfaces, including production equipment, canteen, handles and buttons, common areas, personal work equipment, private items, changing rooms, and office items (Kettelarij et al. 2018a). In a study of metal exposure in three cemented tungsten carbide production facilities, cobalt was found on the surfaces of all the work areas sampled (Day et al. 2009). Cobalt concentrations were significantly higher in the powder-handling facility than in the metal separation facility and the forming/machining facility, and on control panels, hand tools, containers, and ventilation equipment than on other surfaces (Day et al. 2009). The highest mean concentrations of cobalt on skin were measured on workers in the powder-handling facility, ranging from 154-1,328 μg on hands and 7.8 to 342 μg on necks (Day et al. 2009). Julander et al. (2010) studied skin deposition in 24 workers who worked in the development and manufacturing of gas turbines and space propulsion structures; study participants were tasked with sharpening tools, producing combustion structures, and the thermal application of metal-containing powders. Cobalt could be found on all skin surfaces of the forehead and hands. The department with the highest cobalt exposure was the tools sharpening department, in which the highest level detected was 4.5 μg/cm^2/hr on the thumb.

In addition to workers in the hard metal industry and other industries, the general population living near these industrial sites, hazardous waste sites, and agricultural areas may be exposed to high levels of cobalt in air and in soil. People living near industrial and hazardous waste sites or agricultural areas that use

sewage sludge or cobalt containing fertilizers or other soil amendments may be exposed to cobalt by inhaling dust from contaminated sites or through dermal contact with cobalt-contaminated soil. No experimental evidence of higher-than-normal exposures for populations near agricultural areas was found in the literature. People who live in areas that naturally contain higher levels of cobalt minerals may also be exposed to higher levels of cobalt from both the inhalation and dermal contact routes.

Exposure to stable cobalt in communities near mining and smelting facilities or metal shops where cobalt is used in grinding tools is a public health concern, especially for infants and children. Since cobalt can remain in surface soil long past when land use that caused the contamination has changed, people may not realize that they are living in areas where high levels of cobalt may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil that contain metals and other contaminants (Hamel et al. 1998). In the case of children playing in and around unrestricted landfill sites, exposure via dermal and ingestion routes is possible. In communities near industrial and hazardous waste sites, cobalt may have been tracked in from outdoors and contaminate carpeting. Cobalt-containing dust may be brought home in the clothing of parents working in industries where they are exposed to cobalt. Children may be exposed to this cobalt while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with soil, or by inhaling dust and then swallowing it after mucociliary transport up out of the lungs.

A study of trace elements in dust, hair, nail, and serum samples in Punjab, Pakistan found that cobalt concentrations in dust samples were slightly higher in urban areas (3.0 ppm) than in industrial (2.0 ppm) or rural areas (1.7 ppm) (Mohmand et al. 2015). Cobalt levels were 0.04-0.5 ppm in hair samples and were similar at all sites. Levels in nail samples and serum were the highest in rural areas (Mohmand et al. 2015). A study of metal concentrations in air was conducted in four communities near metal recyclers in Houston, Texas (Han et al. 2020). Mean concentrations in the four communities ranged from 0.59-14.85 ng/m^3 (Han et al. 2020). Han et al. (2020) estimated that the cancer risk due to inhalation of cobalt was 0.25-6.9 cases per million at the fence line, 0.07-1.4 cases per million in near neighborhoods, and 0.05-0.30 cases per million in far neighborhoods. In a mining area of the Democratic Republic of Congo, mean urinary concentrations of cobalt were significantly higher in individuals living less than 3 kilometers from the mining and refining operations (15.7 µg/g creatinine) than in control subjects (1.34 µg/g creatinine) (Banza et al. 2009). Mean urinary cobalt concentrations were 5.72 µg/g creatinine in individuals living between 3 and 10 kilometers from mining and refining (Banza et al. 2008). Urinary cobalt exceeded 15 µg/g creatinine in 53% of all subjects living very close to mine pollution areas and in 87% of children living closest to mining and smelting sites (Banza et al. 2008). Cheyns et al. (2014) measured the concentrations of cobalt in urine samples and environmental media in communities close to metal mining

and refining plants, lakes receiving effluents from metal refining plants, and control areas without pollution from the metal mining and refining industry. Mean urinary cobalt was 4.5 times higher in adults and 6.6 times higher in children in polluted areas (Cheyns et al. 2014). Mean cobalt concentrations were significantly higher in soil, outdoor and indoor dust, drinking water, maize flour, tubers, cassava leaves, sweet potato leaves, and other vegetable samples in polluted areas than in control areas (Cheyns et al. 2014).

Individuals working in other occupations who use cobalt-containing materials may also be at higher risk of cobalt exposure. Richter et al. (2002) found that opera singers were exposed to cobalt as pigment components in swept dust while working on stage. Cobalt was found at a concentration of 7.17 mg/kg dust in the fine dust swept from the stage (Richter et al. 2002). Cases of dermatitis have been reported in individuals who worked with polyester resins that contained cobalt as an accelerator (Anavekar and Nixon 2006; Cahill and Andersen 2010). Dental technicians who work with alloys and tools that release cobalt are at greater risk of exposure than the general population. A study of dental technicians in Sweden found that technicians exposed to a cobalt and chromium (CoCr) alloy in a two-hour period without handwashing had more cobalt on the skin than non-exposed technicians (Kettelarij et al. 2016). Before work, the median concentrations of CoCr were 0.0012 $\mu g/cm^3$ in exposed technicians and 0.0017 $\mu g/cm^3$ in non-exposed technicians (Kettelarij et al. 2016). After 2 hours of work without hand washing, concentrations had increased to 0.15 $\mu g/cm^3$ for exposed individuals and 0.0026 $\mu g/cm^3$ for non-exposed individuals (Kettelarij et al. 2016). At the end of the day, the median concentrations had increased overall to 0.014 $\mu g/cm^3$ in exposed individuals and 0.0057 $\mu g/cm^3$ in non-exposed individuals (Kettelarij et al. 2016). Cobalt was found in all 10 air samples taken during this study at concentrations ranging from 0.22-155 $\mu g/m^3$ (Kettelarij et al. 2016). Metal urine concentrations were normal (Kettelarij et al. 2016). The exposed technicians had been preparing prostheses, metal constructions for dental crowns, and porcelain parts of dental crowns (Kettelarij et al. 2016). At least one case of occupational exposure to cobalt resulting in contact dermatitis has been reported in a baker, who frequently used metallic tools and baking sheets (Bregnbak et al. 2015a).

Surgical implants for knee and hip replacements often use cobalt-containing alloys, which may lead to elevated cobalt levels in body fluids. Indeed, cobalt levels in serum and urine have been used as an index of prosthesis wear. In some cases, significant increases in cobalt levels have been observed, while in other cases, elevations were much lower or only sporadic (IARC 1991). These differences have been ascribed to greater release rates from metal to metal than metal to polyethylene articular surfaces as well to differences in the cobalt-containing alloys. The higher exposure of cobalt in patients with cobalt-chromium knee implants has been demonstrated by the slightly higher levels of cobalt in whole blood,

serum, and urine, and by very high levels of cobalt in bone of these patients (IARC 1991; Ostapczuk et al. 1985; Sunderman et al. 1989). While the normal range of blood cobalt is 0.05-0.1 µg/L, one man who had undergone a hip replacement had a blood cobalt level of 14.3 µg/L (Briani et al. 2015). Prosthetic devices that contain polyethylene components to avoid metal-to-metal contact do not appear to cause elevated levels of cobalt in tissues and body fluids (IARC 1991; Ostapczuk et al. 1985; Sundaram et al. 2001). There has been at least one case of a cobalt allergy in a person with a prosthetic leg (Arslan et al. 2015). The potential for ototoxicity to be associated with cobalt exposure was addressed in several case and case control studies, primarily in patients with metal-on-metal hip replacements for which it was known or assumed that cobalt was a component. The health effects in these case-studies were self-reported, often lacked a dose response relative to cobalt blood concentration, had a very small sample population, were not classifiable as to clinical dysfunction, or were not discernable between individuals whose implants did or did not contain cobalt (Ho et al. 2017; Leikin et al. 2013; Leyssens et al. 2021; Leyssens et al. 2020; Prentice et al. 2014). Two cases of hearing loss caused by massive deterioration or failure of metal hips were associated with neuropathy (Pazzaglia et al. 2011) or death (Zywiel et al. 2013). Transient hearing loss was reported in individuals undergoing cobalt therapy attempting to increase hematocrit (Bowie and Hurley 1975).

People who use cobalt supplements as a treatment for anemia and those who take large amounts of vitamin B_{12} as a dietary supplement would have higher intakes of cobalt than the general population. In a study of four healthy adult males who volunteered to take cobalt supplements of 0.4 mg Co/day, after 15 or 16 days mean whole blood cobalt was 3.6 µg/L, with a range of 1.8 to 5.1 µg/L (Tvermoes et al. 2013). Whole blood concentrations decreased to 1.1 µg/L two weeks post-dose (Tvermoes et al. 2013). Background concentrations are reported to be 0.1-0.4 µg/L (Tvermoes et al. 2013). Using a cobalt specific biokinetic model, Unice et al. (2012) estimated that 10 days of taking cobalt supplements at the recommended daily dose values of the European Food Safety Authority and the UK Expert Group on Vitamins and Minerals (600-1400 µg/day) would result in mean whole blood concentrations of 5.0-12 µg/L and urinary concentrations of 57-130 µg/L after 30 days. After one year, mean whole blood concentrations would increase to 5.7-13 µg/L and urinary concentrations would increase to 66-150 µg/L (Unice et al. 2012). There is some evidence that cobalt chloride could be used as an alternative doping technique in athletes wanting to improve performance, and increased serum concentrations are occasionally measured in athletes (Lippi et al. 2006).

Cobalt has been detected in tobacco from U.S. cigarettes at mean values of 0.44 to 1.11 µg/g dry tobacco and in popular smokeless tobacco products at concentrations of 0.26±0.02 to 1.22±0.05 µg/g (Fresquez et

al. 2013; Pappas et al. 2008). People who smoke cigarettes or use smokeless tobacco products may be at higher risk of cobalt exposure.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of Environmental Protection Agency (EPA) and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cobalt is available. Where adequate information is not available, ATSDR, in conjunction with National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of cobalt.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

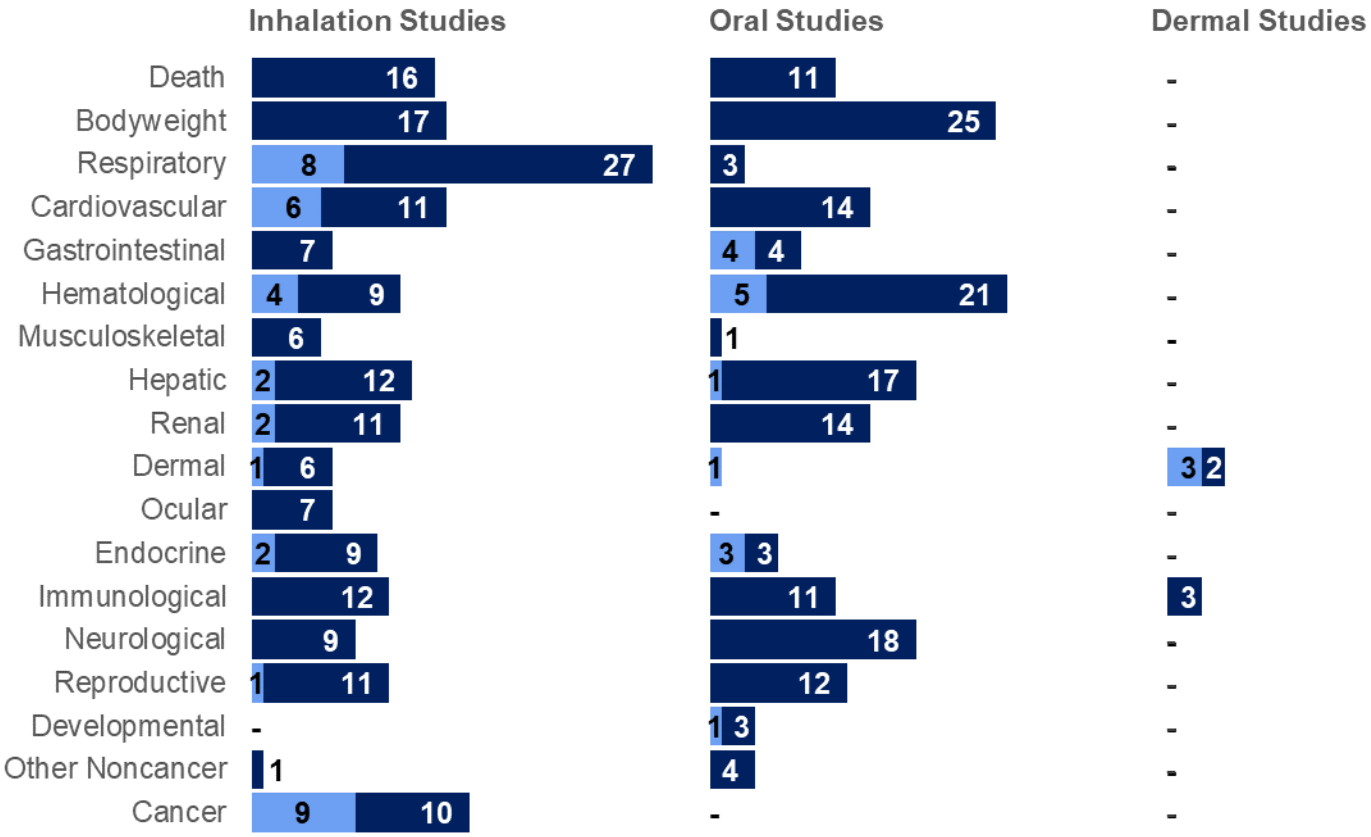
6.1. EXISTING INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to cobalt that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of cobalt. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies (Palmes et al. 1959).

As shown in Figure 6-1, information on the health effects in humans and animals exposed to cobalt primarily examine oral ingestion and inhalation. Many of these studies are case reports of individuals who intentionally or accidentally ingested cobalt or cobalt-containing substances. Controlled-exposure studies in humans primarily examined effects following ingestion of cobalt as a capsule. In these studies, hematological findings were the most observed health effect. A robust number of experimental studies in animals examined oral exposure to cobalt and cobalt compounds and have examined a wide range of health effects, particularly hepatic and renal endpoints in addition to hematological effects. Epidemiological observation studies in humans examined effects following inhalation exposure to cobalt as occupational exposure. Decreased pulmonary function was consistently seen in workers exposed to cobalt in occupational settings. Animal studies also showed pulmonary effects where inflammation and edema in lungs were observed. Dermal studies were limited in both animals and humans, but observed effects generally support the effects seen from oral ingestion.

Figure 6-1. Summary of Existing Health Effects Studies on Cobalt by Route and Endpoint*

Potential body weight, respiratory, and hematological effects were the most studied endpoints.
The majority of these studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies includes those finding no effect and a study may have examined more than one endpoint for health effect.

6.2. IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The acute-duration database is inadequate for deriving an MRL for cobalt for inhalation exposure. The database was limited to one experimental study in humans (Kusaka et al. 1986a) where there was a non-dose related decrease in FVC observed in the exposed workers. Studies in rat and

mice showed high mortality and serious respiratory effects such as necrosis and severe edema following acute-duration inhalation exposure to cobalt concentrations ≥2.5 mg Co/m^3 (NTP 2014; Palmes et al. 1959). Additional studies are needed to characterize health effects for lower cobalt air concentrations. An oral acute-duration MRL was derived from a human study based on changes in hematological parameters (Davis and Fields 1958). A study in rats support that hematological effects manifest as a result of acute ingestion of cobalt (Awoyemi et al. 2017; Davis and Fields 1958). Acute-duration oral exposure to cobalt in Davis and Fields (1958) included only one exposure concentration in 4 subjects where each individual served as their own control. Additional controlled-exposure human and animal studies are needed to better characterize the health effects for oral exposure to cobalt at lower doses.

Intermediate-Duration MRLs. The available intermediate-duration database was inadequate for deriving an inhalation MRL for cobalt. The database has no human studies. Animal studies found serious respiratory effects (Johansson et al. 1987; Johansson et al. 1991; Johansson et al. 1992; Kerfoot 1974; NTP 1991, 2014; Palmes et al. 1959). Since respiratory effects seen in animals, such as lung hemorrhage, inflammation, and abnormal breathing, are serious effects, derivation of an MRL is not appropriate for intermediate-duration inhalation exposure (ATSDR 2018). The intermediate-duration MRL for oral exposure was derived from a human study which observed hematological effects after ingestion of cobalt capsules (Davis and Fields 1958). Oral studies in animals also corroborate the hematological effects seen in humans, albeit at higher dose levels (Chetty et al. 1979; Domingo and Llobet 1984; Gluhcheva et al. 2020; Krasovskii and Fridlyand 1971). There is a need for toxicity studies that examine both oral and inhalation exposures at lower doses that are more likely to occur in humans. Additionally, it would be useful for toxicity studies to establish concentration-response relationships. Intermediate-duration toxicity information is crucial to people living near hazardous waste sites as they could potentially be exposed for similar time periods.

Chronic-Duration MRLs. The available chronic-duration database for inhalation included 3 human studies and 2 animal studies (Gennart and Lauwerys 1990; Kusaka et al. 1986a; Nemery et al. 1992; NTP 1998, 2014). All 5 studies examined respiratory endpoints and identified that the pulmonary system is a sensitive target to cobalt exposure based on alterations seen in lung function. These alterations in lung function observed in a human occupational exposure study were used to derive the MRL for chronic-duration inhaled cobalt exposure based on a NOAEL of 0.0053 mg Co/m^3 (Nemery et al. 1992). The animal studies by NTP (1998) showed serious adverse effects even at the lowest concentration tested and were thus not used for MRL derivation (NTP 1998, 2014). There is a need for controlled exposure human studies to establish a concentration-response relationship for cobalt, as chronic-duration inhalation exposure is likely to occur in occupational settings. Animal studies should be designed to mimic human

exposure levels to better understand toxicity and concentration-response relationships. No adequately conducted chronic-duration human or animal studies for oral exposure were located for cobalt; thus, the databases were inadequate for deriving chronic-duration oral MRLs. Chronic-duration inhalation exposure in animal studies showed carcinogenic effects (NTP 1998, 2014), and therefore were not appropriate for MRL derivation. There is a need for chronic-duration animal exposure studies at doses where no carcinogenic effects are observed. Additionally, epidemiological studies are needed to examine the carcinogenic effects of cobalt exposure in humans. These chronic-duration oral and chronic-duration inhalation studies in humans and animals can help to better define the carcinogenic potential of cobalt.

Health Effects

Respiratory. Symptoms of respiratory effects of exposure to cobalt include decrease in lung capacity, changes in lung weight, inflammation in lungs along with increased cough, sputum, and dyspnea in workers following inhalation of cobalt in occupational settings (Gennart and Lauwerys 1990; Kusaka et al. 1986a). Animal studies showed changes in lung weight, lung inflammation, edema, congestion, and bronchitis after acute-duration exposure (NTP 1991; Palmes et al. 1959). The severity of respiratory effects increased with an increase in exposure duration (Behl et al. 2015; Hong et al. 2015; NTP 1998, 2014). The intermediate- and chronic-durations of exposure in animals showed increased pulmonary inflammation and changes in epithelium and lung weight. The current database of literature that examines chronic-duration exposure to cobalt is limited. Nemery et al. (1992) reported that the higher dose group had minimal effects based on pulmonary function tests; however, a covariate analysis of lung function indices against smoking concluded that increasing cobalt exposure resulted in decreasing function. In another chronic-duration exposure study by Gennart and Lauwerys (1990) involving occupational human exposure, the authors failed to provide sufficient data to determine the average combined cobalt concentration to which the workers were exposed. At intermediate- and chronic-durations of exposure, even the lowest cobalt concentrations were greater than those that would likely cause serious health effects in humans. Therefore, there is a need to design animal studies that model human exposures in occupational settings. Further, studies are needed to characterize respiratory toxicity of cobalt, especially in workers who likely inhale cobalt dust or fumes in occupational settings. Additionally, concentration-response relationships are yet to be established.

Hematological. Inhalation exposure to cobalt caused absolute polycythemia and changes in blood count levels. In one chronic-duration exposure study in refinery workers there were no changes in hemoglobin and hematocrit (Lantin et al. 2011). Intermediate-duration animal inhalation studies showed increased levels of hemoglobin, basophils, and monocytes in rats and guinea pigs at 9 mg Co/m^3 , but at a lower

dose of 0.1 mg Co/m^3 , there were no changes seen in the guinea pigs (Kerfoot 1974; Palmes et al. 1959). Changes in hematocrit and hemoglobin levels were seen in both rats and mice after intermediate and chronic durations of exposure (Hong et al. 2015; NTP 1991, 1998, 2014). Controlled exposure to oral cobalt in humans has also been known to cause polycythemia (as reported by the study authors) (Davis and Fields 1958). Acute- and intermediate-duration exposures in animals (rats, mice, dogs, and hamsters) also show hematological effects in doses ranging from 11-161 mg Co/kg/day (Bryan and Bright 1973; Corrier et al. 1985; Domingo and Llobet 1984; Domingo et al. 1985a; Gluhcheva et al. 2014; Holly 1955; Krasovskii and Fridlyand 1971; Pedigo et al. 1988; Shrivastava et al. 2008). While these doses do show a significant effect in animal models, these doses are much greater than what human exposure is likely to be, therefore there is need for oral exposure studies that use lower doses for all exposure durations. These studies would likely better characterize the oral toxicity of cobalt along with concentration-response relationships.

Neurological. There is limited evidence from human and animal studies that indicate cobalt may be a neurotoxin. Animal studies after inhalation exposure either had no effect at the doses that were examined or caused minimal physiological changes in the brain (NTP 1991, 2014). Behavioral studies could be conducted to examine the effects of cobalt at lower doses. These low dose exposure studies could provide more information on neurotoxic effects that could potentially be examined in workers who likely inhale cobalt dust or fumes in occupational settings. Oral exposure to cobalt caused neurobehavioral deficits in rats and mice at higher doses (Abdel-Rahman Mohamed et al. 2019; Akinrinde and Adebiyi 2019; Bourg and Nation 1985; Chetty et al. 1979; Garoui et al. 2013; Khalil et al. 2020; Morvai et al. 1993; Singh and Junnarkar 1991; Umar et al. 2016; Zaksas et al. 2013). Neurobehavioral and physiological changes as a result of oral exposure to cobalt levels that mimic human exposure need to be examined in future studies.

Developmental. There are currently no studies that examine developmental toxicity in humans. There is minimal evidence of oral cobalt toxicity at relatively higher doses of 5- 25 mg Co/kg/day in animals (Domingo et al. 1985b; Paternian and Domingo 1988; Seidenberg et al. 1986). Developmental toxicity needs be examined at lower doses in animals that mimic potential human exposure levels. Based on the current database, there are no studies in laboratory animals that indicate that there exists a risk for developmental toxicity after cobalt exposure at lower doses. There is need to examine the potential for developmental toxicity from exposure to cobalt in humans and animals.

Epidemiology and Human Dosimetry Studies. Numerous epidemiological studies relating to occupational cobalt exposure are available in the literature (Kusaka et al. 1986a; Linna et al. 2003; Linna et al. 2004; Sauni et al. 2010; Shirakawa et al. 1988; Shirakawa et al. 1989; Sprince et al. 1988) and 3

studies where the subjects are exposed to cobalt under medical supervision (Davis and Fields 1958; Holly 1955; Taylor et al. 1977). Further studies assessing the cause/effect relationship between cobalt exposure and human health effects would be helpful in monitoring individuals living near a hazardous waste site to verify whether documented exposure levels are associated with adverse health effects. Studies of both children and adults could elucidate the understanding of possible age-related differences in toxicity. It would also be beneficial to examine sex differences in health effects caused by cobalt exposure.

Biomarkers of Exposure and Effect

Exposure. Cobalt levels have been measured in tissue (primarily via autopsies of workers), skin, blood, feces, and urine. Whole blood, serum, and urine cobalt levels have been established in healthy individuals. These biomarkers increase with prolonged exposure and decrease upon cessation of exposure. Serum and urinary cobalt levels along with clinical manifestations are indicators of cobalt exposure status. Current biomarkers appear sufficient in assessing cobalt exposure.

Effect. There are no specific biomarkers of effect for cobalt toxicity. Even though changes in blood count levels and serum antibodies may be caused by exposure to cobalt, these physiological manifestations are not exclusive to cobalt toxicity. More studies are required to identify a unique biomarker for cobalt induced toxicity that could assist in early diagnosis and prevention or slowing of the development of serious health effects from cobalt exposure.

Absorption, Distribution, Metabolism, and Excretion. The absorption, distribution, metabolism, and excretion of inhaled and orally administered cobalt have been studied predominantly in animals and minimally in humans. Pharmacokinetic data in humans and animals indicate that cobalt is absorbed through the lungs and the gastrointestinal tract after inhalation and oral exposure, respectively. The highest concentration of cobalt is found in lungs after inhalation exposure, but it is well-distributed throughout the body. Inhaled and ingested cobalt is rapidly excreted through feces and the remaining amount is released slowly in urine. There are minimal data regarding the pharmacokinetics of cobalt after dermal exposure, but the few studies that examine the dermal absorption of cobalt indicate that small amounts of cobalt are absorbed dermally with greater absorption happening through damaged skin than intact skin. There is no apparent need for additional studies on this topic.

Comparative Toxicokinetics. Toxicokinetics of cobalt after inhalation and oral exposure have been examined in rats, mice, pigs, hamsters, and humans. No comparative toxicokinetic studies following dermal exposure were located. These studies would be useful because humans are exposed via the skin and inhalation in the workplace and communities surrounding cobalt industry/waste sites may potentially be exposed via these routes. Additionally, it would be beneficial to examine how people with existing

hematological changes (including absolute polycythemia), which is an increase in red cell mass, might respond to environmental exposure to cobalt compared to a population without hematological changes (including polycythemia). Polycythemia is described in detail in Chapter 2, Section 2.1.

Children's Susceptibility. There are no studies that examine cobalt toxicity in infants and children. Studies are needed to determine the risk of cobalt exposure, the mechanism of cobalt toxicity, and clinical effects caused by exposure to cobalt by different routes and durations. Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether prenatally or during childhood, are discussed in detail in the *Developmental Toxicity* subsection above**.**

Physical and Chemical Properties. The relevant physical and chemical properties of cobalt and its compounds are sufficiently known to enable prediction of environmental fate and transport of cobalt compounds. No data needs were identified.

Production, Import/Export, Use, Release, and Disposal. USGS provides information on cobalt consumption, production, and import/export in the U.S. However, production volumes of individual cobalt compounds are not available and information on the production of individual compounds would be useful in assessing exposure to specific cobalt compounds. Information on the uses of cobalt and cobalt compounds is available. The TRI contains information on the onsite and offsite disposal and management of wastes (e.g., recycling, treatment, transfer to publicly owned treatment works [POTWs]). However, only certain types of facilities are required to report to TRI. More recent data on environmental releases would be helpful in evaluating current exposure risks.

Environmental Fate. There are data that permit assessment of the environmental fate and transport of cobalt in water and soil (Section 5.4). Frequently, sediment and soil are the ultimate sinks for cobalt; however, this process is dynamic, and cobalt can be released into the water depending upon various conditions. There is a paucity of data in the literature regarding the chemical forms of cobalt released to the atmosphere and their transformations in air and this information would facilitate the determination of the transport and persistence of cobalt in the atmosphere. Additional data elucidating the mode of speciation of cobalt in water and soil would also be desirable. For example, under what circumstances Co (III) compounds might be formed in the environment and might remain unchanged in the environment.

Food Chain Bioaccumulation. Data are available that indicate that cobalt is not taken up appreciably by plants and does not biomagnify within the food chain. There does not appear to be a need for additional research on this topic.

Exposure Levels in Environmental Media. Data are available on the cobalt levels in ambient air from EPA and in the scientific literature. However, the data are not sufficiently recent or broad-based for estimating the current levels of exposure to cobalt in the general U.S. population and particularly those living near cobalt-containing hazardous waste sites. The levels of cobalt in sediment are available, but more data on levels in soil and in the vicinity of industrial and hazardous waste sites would be useful. Few data on the levels of cobalt in U.S. foods are available. Cobalt was detected at 1 μg/L in drinking water in the US (EPA 2017), and as such, special monitoring of cobalt in drinking water does not appear to be needed. An updated market basket type survey of U.S. foods would be useful to better understand exposure levels.

Exposure Levels in Humans. The levels of cobalt in hair, nail, and adipose tissues of the general U.S. population are known. NHANES provides data on the levels of cobalt in urine of the general U.S. population. Data are also available on serum and urinary concentrations of cobalt in occupationally exposed individuals. Limited data on the levels of cobalt in body tissue or fluid for populations living near mines for cobalt and other hazardous waste sites are available. Additional data would be important in assessing the exposure levels of this group of people.

Exposures of Children. The levels of cobalt in baby formula, milk, and other foods ingested by children have been studied. More recent information is needed. Studies on cobalt levels in tissue, serum, and urine of children were identified after inhalation and oral exposure; some studies examined cobalt levels in children living near mines and in other heavily industrialized and polluted areas.

6.3. ONGOING STUDIES

No ongoing studies were identified for cobalt.

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CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding cobalt in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for cobalt.

Table 7-1. Regulations and Guidelines Applicable to Cobalt

Agency	Description	Information	Reference
	Air		
EPA	Subchronic p-RfC Chronic p-RfC	0.00002 mg/m^3 0.000006 mg/m^3	EPA 2008
WHO	Air quality guidelines	No data	WHO 2010
USC	HAP		USC 2011 42 USC 7412
	Cobalt compounds	Included in the Clean Air Acts list of HAPs to be regulated by EPA	
	Water & Food		
EPA	Drinking water standards National primary drinking water regulations Subchronic p-RfD Chronic p-RfD	No data No data 0.003 mg/kg-day 0.0003 mg/kg-day	EPA 2018 EPA 2009 EPA 2008
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	Substances Added to Food (EAFUS)		
	Cobalt sulfate (as catalyst)	Permitted as boiler water additive in preparation of food for human consumption	FDA 2020b 21CFR173.310
	Cobaltous salts and its derivatives	Prohibited from use in human food	FDA 2020a 21CFR189.120
	Cancer		
HHS	Carcinogenicity classification		NTP 2016
	Cobalt and cobalt compounds that release cobalt ions in vivo	Reasonably anticipated to be human carcinogens	
EPA	Carcinogenicity classification	No data	EPA 2000
IARC	Carcinogenicity classification		IARC 2020
	Cobalt sulfate and other soluble cobalt(II) salts	Group 2B[a]	
	Cobalt and cobalt compounds	Group 2B	
	Cobalt metal without tungsten carbide	Group 2B	

Table 7-1. Regulations and Guidelines Applicable to Cobalt

Agency	Description	Information	Reference
	Cobalt metal with tungsten carbide	Group 2A[b]	
	Occupational		
OSHA	PEL (8-hour TWA) for general industry		OSHA 2020a
	Cobalt metal, dust, and fume (as Co)	0.1 mg/m^3	29CFR1910.1000
	PEL (8-hour TWA) for construction industry		OSHA 2020a
	Cobalt metal, dust, and fume (as Co)	0.1 mg/m^3	29CFR1926.55
	PEL (8-hour TWA) for shipyard industry		OSHA 2020b
	Cobalt metal, dust, and fume (as Co)	0.1 mg/m^3	29CFR1915.1000
NIOSH	REL (TWA)		NIOSH 2019
	Cobalt metal dust and fume (as Co)	0.05 mg/m^3	
	Emergency Criteria		
AIHA	ERPGs		AIHA 2016
	Cobalt hydrocarbonyl[c]		
	ERPG-1	Insufficient data	
	ERPG-2	0.9 mg/m^3	
	ERPG-3	3 mg/m^3	
NIOSH	IDLH		
	Cobalt metal dust and fume (as Co)	20 mg/m^3	NIOSH 2014
EPA	AEGLS-air	No data	AEGLs 2018
DOE	PACs-air		DOE 2018
	Cobalt		
	PAC-1	0.18 mg/m^3	
	PAC-2	2 mg/m^3	
	PAC-3	20 mg/m^3	
	Cobalt acetate tetrahydrate		
	PAC-1	2.1 mg/m^3	
	PAC-2	23 mg/m^3	
	PAC-3	140 mg/m^3	
	Cobalt carbonyl		
	PAC-1	0.3 mg/m^3	
	PAC-2	3.3 mg/m^3	
	PAC-3	20 mg/m^3	
	Cobalt chloride		
	PAC-1	0.13 mg/m^3	
	PAC-2	18 mg/m^3	
	PAC-3	83 mg/m^3	
	Cobalt hydrocarbonyl		
	PAC-1	0.3 mg/m^3	
	PAC-2	0.9 mg/m^3	
	PAC-3	3 mg/m^3	
	Cobalt hydroxide		
	PAC-1	0.095 mg/m^3	
	PAC-2	1.1 mg/m^3	
	PAC-3	6.3 mg/m^3	
	Cobalt nitrate hexahydrate		
	PAC-1	0.3 mg/m^3	
	PAC-2	23 mg/m^3	
	PAC-3	140 mg/m^3	
	Cobalt nitrate		
	PAC-1	0.19 mg/m^3	
	PAC-2	14 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Cobalt

Agency	Description	Information	Reference
	PAC-3	86 mg/m^3	
	Cobalt nitrite		
	PAC-1	0.15 mg/m^3	
	PAC-2	1.7 mg/m^3	
	PAC-3	10 mg/m^3	
	Cobalt oxide		
	PAC-1	0.082 mg/m^3	
	PAC-2	4.5 mg/m^3	
	PAC-3	27 mg/m^3	
	Cobalt sulfate		
	PAC-1	0.16 mg/m^3	
	PAC-2	14 mg/m^3	
	PAC-3	84 mg/m^3	
	Cobalt sulfate heptahydrate		
	PAC-1	0.29 mg/m^3	
	PAC-2	19 mg/m^3	
	PAC-3	120 mg/m^3	
	Cobalt tetraphenylporphine		
	PAC-1	120 mg/m^3	
	PAC-2	1,300 mg/m^3	
	PAC-3	7,900 mg/m^3	
	Cobalt(II) chloride hexahydrate		
	PAC-1	0.24 mg/m^3	
	PAC-2	25 mg/m^3	
	PAC-3	150 mg/m^3	
	Cobalt(II) oxide		
	PAC-1	0.076 mg/m^3	
	PAC-2	4.2 mg/m^3	
	PAC-3	25 mg/m^3	
	Cobalt(II) perchlorate, hexahydrate		
	PAC-1	0.37 mg/m^3	
	PAC-2	5.8 mg/m^3	
	PAC-3	35 mg/m^3	
	Cobalt(II) sulfate hydrate		
	PAC-1	0.18 mg/m^3	
	PAC-2	1.9 mg/m^3	
	PAC-3	12 mg/m^3	
	Cobalt, ((2,2'-(1,2-ethanediylbis(nitrilomethylidyne))bis(6-fluorophenolato))(2-)-N,N',O,O')-; (Fluomine)		
	PAC-1	0.27 mg/m^3	
	PAC-2	3 mg/m^3	
	PAC-3	5.7 mg/m^3	
	Cobaltous bromide		
	PAC-1	0.22 mg/m^3	
	PAC-2	13 mg/m^3	
	PAC-3	80 mg/m^3	
	Cobaltous carbonate		
	PAC-1	0.12 mg/m^3	
	PAC-2	210 mg/m^3	
	PAC-3	1,200 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Cobalt

Agency	Description	Information	Reference

[a]Group 2B: Possibly carcinogenic to humans.
[b]Group 2A: Probably carcinogenic to humans.
[c]Values are given as cobalt.

AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; HAP = hazardous air pollutant; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; p-RfC = provisional inhalation reference concentration; p-RfD = provisional oral reference dose; REL = recommended exposure limit; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substances than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide

MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

This section only discusses the MRLs for cobalt. The Agency for Toxic Substances and Disease Registry has derived MRLs for external exposure to ionizing radiation, which are applicable to external exposures to cobalt radiation, so additional data for the derivation of MRLs for radioactive cobalt are not needed. The MRLs for ionizing radiation are discussed in the Toxicological Profile for Ionizing Radiation (ATSDR 1999).

APPENDIX A

MRL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
Date: January 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL as evidence of a critical effect is limited to one study in humans and two animal studies. These studies did not allow for the determination of a critical effect.

Rationale for Not Deriving an MRL: Human toxicity for acute-duration inhalation exposure to cobalt is only examined in one study in humans where a group of 15 young men were exposed to 0.038 mg Co/m^3 as hard metal dust (Kusaka et al. 1986a). At a concentration of 0.038 mg Co/m^3, there were no adverse health effects in the exposed workers and a non-dose related decrease in FVC (forced vital capacity) was observed. This study is of insufficient quality to inform an MRL as no significant correlation between any of the examined health effects and exposure to cobalt in air are identified. Previous case studies by Harding (1950) and Davison et al. (1983) indicate that cobalt is a potentially toxic substance in hard metal exposure, where hard metal is composed of a combination of cobalt, tungsten, and/or tungsten carbide. Respiratory effects following acute-duration inhalation exposure to cobalt after a single exposure was observed in rats where severe edema was seen at 90 mg Co/m^3 and edema was seen at 26 mg Co/m^3. Animal toxicity studies were limited to studies that examined relatively higher doses of cobalt that are not relevant to human exposure.

The human and animal NOAELs and LOAELs for acute-duration inhalation exposure are presented below in Table A-1.

Table A-1. Summary of NOAEL, LOAEL and SLOAEL Values Following Acute Duration Inhalation Exposure to Cobalt and Compounds

Species (N/sex)	Duration/ route	NOAEL (mg/m^3)	LOAEL (mg/m^3)	SLOAEL (mg/m^3)	Effect	Reference
Respiratory effects						
Human 15 M	6 hours	0.038			Non-dose related decrease in FVC	Kusaka et al. 1986
RAT (NS) 5M	30 minutes, once	7	26		LOAEL: Edema (not otherwise described)	Palmes et al. 1959
				90	SLOAEL: Severe Edema (not otherwise described)	

B = both males and females; F=females; M=males; NS= Not Specified; min= minutes

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
Date: January 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

MRL Summary: The available intermediate-duration inhalation data are not considered adequate for derivation of an intermediate-duration inhalation MRL for cobalt. Studies are limited to a few studies in animals that did not establish a dose-response relationship.

Rationale for Not Deriving an MRL: There are no studies that provide sufficient dose information on cobalt toxicity in humans following intermediate-duration inhalation exposure. Animal toxicity studies primarily examine respiratory health effects in rats, mice, rabbits, and pigs that occur at low concentrations of cobalt exposure (0.1- 2.5 mg Co/m^3). Adverse respiratory effects, including changes in lung weight, larynx inflammation, and cancerous effects of squamous metaplasia in the larynx, were seen in rats and mice exposed to cobalt sulfate heptahydrate concentrations of 0.06 to 6.29 mg Co/m^3 for 7 hours/day, 5 days/week for 13 weeks (NTP 1991).

In a 16-day study, rats showed degeneration of olfactory epithelium at high doses of 19mg Co/m^3 after exposure to cobalt sulfate for 6 hours/day, 5 days/week (NTP 1991). Palmes et al. (1959) observed lung inflammation in rats exposed to 9 mg Co/m^3 as cobalt hydrocarbonyl for 6 hours/day, 5 days/week for three months. Fourteen-week exposure to cobalt metal in rats and mice caused serious respiratory effects, such as lung inflammation, at the lowest concentration (0.625 mg/m^3) (NTP 2014).

Respiratory effects were seen at concentrations of 0.4 to 2 mg/m^3 in multiple intermediate-duration inhalation studies in rabbits (Johansson 1987; Johansson 1991; Johansson 1992). Rabbits showed severe lung inflammation and macrophage accumulation after exposure to 2 mg Co/m^3 for 17 weeks (Johansson et al. 1987). Two 4-month studies in rabbits only tested one concentration each of either 0.5 or 0.6 mg Co/m^3; therefore, a dose-response relationship between cobalt and adverse respiratory health effects cannot be ascertained (Johansson et al. 1991, 1992). Johansson et al. (1987) reported a LOAEL at 0.4 mg Co/m^3 which was greater than the doses observed in the NTP studies (0.1 mg Co/m^3) (NTP 1991; NTP 2014). Additionally, the Johansson studies gave conflicting results. In Johansson et al. (1991), there were no effects reported on respiratory endpoints at 0.5 mg Co/m^3 , while in Johansson et al. (1987) and Johansson et al. (1992), there were alterations in pulmonary tissue along with other respiratory effects at 0.4 and 0.6 mg Co/m^3. Kerfoot (1975) exposed pigs to 0.1 mg Co/m^3 as cobalt dust for 3 months resulting in a 29% decrease in lung compliance which could potentially be a serious health effects and thus could not be used to derive an MRL. Additionally, all the health effects in Kerfoot (1975) were observed at a lower dose of 0.1 mg Co/m^3 and the higher level dose (1 mg/m^3) did not produce more severe effects and thus a dose-response relationship was not established.

The lowest LOAEL identified for intermediate-duration inhalation exposure was associated with severe health effects and thus was not used to derive an MRL. The NOAELs and LOAELs from intermediate-duration inhalation studies are presented below in Table A-2.

Table A-2. Summary of NOAEL, LOAEL, SLOAEL Values Following Intermediate Duration Inhalation Exposure to Cobalt and Compounds

Species	Duration/ route	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	SLOAEL ($SLOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
Respiratory effects						
RAT (F344/N) 5M, 5F	6 hours + T90 (12 min)/day, 5 days/week, 16 days		2.5 (0.45)		LOAEL: Significantly increased incidence of cytoplasmic vacuolization of bronchiole epithelium; atrophy and necrosis of olfactory epithelium at 2.5 mg Co/m^3	NTP 2014
				20 (3.57)	SLOAEL: Abnormal breathing; increased incidence of lung hemorrhage and acute inflammation at 20 mg Co/m^3	
MOUSE (B6C3F1) 5M, 5F	6 hours + T90 (12 min)/day, 5 days/week, 16 days			2.5 (0.45)	Increased incidence of cytoplasmic vacuolization of bronchiole and respiratory epithelium, and atrophy of olfactory epithelium	NTP 2014
Pigs 5NS	6 hours/day, 5 days/week, 3 months		0.1 (0.02)		29% decrease in lung compliance	Kerfoot 1975
RAT (F344/N) 10M, 10F	6 hours+T90 (12 mins)/ day, 5 days/week, 14 weeks			0.625 (0.11)	Increased incidence of chronic active inflammation in lung, pulmonary alveolar proteinosis; increased relative lung weight (16-22%), all compared to controls	NTP 2014
MOUSE (B6C3F1) 10M, 9-10F	6 hours+T90 (12 mins)/ day, 5 days/week, 14 weeks			0.625 (0.11)	Cytoplasmic vacuolization of bronchiole epithelium; squamous metaplasia of larynx in all mice (10/10)	NTP 2014
RAT (F344/N) 10M, 10F	7 hours/day, 5 days/week, 13 weeks	0.06M 0.06F (0.01)	0.21F (0.038)		14% increase in relative lung weight in females at 0.21 mg/m^3	NTP 1991

Table A-2. Summary of NOAEL, LOAEL, SLOAEL Values Following Intermediate Duration Inhalation Exposure to Cobalt and Compounds

Species	Duration/ route	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	SLOAEL ($SLOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
MOUSE (B6C3F1) 10M, 10F	7 hours/day, 5 days/week, 13 weeks	0.06 F (0.01)		0.21F (0.038) 0.06M (0.01)	9/10 showed histiocytic infiltrates of the lung at 0.21 mg/m^3 in females and 10/10 showed histiocytic infiltrates at 0.06mg/m^3 in males	NTP 1991
RAT (F344/N) 5M, 5F	6 hours/day, 5 days/week, 16 days	0.99 (0.18)	10.5 (1.91)		Degeneration of olfactory epithelium, hyperplasia, and squamous metaplasia in the epithelium of respiratory turbinates; Inflammation in the nose and lungs (not otherwise described).	NTP 1991
MOUSE (B6C3F1) 5M, 5F	6 hours/day, 5 days/week, 16 days			0.99 (M, F) (0.18)	SLOAEL: Gray discoloration of lungs and fluid in larynx and trachea; 22% and 25% increase in relative lung weight in male and female mice, respectively; Degeneration of olfactory epithelium at 0.99 mg/m^3	NTP 1991
Rat (ALBINO) 34-57M	6 hours/day, 5 days/week, 3 months		9 (1.61)		Lung inflammation (not otherwise described)	Palmes et al 1959
RABBIT 8M	6 hours/day, 5 days/week, 17 weeks		0.4 (0.07)	2 (0.36)	LOAEL: Moderate inflammation observed in lungs; accumulation of macrophages in lungs (not otherwise described) SLOAEL: Severe lung inflammation and accumulation of macrophages (not otherwise described); Increase in weight of lower lung lobe by 25%	Johansson et al. 1987
RABBIT 8M	6 hours/day, 5	0.5 (0.09)				Johansson et al. 1991

Table A-2. Summary of NOAEL, LOAEL, SLOAEL Values Following Intermediate Duration Inhalation Exposure to Cobalt and Compounds

Species	Duration/ route	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	SLOAEL ($SLOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
	days/week, 4 months					
RABBIT 8M	6 hours/day, 5 days/week, 4 months		0.6 (0.11)		Histologic alterations in pulmonary tissue; altered BAL parameters; 22% decrease in macrophages	Johansson et al. 1992

F=females; M=males; NS= Not Specified

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Cobalt and compounds
CAS Numbers:	7440-48-8
Date:	January 2023
Profile Status:	Draft for Public Comment
Route:	Inhalation
Duration:	Chronic
MRL:	0.0001 mg/m^3 (0.1 µg/m^3) (provisional)
Critical Effect:	Respiratory reduced spirometry parameter values
Reference:	Nemery et al. 1992
Point of Departure:	NOAEL of 0.0053 mg/m^3 (NOAEL$_{ADJ}$ of 0.0013 mg/m^3)
Uncertainty Factor:	10
LSE Graph Key:	20
Species:	Humans

MRL Summary: A chronic-duration inhalation provisional MRL of 0.0001 mg/m^3 (0.1 µg/m^3) was derived for cobalt based on reduced respiratory spirometry parameter values in workers exposed chronically to cobalt in air (Nemery et al. 1992). The MRL is based on a NOAEL of 0.0053 mg /m^3 which was adjusted for intermittent exposure to a continuous exposure concentration of 0.0013 mg /m^3 and divided by a total uncertainty factor of 10 (10 for human variability).

Selection of the Critical Effect:
Several occupational studies examining chronic inhalation exposure to cobalt support respiratory toxicity as the critical effect (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986; Nemery et al. 1992). Multiple human and animal studies report altered pulmonary function (Kusaka et al. 1986; Krakowiak et al. 2005; Krakowiak et al. 2008; Nemery et al 1992; Gennart and Lauwerys 1990; NTP 1998; NTP 2014; Wehner et al. 1977). The lowest LOAEL for respiratory effects is 0.0151 mg Co/m^3 for reduced spirometry parameters, coughing, wheezing, and upper airway irritation, and the lowest NOAEL is 0.0053 mg Co/m^3 (Nemery et al. 1992). Similar respiratory effects are observed in other studies where the workers were exposed to cobalt salts and other inorganic cobalt dust (Krakowiak et al. 2005; Krakowiak et al. 2008). Using a case-study design, Krakowiak et al. (2005) showed that exposure to cobalt salts like cobalt chloride caused an Ig-E mediated asthma. The sensitization of lymphocytes by cobalt potentially plays a crucial role in the occupational asthma that is observed in the exposed workers (Krakowiak et al. 2005). An increased expression of IL-18 in nasal washings was observed in bakers exposed to cobalt salts through flour allergens (Krakowiak et al. 2008). A limitation of Kusaka et al. (1986) is the workers' co-exposure to tungsten, carbide, and cobalt. A study by Gennart and Lauwerys (1990) measured the cobalt air concentrations from 2 rooms that the workers were moving between freely and no individual room stay times were provided. The absence of this information did not allow estimation of the average exposure for the workers; therefore, this study cannot be used to derive an MRL. Sauni et al. (2010) conducted a case study of occupational asthma in cobalt plant workers in Finland from 1967-2003 where the mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m^3. Until 1987, cobalt was being produced from pyrite ore concentrate which led to co-exposures with irritant gases like sulfur dioxide (SO_2) and ammonia (NH_3) that are known respiratory irritants (Andersson et al. 2006; ATSDR 1998; Huber and Loving 1991). After 1987, cobalt was produced using by-products of the metallurgic industry as raw material which eliminated the co-exposure to the irritant gases and the incidence of asthma decreased to only 1 case between 1987-2003 compared to 21 cases between 1967-1987 (Sauni et al. 2010). Therefore, it is likely that the health effects observed in this

study were due the co-exposures to sulfur dioxide and ammonia with cobalt and not cobalt alone. Due to this reason, Sauni et al. (2010) cannot be used to derive an MRL.

Rats, mice, and hamsters showed lethality, respiratory, and cancer effects from chronic-duration inhalation exposure to cobalt at concentrations higher than those in the human studies (Wehner 1977, NTP 1998 and 2014). Wehner et al. (1977) used a high concentration of 7.9 mg Co/m^3 for a lifetime exposure in hamsters resulting in lung inflammation and emphysema. In NTP (1998), mice showed respiratory effects at the lowest exposure concentration in the chronic inhalation database (0.06 mg Co/m^3) in addition to cancer effects that include hyperplasia of the squamous epithelium in the larynx. Even though rats did not show serious respiratory health effects, the lowest concentration caused cancer, specifically alveolar/bronchiolar neoplasms along with metaplasia of the nose and epiglottis. (NTP 1998). In NTP (2014), the concentration of 1.25 mg Co/m^3 produced serious respiratory and cancer effects in both rats and mice where the cancer effect included increased incidence of mononuclear cell leukemia in rats and increased rate of alveolar/bronchiolar carcinoma in mice. The NOAELs and LOAELs for chronic-duration inhalation exposure are presented below in Table A-3.

Table A-3. Summary of Respiratory NOAEL and LOAEL Values of Chronic-Duration Inhalation Exposure to Cobalt

Species (sex)	Frequency/ Duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	SLOAEL ($SLOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
Human (M, F)	3 years	0.085 (0.0202)	0.126 (0.03)		2.7% decrease in FEV1% in exposed workers, suggestive of bronchial obstruction	Kusaka et al. 1986
Human (M, F)	Occupational	0.0053 (0.0013)	0.0151 (0.0027)		Decreased FEV1 (5%) and FVC (5%); Increased cough (11/91), wheezing (4/91), and upper airway irritation (40/91) observed in the subjects	Nemery et al. 1992
Human (M, F)	Occupational		0.0152 and 0.1355 combined for unreported periods (0.00271)		Decreased FEV1 and FVC by ~10%; Increased cough, sputum, dyspnea (not otherwise described)	Gennart and Lauwerys 1990

Table A-3. Summary of Respiratory NOAEL and LOAEL Values of Chronic-Duration Inhalation Exposure to Cobalt

Species (sex)	Frequency/ Duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	SLOAEL ($SLOAEL_{ADJ}$) (mg/m^3)	Effect	Reference
Human (M)	Occupational	0.03 to 0.15 (0.005-0.026)			In departments with higher air concentrations of cobalt, incidence of asthma was higher and latency period before symptoms occurred was shorter; Co-exposures to irritant gases such as SO_2 and NH_3 occurred	Sauni et al. (2010)
RAT (F344/N) (M, F)	6 hours/day, 5 days/week, 105 weeks	0.06 (0.0107)	0.21 (0.0375)		Alveolar inflammation and lung lesions (not otherwise described)	NTP 1998
MOUSE (M, F)	6 hours/day, 5 days/week, 105 weeks		0.06 (0.0107)		Non-neoplastic lesions on nose and larynx in 37 males and 45 females	NTP 1998
RAT (F344/N) (M, F)	6 hours/day, 5 days/week, 105 weeks			1.25 (0.223)	Significantly increased incidence of lung neoplasms and nonneoplastic lesions of lungs and nose; including hyperplasia of alveolar and bronchiole epithelium, chronic active inflammation (lung and nose), metaplasia and atrophy of olfactory epithelium	NTP 2014
MOUSE (B6C3F1) (M, F)	6 hours/day, 5 days/week, 105 weeks			1.25 (0.223)	Increased incidence of lung neoplasms and neoplastic lesions in the lung, nose, larynx, and trachea, compared to controls, including hyperplasia and cytoplasmic vacuolization of alveolar/bronchiolar epithelium	NTP 2014

Table A-3. Summary of Respiratory NOAEL and LOAEL Values of Chronic-Duration Inhalation Exposure to Cobalt

Species (sex)	Frequency/ Duration	NOAEL ($NOAEL_{ADJ}$) (mg/m^3)	LOAEL ($LOAEL_{ADJ}$) (mg/m^3)	SLOAEL ($SLOAEL_{ADJ}$) (mg/m^3)	Effect	Reference

ADJ= Adjusted; F= females; FEV1=Forced expiratory volume; FVC=forced vital capacity; M= males

Selection of the Principal Study: The Nemery et al. (1992) study tested the lowest concentrations among all human and animal studies and demonstrated a dose-response relationship between reduced spirometry parameter values and cobalt exposure. Therefore, the Nemery et al (1992) study was selected as the critical study because it identified the lowest NOAEL for chronic-duration inhalation exposure and a corresponding LOAEL.

Summary of the Principal Study: Nemery B, Casier P, Roosels D, et al. 1992. Survey of cobalt exposure and respiratory health in diamond polishers. Am Rev Respir Dis 145:610-616.

In a cross-sectional study, 194 diamond polishers from 10 different workshops were examined with 6-28 people from each workshop participating. In 8 out of 10 workshops, the polishing disks used were primarily cobalt-containing disks, while two workshops exclusively used cast iron polishing disks. Participation in the workshops varied from 56% to 100% and low participation from some workshops reflects the fact that only workers who used cobalt disks were initially asked to be in the study, rather than a high refusal rate (only eight refusals were documented). A year later, three additional workshops with workers engaged in diamond sawing, cleaving, or jewelry drawing were studied as an unexposed control group (n=59 workers). All study subjects were administered questionnaires to report medical history and lifestyle factors, provided urine samples, and underwent clinical examination and lung function tests. Area and personal air samples were collected and analyzed for cobalt and iron. Other potential co-exposure substances, e.g., diamond dust and carbide were not assessed. Sampling for area air determinations started 2 hours after work began and continued until 1 hour before the end of the workday. Personal air samples were collected from the breathing zone of a few workers per workshop for four successive 1-hour periods. Air samples were not collected for one workshop; however, data from an identical workshop were used as a proxy since urinary cobalt levels between workers from both workshops were similar.

Nemery et al (1992) showed a correlation (R=0.92) between the results of work area cobalt levels and personal cobalt air sampling, with area air sampling reporting lower concentrations than personal air samples in all workshops except one. The correlation between cobalt exposure, measured as urinary levels of cobalt, and air samples were significant (R = 0.85 to 0.88) when one workshop with poor hygienic conditions was excluded. Study authors did note that the available methods used for air sampling may have underestimated the exposure levels. The polishing workshops were divided into two cobalt exposure groups: low (n=102) and high (n=91). Mean personal air sampling cobalt exposure concentrations were 0.0004, 0.0053, and 0.0151 mg/m^3 in the control, low-exposure, and high exposure groups, respectively. Other metals, such as copper and chromium were detected, and some workers had previous occupational exposure to asbestos (use of asbestos containing glues) which was judged insufficient by the authors to produce a functional impairment. Study authors noted that cobalt appears to be the only relevant exposure; however, details on the exposure duration were not provided.

Workers in the high exposure groups were more likely to report eye, nose, and throat irritation and cough compared to other groups. Cough was more frequently reported by female polishers than male polishers. No exposure-related difference was observed for other respiratory symptoms including dyspnea and wheezing. Reduced lung function in the high-exposure group was demonstrated by significantly lowered forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), even after consideration of smoking status. Additionally, maximal mid-expiratory flow (MMEF) and mean peak expiratory flow rates (PEF) were significantly lower in the high-exposure group compared to controls and the low exposure group. The work-related upper airway effects were seen in 30% of controls, 26% of low dose individuals, and 43% of high dose individuals. Work-related cough was not observed in the control subjects but was observed in 4% of the low dose exposure group, and in 12% of the high dose exposure group. While the respiratory effects appear at a greater rate in individuals who were exposed to higher concentrations of Co, the study does not provide any information on the smoking status of individuals in the highest treatment group. There was no correlation between cobalt exposure and respiratory effects on an individual level within this group; correlations occurred only on a group level: low, high, control. Therefore, it is possible that smoking is causing an increase in cough in the 12% of individuals in the higher concentration exposure group. Two-way analysis of variance showed that exposure-related effects on spirometric parameters in the high dose exposure groups were present in men and women. Women appeared to be more affected than men, but the difference was not significant. Spirometric parameters did not differ significantly between the controls and low-exposure dose group. Smoking did exert a strong effect on lung function, but lung function remained inversely correlated with exposure to cobalt, independent of smoking. The spirometric parameters for men and women, and the combined unweighted values for FVC and FEV1 are presented in Table A-4.

Table A-4. FVC and FEV1 Values in Humans Exposed to Inhaled Cobalt in an Occupational Setting (Nemery et al. 1992)*

Dose (mg/m^3)		0.0004 (control)		0.0053 (Low-exposure)		0.0151 (High-exposure)	
N (Total/Men/Women)		59/46/13		102/93/9		92/73/19	
Parameter		Mean	SD	Mean	SD	Mean	SD
FVC (ml)	Men	5648	936	5445	754	5184	799
	Women	4033	688	4018	627	3733	592
	Total (Weighted)	5292	1110.6	5319	845.2	4884	960.85
FEV1 (ml)	Men	4644	803	4451	679	4191	712
	Women	3416	634	3468	384	3123	599
	Total (Weighted)	4373	920.31	4364	714.24	3970	813.04

*Means and standard deviations for men and women are raw data from Nemery et al. (1992), Table 4. Total (weighted) combines data for men and women to calculate the weighted means and standard deviations of the data.

FEV1= forced expiratory volume in 1 second; FVC = forced vital capacity

Selection of the Point of Departure for the MRL: The NOAEL of 0.0053 mg/m^3 in air as related to reduced respiratory function in male and female workers was selected as the basis for the chronic-duration inhalation MRL. The weighted data for spirometric parameters in both males and females (presented in Table A-4) were suitable to BMD modeling. The weighted data for FVC and FEV1 were modeled separately. Each data set was fit to all available continuous models in EPA's BMDS (version

3.2) using constant variance. Adequate model fit was judged by four criteria: chi squared goodness-of-fit (p>0.1), visual inspection of the dose-response curve, BMDLs <10 times lower than the lowest non-zero dose, and scaled residual (>-2 and <+2) at the data point (except the control) closest to the predefined BMR. A BMR of 1 standard deviation from the control mean was selected in the absence of a biologically based BMR. Using these criteria on FVC and FEV1 spirometric data, the Exponential 2, Exponential 4, Polynomial Degree 2, and Linear models provided adequate fit to both the FVC and FEV1 data. Generally, the number of parameters used in a model that affect the overall shape of the dose-response curve cannot exceed the number of dose groups in the data. In this case, the Exponential 4 and Polynomial Degree 2 models use 4 parameters, exceeding the 3 dose groups used in the data. Therefore, these models were not chosen for the POD.

Among the remaining models for both FVC and FEV1 data, the Linear model for FEV1 data had the lower AIC. Thus, the BMDL of 0.018 mg Co/m^3 was considered as the POD. It is higher than the study NOAEL and LOAEL of 0.0053 and 0.0151 mg Co/m^3, respectively, and would subsequently result in a higher MRL than one derived using the study NOAEL. Accordingly, the BMDL was not chosen as the POD. The NOAEL was chosen as the POD. Using the NOAEL is more protective of human health and supported by the fact that there is uncertainty in the exposure duration due to lack of information in the Nemery et al. (1992) study. The study assumed that all workers were chronically exposed to cobalt, but the length of employment was not stated and the workplace exposure concentrations prior to air sampling were unknown. The study authors also stated there was uncertainty in the methodology used to sample air, stating that exposure could have been underestimated. For this reason, the lower concentration between the NOAEL and BMDL was chosen as it is a more protective. Additionally, there were more smokers in the low and high dose exposure groups compared to the control group. It is important to note that lung function is affected by smoking status and it can alter lung function and accelerate aging. The sex differences observed in the study were potentially due to physiological differences between forced vital capacity in males and females.

Adjustment for Intermittent Exposure: Assuming that the workers in Nemery et al. (1992) were exposed only at work, the NOAEL was adjusted to account for a continuous work-day exposure (0.0053 mg/m^3, Table A-4). A typical workweek of 8 hours/day, 5 days/week was assumed:

$$NOAEL_{ADJ} = 0.0053\ mg/m^3 \times \frac{8\ hours}{24\ hours} \times \frac{5\ days}{7\ days} = 0.0013\ mg/m^3$$

Uncertainty Factor: The $NOAEL_{ADJ}$ is divided by a total uncertainty factor of 10:

- 10 for human variability

$$Provisional\ MRL = \frac{NOAEL}{UFs} = \frac{0.0013\ mg/m^3}{10}$$

$$= 0.00013\ mg/m^3\ (Rounded\ to\ 0.0001\ mg/m^3)$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL:

Kusaka et al. (1986b) in a 3 year exposure study observed a small significant decrease in FEV1% (2.7%), but other changes in lung function were not significant. In this study by Kusaka et al. (1986b) there was co-exposure with other metals in addition to cobalt (18:1 hard-metal to Co). Another study by Gennart and Lauwerys (1990) observed a decreased FEV1 and FVC by ~10% along with an increase in cough, sputum, and dyspnea. The cobalt exposure in air in this study was combined for unreported periods and therefore exact exposures could not be calculated. Other studies also saw respiratory effect deficits, but in

these studies there were co-exposures with other metals and compounds including Cr, Ni, H_2S and NH_4 (Hamzah et al 2014; Linna et al. 2003; Walter et al. 2013).

Animal studies showed similar respiratory system effects. Necrosis and inflammation of the respiratory tract epithelium (larynx, trachea, bronchioles, and nasal turbinates) were seen. Exposure of rats and mice to aerosols of cobalt (as cobalt sulfate heptahydrate and cobalt metal) at concentrations ranging from 0.06 to 1.25 mg Co /m^3 for 2 years resulted in a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice (NTP 1998; NTP 2014).

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Cobalt and compounds
CAS Numbers:	7440-48-8
Date:	January 2023
Profile Status:	Draft for Public Comment
Route:	Oral
Duration:	Acute
MRL:	0.03 mg/kg/day (provisional)
Critical Effect:	Production of polycythemia
Reference:	Davis and Fields 1958
Point of Departure:	Minimal LOAEL of 1 mg/kg/day
Uncertainty Factor:	30
LSE Graph Key:	2
Species:	Humans

MRL Summary: An acute-duration oral provisional MRL of 0.03 mg/kg/day was derived for cobalt based on a hematological endpoint of production of polycythemia (specifically absolute polycythemia) in humans orally exposed to cobalt chloride for 6-14 days (Davis and Fields 1958). The MRL is based on a minimal LOAEL of 1 mg Co/kg/day which was divided by a total uncertainty factor of 30 (10 for human variability, 3 for use of a minimal LOAEL).

Selection of the Critical Effect: Humans orally exposed to cobalt for acute durations show adverse effects on the gastrointestinal, hematological, hepatic, renal, and cardiovascular systems. Among all of the endpoints, effects on the hematological system were observed at the lowest dose levels of exposure and were therefore deemed as the critical effect. One human and one animal study reported alterations of hematological parameters (Davis and Fields 1958; Awoyemi et al. 2017). In humans, increased erythrocyte number and a significant increase in hemoglobin was observed following oral exposure to 1 mg Co/kg/day as cobalt chloride for 6-14 days (Davis and Fields, 1958). A study by Roche and Layrisse (1956) examined iodine uptake in 12 euthyroid (normal thyroid) patients who were orally exposed to 1 mg Co/kg-day (assuming a body weight of 70 kg) for 2 weeks which resulted in a greatly reduced uptake of 48-hour radioactive iodine by the thyroid when measured after 1 week of exposure to cobalt. The decreased uptake is likely resulting from cobalt blocking the organic binding of iodine (Paley et al. 1958). This effect was reversed by the second week of exposure nearly completely (Roche and Layrisse, 1956). No other clinical details (e.g., including effects on thyroid stimulating hormone [TSH]) were provided for the human subjects in this study, therefore, the mechanism for the effect of cobalt on thyroidal iodine uptake cannot be ascertained.

In rats, Awoyemi et al. (2017) observed a 16% increase in the liver enzyme, alanine aminotransferase (ALT), following oral exposure to 6 mg Co/kg/day for 1 week; no lower doses were tested. The NOAELs and LOAELs for acute-duration oral exposure are presented below in Table A-5.

Table A-5. Summary of NOAEL and LOAEL Values Following Acute Duration Oral Exposure to Cobalt and Compounds

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
Human 3M	Daily, 6-14 days		1	Polycythemia was observed with an 8.7% increase in erythrocyte numbers after exposure to 1 mg Co/kg/day compared to controls	Davis and Fields 1958
RAT (Wistar) 10M	Daily, 7 days/ week, 1 week	6	11	~400% increase in the frequency of micronucleated polychromatic erythrocytes	Awoyemi et al. 2017
Hepatic effects					
RAT (Wistar) 10M	Daily, 7 days/ week, 1 week		6	Alteration in liver enzyme levels (16%) increase of ALT	Awoyemi et al. 2017

ALT= alanine aminotransferase; B=both males and females; F=females; M=males; NS= Not Specified; polycythemia (meaning absolute polycythemia) = the classification term authors used to address increased hemoglobin or erythrocyte count

Selection of the Principal Study: The Davis and Fields (1958) study identified a LOAEL for hematological effects in humans. Therefore, the Davis and Fields (1958) study was selected as the critical study because it identified the lowest LOAEL in the oral-acute duration database.

Summary of the Principal Study: Davis, J.E. and Fields, J.P. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc Soc Exp Biol Med 99:493-495.

Four apparently healthy men, ages 20–47, were administered a daily dose split equally across mealtimes of cobalt chloride, as a 2% solution diluted in either water or milk daily. The subjects were regularly dosed for 14 days with equally divided doses at mealtimes. In this study each subject served as their own control, and blood samples were collected from each subject 7 to 14 days prior to the onset of oral administration. Each of the four subjects received 150 mg cobalt chloride per day for 8, 11, or 13 days. Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell count, hemoglobin percentage, leukocyte count, reticulocyte percentage, and thrombocyte count. A crucial limitation of this study was that there was only 1 dose used in this study which all 4 participants received.

Exposure to cobalt resulted in the development of polycythemia (as reported by the study authors) in all 4 subjects. Increases in red blood cell numbers averaged 6.2 million cells/mm^3. Erythrocyte counts returned to normal for the 4 individuals 4-9 days after cessation of cobalt administration. Hemoglobin levels were also increased by cobalt treatment, though to a lesser extent than the erythrocyte values, with increases of 8.7% over pretreatment values for the 4 individuals.

The erythrocyte data from the study were only presented as a graph (Figure A-1). In order to understand the magnitude of the effect, the graph was digitized using an open-source software Curve Snap to better inform the oral acute-duration MRL derivation. The data extracted from the graph are listed in Table A-6 and A-7.

Figure A-1: Erythrocyte Counts in 6 Subjects Before and During Daily Cobalt Treatments (Davis and Fields 1958)

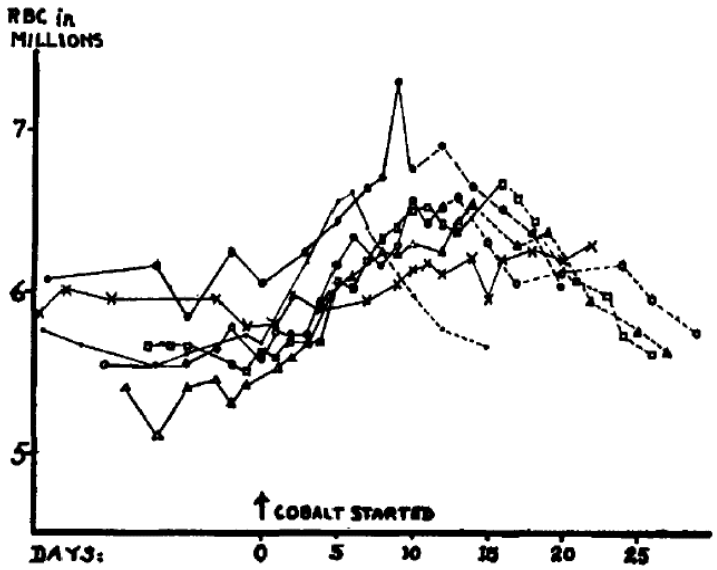


Figure A-1. The graph from Davis and Field 1958 shows erythrocyte numbers for 6 men who were exposed to cobalt. 4/6 men were exposed for 14 days (acute-duration exposure) and 2/6 men were exposed for more than 14 days (intermediate-duration exposure). Each subject was treated as a control for themselves.

Table A-6 Data Extracted from Figure A-1 - Erythrocyte Levels Before Administered Cobalt Exposure (RBC in millions)

Person #	Symbol	Pretreatment Day 1	Pretreatment Day 2	Pretreatment Day 3	Pretreatment Day 4
1	●	6.0	6.1	5.8	6.2
3	.	5.7	5.6	5.5	5.6
5	o	5.5	5.5	5.6	5.7
6	Δ	5.6	5.3	5.5	5.4
Average Increase in Erythrocytes-Control (Pretreatment Levels)				5.7	

Table A-7 Data Extracted from Figure A-1- Erythrocyte Levels During Acute-Duration Cobalt Exposure (RBC in millions)

Person #	Symbol	Days of Acute Cobalt Exposure														
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	●	6.0			6.2		6.4		6.5	6.6	7.2	6.7				
3	.	5.6	5.8	5.9	6.1	6.4	6.5	6.5	6.3							
5	o	5.5	5.7	5.9		5.8	6.0		6.1		6.3	6.5		6.4	6.4	
6	Δ	5.4	5.5	5.5		5.6	5.9	6.0		6.2		6.2		6.2	6.4	6.4
Average Increase in Erythrocytes Caused by Acute Levels of Exposure													**6.2**			

Thrombocyte and total leukocyte counts did not deviate significantly from pretreatment values. Changes in hemoglobin presented in the study are not presented here as they do not consider the duration of exposure for each subject and there is not enough information presented to calculate the changes in hemoglobin. The health effects of the study by Davis and Fields (1958) are presented in Table A-8.

Table A-8. Erythrocytes and Hemoglobin Levels in Humans Orally Exposed to Cobalt Chloride for 6-14 days (Davis and Fields 1958)

Effects	Dose (1 mg Co/kg/day)
Average Increase in Erythrocytes (cells/mm^3)	8.7% increase

Selection of the Point of Departure for the MRL: Davis and Fields (1958) identified a LOAEL of 1 mg Co/kg/day for polycythemia indicated by increased levels of erythrocytes in human males exposed daily for up to 14 days. Data from the study identified a minimal LOAEL of 1 mg Co/kg/day for this effect which was used as the POD to derive an MRL. The study reported a daily high dose intake of 150 mg cobalt chloride($CoCl_2$)/day which was converted to a daily dose of cobalt (Co) using a reference body weight of 70 kg for adult humans:

$$150\ mg\ CoCl2/day = 150 \times \frac{58.9 \frac{g}{mol}\ Co}{128.8 \frac{g}{mol}\ CoCl2} = 68.1\ mg\ Co/day$$

Based on assuming a 70 kg body weight of the subjects in the study,

$$\frac{68\ mg\ Co/day}{70\ kg\ (body\ weight\ of\ an\ adult\ human\ male)} = \sim 1\ mg\ Co/kg/day$$

The available data in Davis and Fields (1958) are not amenable to benchmark dose modeling as the study only tested one exposure dose.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The minimal LOAEL is divided by a total uncertainty factor of 30:

- 10 for human variability
- 3 for use of a minimal LOAEL

$$Provisional\ MRL = \frac{LOAEL}{UFs} = \frac{1\ mg/kg/day}{10 \times 3}$$

$$= 0.03\ \text{mg Co/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL:

A study by Roche and Layrisse (1956) examined iodine uptake in 12 euthyroid (normal thyroid) patients who were orally exposed to 1mg Co/kg-day (assuming a body weight of 70 kg) for 2 weeks which resulted in a greatly reduced uptake of 48-hour radioactive iodine by the thyroid when measured after 1 week of exposure to cobalt. The decreased uptake is likely resulting from cobalt blocking the organic binding of iodine (Paley et al. 1958). This effect was reversed by the second week of exposure nearly completely (Roche and Layrisse, 1956). No other clinical details (e.g., including effects on thyroid stimulating hormone [TSH]) were provided for the human subjects in this study, therefore, the

mechanism for the effect of cobalt on thyroidal iodine uptake cannot be ascertained. Awoyemi et al. (2017) also observed an increase in polychromatic erythrocytes after daily oral exposure to cobalt for 1 week in rats at 6 mg Co/kg/day.

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Cobalt and compounds
CAS Numbers:	7440-48-8
Date:	January 2023
Profile Status:	Draft for Public Comment
Route:	Oral
Duration:	Intermediate
MRL:	0.03 mg Co/kg/day (provisional)
Critical Effect:	Production of polycythemia
Reference:	Davis and Fields 1958
Point of Departure:	NOAEL of 0.8 mg/kg/day
Uncertainty Factor:	30
LSE Graph Key:	22
Species:	Humans

MRL Summary: An intermediate-duration oral provisional MRL of 0.03 mg/kg/day was derived for cobalt based on a hematological endpoint of production of polycythemia (specifically absolute polycythemia) in humans orally exposed to cobalt chloride for 25 days (Davis and Fields 1958). The MRL is based on a NOAEL of 0.8 mg Co/kg/day which was divided by an uncertainty factor of 10 (for human variability) and a modifying factor of 3 (for a limited database). This modifying factor for a limited database was used as there is a lack of well conducted peer reviewed studies that examine the health effects of oral exposure to Co for an intermediate-duration. This is also summarized in Chapter 6, Section 6.2.

Selection of the Critical Effect: Oral intermediate-duration exposure to cobalt caused adverse effects on gastrointestinal, hematological, hepatic, renal, and cardiovascular systems. Among all the endpoints, effects on the hematological system were observed at the lowest levels of exposure and are deemed as a critical effect. Human and multiple animal studies report alterations or ameliorations of hematological parameters (Davis and Fields 1958; Holly 1955; Duckham and Lee 1976; Gluchehva et al. 2014; Glucheva et al. 2020). The lowest dose for which hematological effects were reported was 0.18 mg Co/kg/day in anephric patients (without functioning kidneys) undergoing therapy where they were orally treated with cobalt. This exposure to cobalt was only partially successful in raising hemoglobin toward the normal range and reducing transfusion frequency; as such, this study in anephric individuals is not suitable for MRL derivation (Duckham and Lee 1976). The next lowest dose resulting in hematological effects was 1 mg Co/kg/day where humans were exposed to oral cobalt chloride for 15-22 days and showed an approximate 16-21% increase in erythrocyte number and a significant increase in hemoglobin. Exposure to 0.8 mg Co/kg/day for 15 days did not affect the erythrocyte number, and additional exposure to 1 mg Co/kg/day for 7 days resulted in a variable change with a maximum 6% increase. (Davis and Fields, 1958). Additionally, a daily oral exposure to 0.16 mg Co/kg/day in humans for 12-32 weeks caused an increase in hemoglobin which was not quantified in the study (Taylor A et al. 1977); however, a 13 week daily oral exposure to 0.6 mg Co/kg/day in humans did not cause any hematological effects (Holly 1955).

Studies in rats also demonstrate alterations in hematological parameters. Danzeisen et al. (2020) exposed rats to 0.74, 2.48, and 7.44 mg Co/kg/day as cobalt chloride hexahydrate orally daily for 90 days. In this study, male rats showed no alterations in hematological parameters at 0.74 mg Co/kg/day; at a dose of 2.48 mg Co/kg day there was a 10.7%, 9.2%, and 10.2% increase in hemoglobin, erythrocytes, and hematocrit, respectively. Male rats were more sensitive and showed changes in hematological parameters

at lower doses (0.74 and 2.48 mg Co/kg/day) and female rats showed an increase of 13.4% and 9.8% in hemoglobin and erythrocytes, respectively, only at a dose of 7.44 mg Co/kg/day (Danzeisen et al. 2020). Danzeisen et al. (2020) also examined effects of Co_3O_4 on hematological parameters. They observed that a daily oral dose of 220 mg Co/kg/day increased hemoglobin, erythrocytes, and hematocrit by 9.5%, 9.6%, and 9.2%, respectively, in male rats, and a 5.9% increase in hemoglobin level in female rats. At the highest dose of 734 mg Co/kg/day, male and female rats showed an increase in hemoglobin (25.4% males and 16.4% females), erythrocytes (22.7% males and 12.9% females), and hematocrit (24.2% males and 13.9% females) (Danzeisen et al. 2020). Krasovskii and Fridyland (1971) exposed groups of rats to 0, 0.05, 0.5, and 2.5 mg Co/kg/day, daily for 7 months. The group treated with 2.5 mg Co/kg/day showed persistent increases in erythrocytes, the 0.5 mg Co/kg/day group showed a transient increase, and the lowest exposure group had no effects. This study was not used to develop an MRL as there were no numerical data reported and the statistical significance was not reported. Chetty et al. (1979) showed a decrease in hemoglobin levels in Sprague-Dawley rats only at high levels of exposure to cobalt. Exposure to cobalt at these doses (0.5, 11.4, and 30.2) was likely causing a display of hormesis where the responses were greater at the lowest and highest doses, thus eliciting a biphasic response. More studies are needed to establish if such behavior is consistent across a wider range of doses (Krasovskii and Fridlyand 1971; Chetty et al. 1979; Domingo et al. 1984). The group of rats exposed to higher levels of cobalt at 11.4 mg Co/kg/day potentially had alterations in the plasma volume which have a direct effect on hemoglobin concentration (Chetty et al. 1979). The decrease in hemoglobin levels at higher doses (11.4 mg Co/kg/day) for 4 weeks is likely due to competition by cobalt for the iron transporters which prevents iron from being bound to the transporter, thus decreasing the levels of hemoglobin. Higher levels of cobalt exposure (30.2 mg Co/kg/day) increased hemoglobin (Domingo et al. 1984). Chetty et al. (1979), Domingo et al. (1984), and Gluhcheva et al. (2020) used relatively higher doses of cobalt that are not relevant to human exposure. Since hematological effects were consistently seen at lower doses of cobalt exposure, they have been identified as a critical effect and are the basis for developing an MRL. A summary of the NOAEL and LOAEL values for hematological effects that were reviewed for MRL development are presented in Table A-9.

Table A-9. Summary of Lowest NOAEL and LOAEL Values for Hematological Effects Following Intermediate-Duration Oral Exposure to Cobalt

Species (sex)	Frequency/ Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological effects					
Human 1-2 M	Daily, 15 days for low dose, 22-23 days for high dose	0.8	1	NOAEL: A 0.9% increase in erythrocytes at 0.8 mg Co/kg/day LOAEL: Polycythemia, a 9.7% increase in erythrocytes at 1 mg Co/kg/day	Davis and Fields 1958
Human 6M, 6F	12 weeks, 7days/week Twice/day		0.018*	Increased hemoglobin in anephric (with non-functioning kidneys), hemoglobin deficient patients by 26-70%	Duckham and Lee 1976
Rats 1-3 NS	6 days/week, 7 months	0.05	0.5*	Unspecified increased in RBC, RBC diameter, and hemoglobin, mild transient polycythemia	Krasovskii and Fridlyand 1971
Rats-Sprague-Dawley 8-12 M	Daily, 7days/week, 4 weeks	7.59M	11.4M	20% decrease in hemoglobin	Chetty et al. 1979
Rats Sprague-Dawley 10 B	Daily, 90 days	0.74M	2.48M	10.7%, 9.2%, and 10.2% increase in hemoglobin, erythrocytes, and hematocrit, respectively	Danzeisen et al. 2020
Rats-Sprague-Dawley 20 M	Daily, 7 days/week, 13 weeks		30.2 M	29% increase in hematocrit, 31% increase in hemoglobin	Domingo et al. 1984
Rats-Sprague-Dawley 40 M, 40F	Daily, 90 days	0.74	2.48 M, 7.44 F	Males showed 10.7% increase in hemoglobin, 9.2% increase in red blood cells, 10.3% increase in hematocrit. Females showed a 13.4% increase in hemoglobin, 9.8% increase in red blood cells, and a 12% increase in hematocrit	Danzeisen et al. 2020
Mouse (ICR) 7,8 B	In utero and breastmilk, mothers exposed daily 2-3 days before birth and to post-natal day 18		18.57	Statistically significant 17% increase in erythrocyte count, 19% decrease in mean corpuscular hemoglobin, and 10% decrease in mean corpuscular volume, compared to controls	Gluhcheva et al. 2020

B = both males and females; F=females; M=males; NS= Not Specified; polycythemia (specifically absolute polycythemia) = author reported term associated with increased hemoglobin or erythrocyte count
*see text for explanation of why these studies were not chosen as the POD

Selection of the Principal Study: The Davis and Fields (1958) study identified a NOAEL and corresponding LOAEL for hematological effects in humans. Therefore, the Davis and Fields (1958) study was selected as the critical study because it identified the lowest NOAEL in the oral-intermediate duration database.

Summary of the Principal Study: Davis, J.E. and Fields, J.P. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc Soc Exp Biol Med 99:493-495.

For 22 days, two apparently healthy men, ages 20–47, were administered a daily dose of cobalt chloride, as a 2% solution diluted in either water or milk in divided doses across mealtimes each day. In this study each subject served as their own control, and blood samples were collected from each subject 7-14 days prior to the onset of oral administration. One subject received 150 mg cobalt chloride per day for the entire exposure period, while the other was started on 120 mg/day for 15 days and later increased to 150 mg/day for 7 more days (Table A-2). Blood samples were obtained daily from free-flowing punctures of fingertips at least 2 hours after eating, and at least 15 hours after the last dosage of cobalt. Blood was analyzed for red blood cell count, hemoglobin percentage, leukocyte count, reticulocyte percentage, and thrombocyte count. A crucial limitation of this study was that only 2 doses were used with one patient receiving the lower dose and the other receiving the higher dose. Additionally, the doses administered were not uniformly spaced out in time which could potentially have an effect on the outcome. However, data for the low dose individual provided data for establishing the study NOAEL.

Exposure to cobalt resulted in the development of polycythemia in the subject receiving the high dose. Increases in red blood cell numbers averaged 5.9 million for low dose exposure subject and averaged 6 million for the high dose exposure subject (a 9.7% increase for the high- dose subject above the pre-treatment level of approximately 5.4 million). Erythrocyte counts for the low-dose individual receiving 120 mg/day for 15 days changed only by 0.9%, hemoglobin values changed less, reticulocyte count increased less than 2-fold, and leukocyte counts stayed level, indicating that the NOAEL for this study was 120 mg/d (0.8 mg Co/kg/day). Erythrocyte counts returned to normal for the 2 individuals 9–15 days after cessation of cobalt administration.

The erythrocyte data from the study were only presented as a graph (Figure A-2). In order to understand the magnitude of the effect, the graph was digitized using an open-source software Curve Snap to better inform the oral intermediate-duration MRL derivation. The data extracted from the graph are listed in Table A-10 and A-11.

Figure A-2. Erythrocyte Numbers in 6 Subjects Before and During Daily Cobalt Treatments (Davis and Fields 1958)

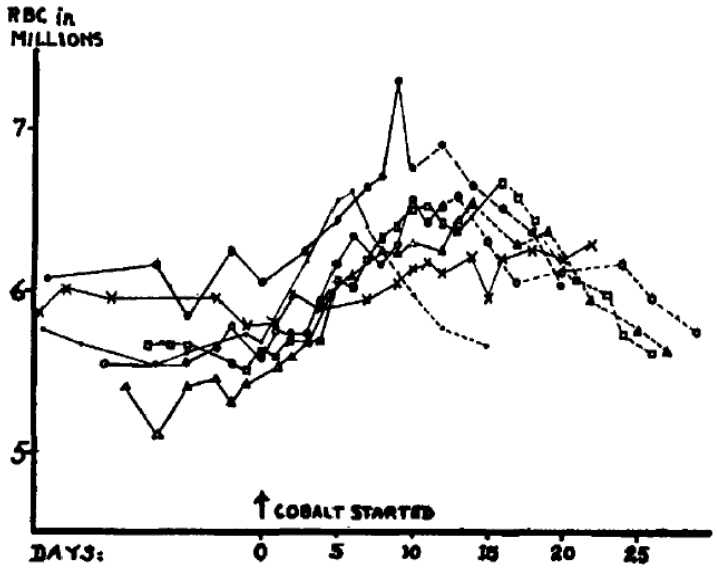


Figure A-2. The graph from Davis and Field 1958 shows erythrocyte numbers for 6 men who were exposed to cobalt; 4/6 men were exposed for 14 days (acute-duration) and 2/6 men were exposed for more than 14 days (intermediate-duration). Each subject was treated as a control for themselves.

Table A-10 Data Extracted from Figure A-2- Erythrocyte Levels before Cobalt exposure (RBC in millions)

Person #	Dose (mg Co/kg/day)	Symbol	Pre-treatment Day 1	Pre-treatment Day 2	Pre-treatment Day 3	Pre-treatment Day 4	Average pretreatment Erythrocyte counts Control (Pretreatment Levels)
2	120	x	5.80	5.94	5.90	5.89	**5.88**
4	150	□	5.40	5.40	5.50	5.40	**5.43**

Table A-11. Data Extracted from Figure A-2- Erythrocyte Levels during Intermediate Duration Cobalt Exposure (RBC in millions)

Per-son#	Dose	Symbol	Days of Acute Cobalt Exposure																	**Average Increase in Erythrocytes**
			0	1	2	4	7	9	10	11	12	14	15	16	17	18	19	20	22	23	
2	120	x	5.72	5.75	5.90	5.84	5.88	5.98	6.07	6.11	6.03	6.10	5.90	6.10		6.20		6.10	6.20	6.20	**5.93**
4	150	□	5.72	5.70	5.80	5.70	5.80	5.90	6.00	6.11	6.03	6.14	5.90		6.12		6.18	6.00		6.20	**5.95**

Thrombocyte and total leukocyte counts did not deviate significantly from pretreatment values. Changes in hemoglobin presented in the study are not presented here as they do not consider the duration of exposure for each subject and there is not enough information presented to calculate the changes in hemoglobin. The health effects of the study by Davis and Fields (1958) are presented in Table A-12.

Table A-12. Erythrocyte and Hemoglobin Levels in Humans Orally Exposed to Cobalt Chloride for 15-23 consecutive days (Davis and Fields 1958)

Effects	Dose (1 mg Co/kg/day) (22-23 days)	Dose (0.8 mg Co/kg/day) (15 days)
Average Increase in Erythrocytes (cells/mm^3)	9.7% increase	0.9% increase

Selection of the Point of Departure for the MRL: Davis and Fields (1958) identified a LOAEL of 1 mg cobalt/kg/day for polycythemia defined by the study authors as increased levels of erythrocytes in human males exposed daily for 23 days. At the dose of 0.8 mg Co/kg/day for 15 days, no effects were observed. This NOAEL is used as a POD to derive an MRL. The available data in Davis and Fields (1958) are not amenable to benchmark dose modeling as the study only tested one exposure dose. The study reported intake of 120 and 150 mg cobalt chloride/day which was converted to a daily dose of cobalt using the EPA reference body weight of 70 kg for adult humans:

For the low dose,

$$120\ mg\ CoCl_2/day = \ 120 \times \frac{58.9\frac{g}{mol}\ Co}{128.8\frac{g}{mol}\ CoCl_2} = 54.9\ mg\ Co/day$$

Based on assuming a 70 kg body weight of the subjects in the study, this dose equals 54.9/70 = 0.78 mg Co/kg/day ~ 0.8 mg Co/kg/day.

For the high dose,

$$150\ mg\ CoCl_2/day = \ 150 \times \frac{58.9\frac{g}{mol}\ Co}{128.8\frac{g}{mol}\ CoCl_2} = 68.1\ mg\ Co/day. Dividing\ by\ 70\ kg$$

$$= 0.97\ mg\ Co/kg/day \sim 1\ mg\ Co/kg/day$$

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty and Modifying Factors: The NOAEL was divided by a total uncertainty factor of 10 for human variability and a modifying factor of 3 to account for a limited database as detailed previously in the introduction.

$$Provisional\ MRL = \frac{NOAEL}{UFs\ x\ MF} = \frac{0.8\ mg/kg/day}{10\ x\ 3}$$

$$= 0.03\ \text{mg Co/kg/day}$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL:

No other studies of the effect of intermediate-duration oral cobalt exposure on erythrocyte levels in healthy human subjects were identified in a search of the literature. Holly (1955) did not see an effect of oral administration of 0.6 mg Co/kg/day as cobalt chloride for 90 days. Duckham and Lee (1976) observed a 26-70% increase in hemoglobin levels after exposure to 0.18 mg Co/kg/day after a 25 day exposure in anephric (with non-functioning kidneys) patients which makes it difficult to extrapolate this finding to healthy human beings.

Animal studies also examined hematological effects and these are listed in LSE Table 2-3. All but one study have considerable methodological limitations including examination of either very high exposure levels or only one exposure level, limited reporting of results, or limited or no statistical analysis. Danzeisen et al. (2020) was used to derive a Derived No-Effect Level (DNEL) for oral cobalt exposure which was calculated as 0.0298 mg Co/kg/day by the Cobalt REACH Consortium. The UFs used to derive the DNEL were a total UF of 25 which included UF of 5 for human variability, and the NOAEL in mg/kg/day was converted to µg/kg/day. The calculated DNEL was 29.8 µg Co/kg/day or 0.0298 mg Co/kg/day which can be rounded to 0.03 mg Co/kg/day. The derived DNEL is effectively identical to ATSDR's intermediate-duration oral MRL (0.03 mg Co/kg/day). Because both values of DNEL and MRL converge on very similar numbers, ATSDR retains the intermediate- duration oral MRL derived from the human exposure study by Davis and Fields 1958. The doses used to derive the DNEL as indicated in Danzeisen et el. (2020) lend strong support to the derived MRL

A 7 month exposure to 0, 0.05, 0.5, or 2.5 mg Co/kg/day in rats showed hematological effects in Krasovskii and Fridyland (1971). An increase in erythrocyte levels was seen at 0.5 mg Co/kg/day, but no numerical data nor statistical analysis and significance were reported and the number of animals in the treatment group were low in Krasovskii and Fridyland (1971). A 4 week exposure to 11.4 mg Co/kg/day caused a 20% decrease in hemoglobin in rats which is contrary to the results seen in Davis and Fields (1958) and this could potentially be due to experimental differences in the study (Chetty et al. 1979). Domingo et al (1984) observed a 31% increase in hemoglobin and a 29% increase in hematocrit in Sprague-Dawley rats for 13 weeks at 30.2 mg Co/kg/day. Gluhcheva et al. (2020) determined that 18.57 mg Co/kg/day caused a significant 17% increase in erythrocyte count, a 19% decrease in mean corpuscular hemoglobin, and a 10% decrease in mean corpuscular volume, compared to control mice. This study included only one dose of exposure similar to another study by the same authors where the observed unspecified hemoglobin changes and hematopoiesis at 18.58 mg Co/kg/day were seen in mice as well (Gluhcheva et al. 2014)

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Cobalt and compounds
CAS Numbers: 7440-48-8
Date: January 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

Provisional MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL as no studies were identified that examined chronic oral exposure to cobalt in either humans or animals.

Rationale for Not Deriving an MRL: No adequately conducted chronic-duration exposure studies in humans and laboratory animals were identified that adhered to ATSDR guidelines and investigated health effects resulting from chronic oral exposure to cobalt or its compounds.

Agency Contact (Chemical Manager): Sam Keith, MS, CHP

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR COBALT

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to cobalt.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for cobalt. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of cobalt have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of cobalt are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

Health Effects
Species
Human
Laboratory mammals
Drosophila (for genotoxicity studies)
In vitro assay (for genotoxicity and for supporting data for other endpoints)
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Endocrine effects
Dermal effects
Ocular effects
Body weight effects
Metabolic effects
Other systemic effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Genotoxicity
Cancer

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for cobalt (ATSDR 1992); thus, the literature search was restricted to studies published between August 21st, 2020 to September 22nd, 2020. The following main databases were searched in August 2020:

- PubMed
- MEDLINE
- Science Direct

- Scopus
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for cobalt. The query strings used for the literature search are presented in Table B-2. The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-2. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to cobalt were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database	Date	Query String
Medline	8/21/20	(MH (Cobalt) OR AB ("Cobalt-59" OR "Cobalt 59" OR "Cobalt Metal") OR RN (7440-48-4)) AND ((MH Death OR "Body Weight" OR "respiratory system" OR "cardiovascular diseases" OR "gastrointestinal diseases" OR "hematologic diseases" OR "musculoskeletal diseases" OR "hepatic infraction" OR "renal insufficiency" OR dermatology OR "endocrine system" OR neurology OR "reproductive health" OR "developmental disabilities" OR "psychology, developmental" OR Neoplasms OR "DNA Damage") OR (Death OR mortality OR lethal OR "lethal dose" OR "Lethal concentration" OR fatal OR fatality OR necrosis) OR ("body weight" OR "weight loss" OR "weight gain" OR "weight change") OR (Respiratory OR "respiratory tract" OR "respiratory organ" OR "respiratory System" OR "respiratory volume" OR "respiratory function" OR "respiratory effect" OR "respiratory organ" OR "respiratory toxicity" OR "pulmonary edema" OR "pulmonary effect" OR "pulmonary system" OR "pulmonary function" OR "pulmonary organ" OR "pulmonary toxicity" OR airway OR Trachea OR tracheobronchial OR "lung function" OR "lung change*" OR "Lung congestion" OR nose OR nasal OR nasopharyngeal OR larynx OR pharynx OR Bronchial or bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation or irritant OR cilia OR mucocilliary) OR (CVD OR Cardio OR Vascular OR "Cardiovascular system" OR "cardiovascular function" OR "cardiovascular effect" OR "cardiovascular organ" OR "cardiovascular toxicity" OR "Circulatory system" OR "circulatory function" OR "circulatory effect" OR "circulatory organ" OR "circulatory toxicity" OR "Cardiac arrest" OR "cardiac palpitation" OR "cardiac arrhythmia" OR "cardiac edema" OR "Heart rate" OR "heart failure" OR "heart attack" OR "heart muscle" OR "heart beat" OR "Blood pressure" OR "blood flow" OR

Table B-2. Database Query Strings

Database	Date	Query String
		"Myocardial infarction" OR "Chest pain" OR Artery OR arteries OR veins OR venules) OR (Gastrointestinal OR "Gastrointestinal system" OR "gastrointestinal function" OR "gastrointestinal effect" OR "gastrointestinal organ" OR "Digestive system" OR "digestive function" OR "digestive effect" OR "digestive organ" OR "Intestinal system" OR "intestinal function" OR "intestinal microbiota" OR "intestinal effect" OR "intestinal organ" OR "GI tract" OR "GI disorder" OR Abdominal OR Esophagus OR Stomach OR Intestine OR Pancreas OR Pancreatic OR Diarrhea OR Nausea OR Vomit OR Ulcer OR Constipation OR Emesis OR "Gut microbes" OR "gut flora" OR "gut microflora OR anorexia) OR (Hematological OR Hematology OR "hematology system" OR "hematology function" OR "hematology effect" OR "hematology toxicity" OR Hemato OR Haemato OR Blood OR "blood chemistry" OR "blood disease" OR Anemia OR Cyanosis OR Erythrocytopenia OR Leukopenia OR Thrombocytopenia OR Hemoglobin OR Erythrocyte OR Hematocrit OR "Bone marrow" OR "bone marrow decrease" OR "bone marrow hyper" OR "bone marrow hypoplasia" OR Reticulocyte OR Methemoglobin OR "Red blood cell") OR (Musculoskeletal OR Skeletal OR "skeletal system" OR "skeletal function" OR "skeletal effect" OR Muscle OR "muscle loss" OR "muscle strength" OR "muscle structure" OR Muscular OR "muscular rigidity" OR "muscular atrophy" OR "muscular structure" OR "muscular system" OR Arthritis OR "Altered bone" OR "joint pain" OR "joint ache" OR "limb pain" OR "limb ache") OR (Hepatic OR "hepatic system" OR "hepatic function" OR "hepatic effect" OR "hepatic organ" OR "hepatic response" OR "hepatic necrosis" OR "hepatic biochemical changes" OR "hepatic toxicity" OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR "gallbladder system" OR "gallbladder function" OR "gallbladder organ" OR "gallbladder effect" OR "gallbladder toxicity" OR Hepatocytes OR Cirrhosis OR Jaundice OR "Hepatocellular degeneration" OR "hepatocellular hypertrophy" OR Hepatomegaly) OR ("Renal system" OR "renal function" OR "renal effect" OR "renal organ" OR "renal tubular" OR "renal toxicity" OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR BUN OR nephropathy) OR ("Dermal system" OR "dermal function" OR "dermal effect" OR "dermal irritation" OR "dermal toxicity" OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin Necrosis" OR "skin acanthosis" OR dermatitis OR edema OR ulceration OR acne) OR ("Ocular system" OR "ocular function" OR "ocular effect" OR "ocular irritation" OR "ocular toxicity" OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR Blindness OR Myopia OR Cataracts) OR

Table B-2. Database Query Strings

Database	Date	Query String
		(“Endocrine system” OR “endocrine function” OR “endocrine effect” OR “endocrine gland” OR “endocrine toxicity” OR “hormone changes” OR “hormone excess” OR “hormone deficiency” OR “hormone gland” OR “hormone secretion” OR “hormone toxicity” OR Pancreas OR “Pancreatic system” OR “pancreatic function” OR “pancreatic effect” OR “pancreatic toxicity” OR “sella turcica” OR thyroid OR adrenal OR pituitary) OR (“Immunological system” OR “immunological function” OR “immunological effect” OR “immunological toxicity” OR Immune OR “immunologic system” OR “immunologic function” OR “immunologic effect” OR “immunologic response” OR “immunologic tissue” OR “immunologic toxicity” OR “Lymphoreticular changes” OR “Lymphoreticular effects” OR “Lymphoreticular function” OR “Lymphoreticular tissue” OR “Lymph node” OR Spleen OR Thymus OR Macrophage OR “white blood cell”) OR (Neurological OR neurologic OR “Neuro system” OR “neuro function” OR “neuro effect” OR “neuro toxicity” OR “Nervous system” OR “Brain function” OR “brain effect” OR “brain toxicity” OR Neurotoxicant OR Neurochemistry OR Neurophysiology OR Neuropathology OR “Motor activity” OR “motor change” OR (Changes AND (behavior OR behavioral OR sensory OR cognitive)) OR Vertigo OR Drowsiness OR Headache OR Ataxia) OR (Reproductive OR “reproduction system” OR “reproduction function” OR “reproduction effect” OR “reproduction toxicity” OR Fertility OR “Maternal toxicity”) OR (Developmental OR “development system” OR “developmental effect” OR “developmental toxicity” OR “developmental function” OR “developmental delay” OR “developmental abnormality” OR “developmental defect” OR (Offspring AND (“child effect” OR toxicity)) OR “In utero”) OR (“altered food consumption” OR “altered water consumption” OR “Metabolic effect” OR “metabolic toxicity” OR fever) OR (Cancer OR Cancerous OR Tumor OR Carcinoma OR Carcinogen OR Mutation) OR (Genotoxicity OR “Genotoxic in vivo” OR “genotoxic in vitro” OR Mutagenicity OR Mutagenic) OR (“Mechanism of action” OR “mechanism of absorption” OR “mechanism of distribution” OR “mechanism of excretion” OR “Mechanism of metabolism” OR “Mechanism of toxic effect”) OR (Human or Animal OR “Occupational workers” OR “Adverse effects” OR Poisoning OR Morbidity OR Inflammation OR antagonist OR inhibitor OR metabolism OR “environmental exposure” OR toxicokinetics OR pharmacokinetics OR “gene expression” OR epidemiology OR epidemiological OR “Population health” OR Inhalation OR “oral intake” OR “oral feed” OR “oral ingestion”) Limit to 2002-Present

Table B-2. Database Query Strings

Database	Date	Query String
Pubmed	8/21/20	((Cobalt[MeSH Terms]) OR TI/AB (“Cobalt 59” OR “Cobalt-59” OR “Cobalt Metal”) OR (7440-48-4[EC/RN Number])) AND ((“Death”[MeSH Terms] OR “Body Weight”[MeSH Terms] OR “respiratory system”[MeSH Terms] OR “cardiovascular diseases”[MeSH Terms] OR “gastrointestinal diseases” [MeSH Terms] OR “hematologic diseases” [MeSH Terms] OR “musculoskeletal diseases” [MeSH Terms] OR “hepatic infraction” [MeSH Terms] OR “renal insufficiency” [MeSH Terms] OR dermatology [MeSH Terms] OR “endocrine system” [MeSH Terms] OR neurology[MeSH Terms] OR “reproductive health” [MeSH Terms] OR “developmental disabilities” [MeSH Terms] OR “psychology, developmental” [MeSH Terms] OR Neoplasms[MeSH Terms] OR “DNA Damage” [MeSH Terms]) OR TI/AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) Limit to 2002-Present
Science Direct	8/21/20	AB (Cobalt OR “Cobalt Metal” OR “Cobalt 59” OR “Cobalt-59” OR “7440-48-4”) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR ((Death OR mortality OR lethal OR “lethal dose” OR “Lethal concentration” OR fatal OR fatality OR necrosis) OR (“body weight” OR “weight loss” OR “weight gain” OR “weight change”) OR (Respiratory OR “respiratory tract” OR “respiratory organ” OR “respiratory System” OR “respiratory volume” OR “respiratory function” OR “respiratory effect” OR “respiratory organ” OR “respiratory toxicity” OR “pulmonary edema” OR “pulmonary effect” OR “pulmonary system” OR “pulmonary function” OR “pulmonary organ” OR “pulmonary toxicity” OR airway OR Trachea OR tracheobronchial OR “lung function” OR “lung change*” OR “Lung congestion” OR nose OR nasal OR nasopharyngeal OR larynx OR pharynx OR Bronchial or bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation or irritant OR cilia OR mucocilliary) OR (CVD OR Cardio OR Vascular OR “Cardiovascular system” OR “cardiovascular function” OR “cardiovascular effect” OR “cardiovascular organ” OR “cardiovascular toxicity” OR “Circulatory system” OR “circulatory function” OR “circulatory effect” OR “circulatory organ” OR “circulatory toxicity” OR “Cardiac arrest” OR “cardiac palpitation” OR “cardiac arrhythmia” OR “cardiac edema” OR “Heart rate” OR “heart failure” OR “heart attack” OR “heart muscle” OR “heart beat” OR “Blood pressure” OR “blood flow” OR

Table B-2. Database Query Strings

Database	Date	Query String
		“Myocardial infarction” OR “Chest pain” OR Artery OR arteries OR veins OR venules) OR (Gastrointestinal OR “Gastrointestinal system” OR “gastrointestinal function” OR “gastrointestinal effect” OR “gastrointestinal organ” OR “Digestive system” OR “digestive function” OR “digestive effect” OR “digestive organ” OR “Intestinal system” OR “intestinal function” OR “intestinal microbiota” OR “intestinal effect” OR “intestinal organ” OR “GI tract” OR “GI disorder” OR Abdominal OR Esophagus OR Stomach OR Intestine OR Pancreas OR Pancreatic OR Diarrhea OR Nausea OR Vomit OR Ulcer OR Constipation OR Emesis OR “Gut microbes” OR “gut flora” OR “gut microflora OR anorexia) OR (Hematological OR Hematology OR “hematology system” OR “hematology function” OR “hematology effect” OR “hematology toxicity” OR Hemato OR Haemato OR Blood OR “blood chemistry” OR “blood disease” OR Anemia OR Cyanosis OR Erythrocytopenia OR Leukopenia OR Thrombocytopenia OR Hemoglobin OR Erythrocyte OR Hematocrit OR “Bone marrow” OR “bone marrow decrease” OR “bone marrow hyper” OR “bone marrow hypoplasia” OR Reticulocyte OR Methemoglobin OR “Red blood cell”) OR (Musculoskeletal OR Skeletal OR “skeletal system” OR “skeletal function” OR “skeletal effect” OR Muscle OR “muscle loss” OR “muscle strength” OR “muscle structure” OR Muscular OR “muscular rigidity” OR “muscular atrophy” OR “muscular structure” OR “muscular system” OR Arthritis OR “Altered bone” OR “joint pain” OR “joint ache” OR “limb pain” OR “limb ache”) OR (Hepatic OR “hepatic system” OR “hepatic function” OR “hepatic effect” OR “hepatic organ” OR “hepatic response” OR “hepatic necrosis” OR “hepatic biochemical changes” OR “hepatic toxicity” OR “liver system” OR “liver function” OR “liver effect” OR “liver organ” OR “Liver enzyme” OR “liver weight” OR “liver congestion” OR “liver changes” OR “liver biochemical changes” OR “liver toxicity” OR “gallbladder system” OR “gallbladder function” OR “gallbladder organ” OR “gallbladder effect” OR “gallbladder toxicity” OR Hepatocytes OR Cirrhosis OR Jaundice OR “Hepatocellular degeneration” OR “hepatocellular hypertrophy” OR Hepatomegaly) OR (“Renal system” OR “renal function” OR “renal effect” OR “renal organ” OR “renal tubular” OR “renal toxicity” OR “kidney system” OR “kidney function” OR “Kidney effect” OR “kidney toxicity” OR “urinary system” OR “urinary function” OR “urinary effect” OR “Urinary toxicity” OR “bladder system” OR “bladder effect” OR “bladder function” OR “bladder toxicity” OR “Urine volume” OR “blood urea nitrogen” OR BUN OR nephropathy) OR (“Dermal system” OR “dermal function” OR “dermal effect” OR “dermal irritation” OR “dermal toxicity” OR “skin rash” OR “skin itch” OR “skin irritation” OR “skin redness” OR “skin effect” OR “skin Necrosis” OR “skin acanthosis” OR dermatitis OR edema OR ulceration OR acne) OR (“Ocular system” OR “ocular function” OR “ocular effect” OR “ocular irritation” OR “ocular toxicity” OR “eye function” OR “eye effect” OR “eye irritation” OR “eye drainage” OR “eye tearing” OR Blindness OR Myopia OR Cataracts) OR

Table B-2. Database Query Strings

Database	Date	Query String
		(“Endocrine system” OR “endocrine function” OR “endocrine effect” OR “endocrine gland” OR “endocrine toxicity” OR “hormone changes” OR “hormone excess” OR “hormone deficiency” OR “hormone gland” OR “hormone secretion” OR “hormone toxicity” OR Pancreas OR “Pancreatic system” OR “pancreatic function” OR “pancreatic effect” OR “pancreatic toxicity” OR “sella turcica” OR thyroid OR adrenal OR pituitary) OR (“Immunological system” OR “immunological function” OR “immunological effect” OR “immunological toxicity” OR Immune OR “immunologic system” OR “immunologic function” OR “immunologic effect” OR “immunologic response” OR “immunologic tissue” OR “immunologic toxicity” OR “Lymphoreticular changes” OR “Lymphoreticular effects” OR “Lymphoreticular function” OR “Lymphoreticular tissue” OR “Lymph node” OR Spleen OR Thymus OR Macrophage OR “white blood cell”) OR (Neurological OR neurologic OR “Neuro system” OR “neuro function” OR “neuro effect” OR “neuro toxicity” OR “Nervous system” OR “Brain function” OR “brain effect” OR “brain toxicity” OR Neurotoxicant OR Neurochemistry OR Neurophysiology OR Neuropathology OR “Motor activity” OR “motor change” OR (Changes AND (behavior OR behavioral OR sensory OR cognitive)) OR Vertigo OR Drowsiness OR Headache OR Ataxia) OR (Reproductive OR “reproduction system” OR “reproduction function” OR “reproduction effect” OR “reproduction toxicity” OR Fertility OR “Maternal toxicity”) OR (Developmental OR “development system” OR “developmental effect” OR “developmental toxicity” OR “developmental function” OR “developmental delay” OR “developmental abnormality” OR “developmental defect” OR (Offspring AND (“child effect” OR toxicity)) OR “In utero”) OR (“altered food consumption” OR “altered water consumption” OR “Metabolic effect” OR “metabolic toxicity” OR fever) OR (Cancer OR Cancerous OR Tumor OR Carcinoma OR Carcinogen OR Mutation) OR (Genotoxicity OR “Genotoxic in vivo” OR “genotoxic in vitro” OR Mutagenicity OR Mutagenic) OR (“Mechanism of action” OR “mechanism of absorption” OR “mechanism of distribution” OR “mechanism of excretion” OR “Mechanism of metabolism” OR “Mechanism of toxic effect”) OR (Human or Animal OR “Occupational workers” OR “Adverse effects” OR Poisoning OR Morbidity OR Inflammation OR antagonist OR inhibitor OR metabolism OR “environmental exposure” OR toxicokinetics OR pharmacokinetics OR “gene expression” OR epidemiology OR epidemiological OR “Population health” OR Inhalation OR “oral intake” OR “oral feed” OR “oral ingestion”)) ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency”

Table B-2. Database Query Strings

Database	Date	Query String
		OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) Limit to 2002-Present
Scopus	8/21/20	AB (Cobalt OR “Cobalt Metal” OR “Cobalt-59” OR “Cobalt 59” OR “7440-48-4”) AND AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR “health effects”) Limit to 2002-Present, Articles

Based on further discussion with ATSDR additional terms listed in Table B-3 were included to ensure that the literature search was inclusive of additional forms of cobalt.

Table B-3. Database Query Strings

Database	Date	Query String
Medline	9/17/20	(MH (Cobalt) OR AB (“Cobalt-59” OR “Cobalt 59” OR “Cobalt Metal” OR “cobalt (II) acetate” OR “cobalt (III) acetate” OR “cobalt (II) carbonate” OR “cobalt carbonyl” OR “cobalt (II) chloride” OR “cobalt (II) hydroxide” OR “cobalt (II) meso-porphyrin” OR “cobalt (II) napthenate” OR “cobalt (II) nitrate” OR “cobalt (II) oxide” OR “cobalt (III) oxide” OR “cobalt (II,III) oxide” OR “cobalt (II) sulfate” OR “cobalt hydride” OR “cobalt fluoride” OR “cobalt nitride” OR “glucosaminic acid cobalt”) OR RN (7440-48-4 OR 71-48-7 OR 917-69-1 OR 513-79-10 OR 10210-68-1 OR 7646-79-8 OR 21041-93-0 OR 21158-51-0 OR 10210-68-1 OR 7646-79-9 OR 21041-93-0 OR 21158-51-0 OR 1308-06-1 OR 10124-43-3)) AND ((MH Death OR “Body Weight” OR “respiratory system” OR “cardiovascular diseases” OR “gastrointestinal diseases” OR “hematologic diseases” OR “musculoskeletal diseases” OR “hepatic infraction” OR “renal insufficiency” OR dermatology OR “endocrine system” OR neurology OR “reproductive health” OR “developmental disabilities” OR “psychology, developmental” OR Neoplasms OR “DNA Damage”) OR (Death OR mortality OR lethal OR “lethal dose” OR “Lethal concentration” OR fatal OR fatality OR necrosis) OR (“body weight” OR “weight loss” OR “weight gain” OR “weight change”)

Table B-3. Database Query Strings

Database	Date	Query String
		OR (Respiratory OR “respiratory tract” OR “respiratory organ” OR “respiratory System” OR “respiratory volume” OR “respiratory function” OR “respiratory effect” OR “respiratory organ” OR “respiratory toxicity” OR “pulmonary edema” OR “pulmonary effect” OR “pulmonary system” OR “pulmonary function” OR “pulmonary organ” OR “pulmonary toxicity” OR airway OR Trachea OR tracheobronchial OR “lung function” OR “lung change*” OR “Lung congestion” OR nose OR nasal OR nasopharyngeal OR larynx OR pharynx OR Bronchial or bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation or irritant OR cilia OR mucocilliary) OR (CVD OR Cardio OR Vascular OR “Cardiovascular system” OR “cardiovascular function” OR “cardiovascular effect” OR “cardiovascular organ” OR “cardiovascular toxicity” OR “Circulatory system” OR “circulatory function” OR “circulatory effect” OR “circulatory organ” OR “circulatory toxicity” OR “Cardiac arrest” OR “cardiac palpitation” OR “cardiac arrhythmia” OR “cardiac edema” OR “Heart rate” OR “heart failure” OR “heart attack” OR “heart muscle” OR “heart beat” OR “Blood pressure” OR “blood flow” OR “Myocardial infarction” OR “Chest pain” OR Artery OR arteries OR veins OR venules) OR (Gastrointestinal OR “Gastrointestinal system” OR “gastrointestinal function” OR “gastrointestinal effect” OR “gastrointestinal organ” OR “Digestive system” OR “digestive function” OR “digestive effect” OR “digestive organ” OR “Intestinal system” OR “intestinal function” OR “intestinal microbiota” OR “intestinal effect” OR “intestinal organ” OR “GI tract” OR “GI disorder” OR Abdominal OR Esophagus OR Stomach OR Intestine OR Pancreas OR Pancreatic OR Diarrhea OR Nausea OR Vomit OR Ulcer OR Constipation OR Emesis OR “Gut microbes” OR “gut flora” OR “gut microflora OR anorexia) OR (Hematological OR Hematology OR “hematology system” OR “hematology function” OR “hematology effect” OR “hematology toxicity” OR Hemato OR Haemato OR Blood OR “blood chemistry” OR “blood disease” OR Anemia OR Cyanosis OR Erythrocytopenia OR Leukopenia OR Thrombocytopenia OR Hemoglobin OR Erythrocyte OR Hematocrit OR “Bone marrow” OR “bone marrow decrease” OR “bone marrow hyper” OR “bone marrow hypoplasia” OR Reticulocyte OR Methemoglobin OR “Red blood cell”) OR (Musculoskeletal OR Skeletal OR “skeletal system” OR “skeletal function” OR “skeletal effect” OR Muscle OR “muscle loss” OR “muscle strength” OR “muscle structure” OR Muscular OR “muscular rigidity” OR “muscular atrophy” OR “muscular structure” OR “muscular system” OR Arthritis OR “Altered bone” OR “joint pain” OR “joint ache” OR “limb pain” OR “limb ache”) OR (Hepatic OR “hepatic system” OR “hepatic function” OR “hepatic effect” OR “hepatic organ” OR “hepatic response” OR “hepatic

Table B-3. Database Query Strings

Database	Date	Query String
		necrosis" OR "hepatic biochemical changes" OR "hepatic toxicity" OR "liver system" OR "liver function" OR "liver effect" OR "liver organ" OR "Liver enzyme" OR "liver weight" OR "liver congestion" OR "liver changes" OR "liver biochemical changes" OR "liver toxicity" OR "gallbladder system" OR "gallbladder function" OR "gallbladder organ" OR "gallbladder effect" OR "gallbladder toxicity" OR Hepatocytes OR Cirrhosis OR Jaundice OR "Hepatocellular degeneration" OR "hepatocellular hypertrophy" OR Hepatomegaly) OR ("Renal system" OR "renal function" OR "renal effect" OR "renal organ" OR "renal tubular" OR "renal toxicity" OR "kidney system" OR "kidney function" OR "Kidney effect" OR "kidney toxicity" OR "urinary system" OR "urinary function" OR "urinary effect" OR "Urinary toxicity" OR "bladder system" OR "bladder effect" OR "bladder function" OR "bladder toxicity" OR "Urine volume" OR "blood urea nitrogen" OR BUN OR nephropathy) OR ("Dermal system" OR "dermal function" OR "dermal effect" OR "dermal irritation" OR "dermal toxicity" OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin Necrosis" OR "skin acanthosis" OR dermatitis OR edema OR ulceration OR acne) OR ("Ocular system" OR "ocular function" OR "ocular effect" OR "ocular irritation" OR "ocular toxicity" OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR Blindness OR Myopia OR Cataracts) OR ("Endocrine system" OR "endocrine function" OR "endocrine effect" OR "endocrine gland" OR "endocrine toxicity" OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR Pancreas OR "Pancreatic system" OR "pancreatic function" OR "pancreatic effect" OR "pancreatic toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary) OR ("Immunological system" OR "immunological function" OR "immunological effect" OR "immunological toxicity" OR Immune OR "immunologic system" OR "immunologic function" OR "immunologic effect" OR "immunologic response" OR "immunologic tissue" OR "immunologic toxicity" OR "Lymphoreticular changes" OR "Lymphoreticular effects" OR "Lymphoreticular function" OR "Lymphoreticular tissue" OR "Lymph node" OR Spleen OR Thymus OR Macrophage OR "white blood cell") OR (Neurological OR neurologic OR "Neuro system" OR "neuro function" OR "neuro effect" OR "neuro toxicity" OR "Nervous system" OR "Brain function" OR "brain effect" OR "brain toxicity" OR Neurotoxicant OR Neurochemistry OR Neurophysiology OR Neuropathology OR "Motor activity" OR "motor change" OR (Changes AND (behavior OR behavioral OR sensory OR cognitive)) OR Vertigo OR Drowsiness OR Headache OR Ataxia)

Table B-3. Database Query Strings

Database	Date	Query String
		OR (Reproductive OR “reproduction system” OR “reproduction function” OR “reproduction effect” OR “reproduction toxicity” OR Fertility OR “Maternal toxicity”) OR (Developmental OR “development system” OR “developmental effect” OR “developmental toxicity” OR “developmental function” OR “developmental delay” OR “developmental abnormality” OR “developmental defect” OR (Offspring AND (“child effect” OR toxicity)) OR “In utero”) OR (“altered food consumption” OR “altered water consumption” OR “Metabolic effect” OR “metabolic toxicity” OR fever) OR (Cancer OR Cancerous OR Tumor OR Carcinoma OR Carcinogen OR Mutation) OR (Genotoxicity OR “Genotoxic in vivo” OR “genotoxic in vitro” OR Mutagenicity OR Mutagenic) OR (“Mechanism of action” OR “mechanism of absorption” OR “mechanism of distribution” OR “mechanism of excretion” OR “Mechanism of metabolism” OR “Mechanism of toxic effect”) OR (Human or Animal OR “Occupational workers” OR “Adverse effects” OR Poisoning OR Morbidity OR Inflammation OR antagonist OR inhibitor OR metabolism OR “environmental exposure” OR toxicokinetics OR pharmacokinetics OR “gene expression” OR epidemiology OR epidemiological OR “Population health” OR Inhalation OR “oral intake” OR “oral feed” OR “oral ingestion”) Limit to 2002-Present
Pubmed	09/17/2020	((Cobalt[MeSH Terms]) OR TI/AB (“Cobalt 59” OR “Cobalt-59” OR “Cobalt Metal” OR “cobalt (II) acetate” OR “cobalt (III) acetate” OR “cobalt (II) carbonate” OR “cobalt carbonyl” OR “cobalt (II) chloride” OR “cobalt (II) hydroxide” OR “cobalt (II) meso-porphyrin” OR “cobalt (II) napthenate” OR “cobalt (II) nitrate” OR “cobalt (II) oxide” OR “cobalt (III) oxide” OR “cobalt (II,III) oxide” OR “cobalt (II) sulfate” OR “cobalt hydride” OR “cobalt fluoride” OR “cobalt nitride” OR “glucosaminic acid cobalt”) OR (7440-48-4 OR 71-48-7 OR 917-69-1 OR 513-79-10 OR 10210-68-1 OR 7646-79-8 OR 21041-93-0 OR 21158-51-0 OR 10210-68-1 OR 7646-79-9 OR 21041-93-0 OR 21158-51-0 OR 1308-06-1 OR 10124-43-3 [EC/RN Number])) AND ((“Death”[MeSH Terms] OR “Body Weight”[MeSH Terms] OR “respiratory system”[MeSH Terms] OR “cardiovascular diseases”[MeSH Terms] OR “gastrointestinal diseases” [MeSH Terms] OR “hematologic diseases” [MeSH Terms] OR “musculoskeletal diseases” [MeSH Terms] OR “hepatic infraction” [MeSH Terms] OR “renal insufficiency” [MeSH Terms] OR dermatology [MeSH Terms] OR “endocrine system” [MeSH Terms] OR neurology[MeSH Terms] OR “reproductive health” [MeSH Terms] OR “developmental disabilities” [MeSH Terms] OR “psychology, developmental” [MeSH Terms] OR Neoplasms[MeSH Terms] OR “DNA Damage” [MeSH Terms]) OR TI/AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR

Table B-3. Database Query Strings

Database	Date	Query String
		hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental OR Cancer OR genotoxicity OR noncancer OR “health effects”)) Limit to 2002-Present
Science Direct	09/17/2020	AB (Cobalt OR “Cobalt 59” OR “Cobalt-59” OR “Cobalt Metal” OR “cobalt (II) acetate” OR “cobalt (III) acetate” OR “cobalt (II) carbonate” OR “cobalt carbonyl” OR “cobalt (II) chloride” OR “cobalt (II) hydroxide” OR “cobalt (II) meso-porphyrin” OR “cobalt (II) napthenate” OR “cobalt (II) nitrate” OR “cobalt (II) oxide” OR “cobalt (III) oxide” OR “cobalt (II,III) oxide” OR “cobalt (II) sulfate” OR “cobalt hydride” OR “cobalt fluoride” OR “cobalt nitride” OR “glucosaminic acid cobalt” OR “7440-48-4” OR “71-48-7” OR “917-69-1” OR “513-79-10” OR “10210-68-1” OR “7646-79-8” OR “21041-93-0” OR “21158-51-0” OR “10210-68-1” OR “7646-79-9” OR “21041-93-0” OR “21158-51-0” OR “1308-06-1” OR “10124-43-3”) AND ((Death OR mortality OR lethal OR “lethal dose” OR “Lethal concentration” OR fatal OR fatality OR necrosis) OR (“body weight” OR “weight loss” OR “weight gain” OR “weight change”) OR (Respiratory OR “respiratory tract” OR “respiratory organ” OR “respiratory System” OR “respiratory volume” OR “respiratory function” OR “respiratory effect” OR “respiratory organ” OR “respiratory toxicity” OR “pulmonary edema” OR “pulmonary effect” OR “pulmonary system” OR “pulmonary function” OR “pulmonary organ” OR “pulmonary toxicity” OR airway OR Trachea OR tracheobronchial OR “lung function” OR “lung change*” OR “Lung congestion” OR nose OR nasal OR nasopharyngeal OR larynx OR pharynx OR Bronchial or bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation or irritant OR cilia OR mucocilliary) OR (CVD OR Cardio OR Vascular OR “Cardiovascular system” OR “cardiovascular function” OR “cardiovascular effect” OR “cardiovascular organ” OR “cardiovascular toxicity” OR “Circulatory system” OR “circulatory function” OR “circulatory effect” OR “circulatory organ” OR “circulatory toxicity” OR “Cardiac arrest” OR “cardiac palpitation” OR “cardiac arrhythmia” OR “cardiac edema” OR “Heart rate” OR “heart failure” OR “heart attack” OR “heart muscle” OR “heart beat” OR “Blood pressure” OR “blood flow” OR “Myocardial infarction” OR “Chest pain” OR Artery OR arteries OR veins OR venules) OR (Gastrointestinal OR “Gastrointestinal system” OR “gastrointestinal function” OR “gastrointestinal effect” OR “gastrointestinal organ” OR “Digestive system” OR “digestive function” OR “digestive effect” OR “digestive organ” OR “Intestinal system” OR “intestinal function” OR “intestinal microbiota” OR “intestinal effect” OR “intestinal organ” OR “GI tract” OR “GI disorder” OR Abdominal OR Esophagus OR

Table B-3. Database Query Strings

Database	Date	Query String
		Stomach OR Intestine OR Pancreas OR Pancreatic OR Diarrhea OR Nausea OR Vomit OR Ulcer OR Constipation OR Emesis OR “Gut microbes” OR “gut flora” OR “gut microflora OR anorexia) OR (Hematological OR Hematology OR “hematology system” OR “hematology function” OR “hematology effect” OR “hematology toxicity” OR Hemato OR Haemato OR Blood OR “blood chemistry” OR “blood disease” OR Anemia OR Cyanosis OR Erythrocytopenia OR Leukopenia OR Thrombocytopenia OR Hemoglobin OR Erythrocyte OR Hematocrit OR “Bone marrow” OR “bone marrow decrease” OR “bone marrow hyper” OR “bone marrow hypoplasia” OR Reticulocyte OR Methemoglobin OR “Red blood cell”) OR (Musculoskeletal OR Skeletal OR “skeletal system” OR “skeletal function” OR “skeletal effect” OR Muscle OR “muscle loss” OR “muscle strength” OR “muscle structure” OR Muscular OR “muscular rigidity” OR “muscular atrophy” OR “muscular structure” OR “muscular system” OR Arthritis OR “Altered bone” OR “joint pain” OR “joint ache” OR “limb pain” OR “limb ache”) OR (Hepatic OR “hepatic system” OR “hepatic function” OR “hepatic effect” OR “hepatic organ” OR “hepatic response” OR “hepatic necrosis” OR “hepatic biochemical changes” OR “hepatic toxicity” OR “liver system” OR “liver function” OR “liver effect” OR “liver organ” OR “Liver enzyme” OR “liver weight” OR “liver congestion” OR “liver changes” OR “liver biochemical changes” OR “liver toxicity” OR “gallbladder system” OR “gallbladder function” OR “gallbladder organ” OR “gallbladder effect” OR “gallbladder toxicity” OR Hepatocytes OR Cirrhosis OR Jaundice OR “Hepatocellular degeneration” OR “hepatocellular hypertrophy” OR Hepatomegaly) OR (“Renal system” OR “renal function” OR “renal effect” OR “renal organ” OR “renal tubular” OR “renal toxicity” OR “kidney system” OR “kidney function” OR “Kidney effect” OR “kidney toxicity” OR “urinary system” OR “urinary function” OR “urinary effect” OR “Urinary toxicity” OR “bladder system” OR “bladder effect” OR “bladder function” OR “bladder toxicity” OR “Urine volume” OR “blood urea nitrogen” OR BUN OR nephropathy) OR (“Dermal system” OR “dermal function” OR “dermal effect” OR “dermal irritation” OR “dermal toxicity” OR “skin rash” OR “skin itch” OR “skin irritation” OR “skin redness” OR “skin effect” OR “skin Necrosis” OR “skin acanthosis” OR dermatitis OR edema OR ulceration OR acne) OR (“Ocular system” OR “ocular function” OR “ocular effect” OR “ocular irritation” OR “ocular toxicity” OR “eye function” OR “eye effect” OR “eye irritation” OR “eye drainage” OR “eye tearing” OR Blindness OR Myopia OR Cataracts) OR (“Endocrine system” OR “endocrine function” OR “endocrine effect” OR “endocrine gland” OR “endocrine toxicity” OR “hormone changes”

Table B-3. Database Query Strings

Database	Date	Query String
		OR “hormone excess” OR “hormone deficiency” OR “hormone gland” OR “hormone secretion” OR “hormone toxicity” OR Pancreas OR “Pancreatic system” OR “pancreatic function” OR “pancreatic effect” OR “pancreatic toxicity” OR “sella turcica” OR thyroid OR adrenal OR pituitary) OR (“Immunological system” OR “immunological function” OR “immunological effect” OR “immunological toxicity” OR Immune OR “immunologic system” OR “immunologic function” OR “immunologic effect” OR “immunologic response” OR “immunologic tissue” OR “immunologic toxicity” OR “Lymphoreticular changes” OR “Lymphoreticular effects” OR “Lymphoreticular function” OR “Lymphoreticular tissue” OR “Lymph node” OR Spleen OR Thymus OR Macrophage OR “white blood cell”) OR (Neurological OR neurologic OR “Neuro system” OR “neuro function” OR “neuro effect” OR “neuro toxicity” OR “Nervous system” OR “Brain function” OR “brain effect” OR “brain toxicity” OR Neurotoxicant OR Neurochemistry OR Neurophysiology OR Neuropathology OR “Motor activity” OR “motor change” OR (Changes AND (behavior OR behavioral OR sensory OR cognitive)) OR Vertigo OR Drowsiness OR Headache OR Ataxia) OR (Reproductive OR “reproduction system” OR “reproduction function” OR “reproduction effect” OR “reproduction toxicity” OR Fertility OR “Maternal toxicity”) OR (Developmental OR “development system” OR “developmental effect” OR “developmental toxicity” OR “developmental function” OR “developmental delay” OR “developmental abnormality” OR “developmental defect” OR (Offspring AND (“child effect” OR toxicity)) OR “In utero”) OR (“altered food consumption” OR “altered water consumption” OR “Metabolic effect” OR “metabolic toxicity” OR fever) OR (Cancer OR Cancerous OR Tumor OR Carcinoma OR Carcinogen OR Mutation) OR (Genotoxicity OR “Genotoxic in vivo” OR “genotoxic in vitro” OR Mutagenicity OR Mutagenic) OR (“Mechanism of action” OR “mechanism of absorption” OR “mechanism of distribution” OR “mechanism of excretion” OR “Mechanism of metabolism” OR “Mechanism of toxic effect”) OR (Human or Animal OR “Occupational workers” OR “Adverse effects” OR Poisoning OR Morbidity OR Inflammation OR antagonist OR inhibitor OR metabolism OR “environmental exposure” OR toxicokinetics OR pharmacokinetics OR “gene expression” OR epidemiology OR epidemiological OR “Population health” OR Inhalation OR “oral intake” OR “oral feed” OR “oral ingestion”)) OR (“health effects”))

Table B-3. Database Query Strings

Database	Date	Query String
		Limit to 2002-Present
Scopus	09/17/2020	AB (Cobalt OR “Cobalt 59” OR “Cobalt-59” OR “Cobalt Metal” OR “cobalt (II) acetate” OR “cobalt (III) acetate” OR “cobalt (II) carbonate” OR “cobalt carbonyl” OR “cobalt (II) chloride” OR “cobalt (II) hydroxide” OR “cobalt (II) meso-porphyrin” OR “cobalt (II) napthenate” OR “cobalt (II) nitrate” OR “cobalt (II) oxide” OR “cobalt (III) oxide” OR “cobalt (II,III) oxide” OR “cobalt (II) sulfate” OR “cobalt hydride” OR “cobalt fluoride” OR “cobalt nitride” OR “glucosaminic acid cobalt” OR 7440-48-4 OR 71-48-7 OR 917-69-1 OR 513-79-10 OR 10210-68-1 OR 7646-79-8 OR 21041-93-0 OR 21158-51-0 OR 10210-68-1 OR 7646-79-9 OR 21041-93-0 OR 21158-51-0 OR 1308-06-1 OR 10124-43-3) AND AB (Death OR “Body weight” OR respiratory OR cardiovascular OR gastrointestinal OR hematological OR musculoskeletal OR hepatic OR Renal OR dermal OR ocular OR endocrine OR immunological OR neurological OR reproductive OR developmental) OR (Cancer OR genotoxicity OR noncancer OR “health effects”) Limit to 2002-Present, Articles

The September 2020 results were:

- Number of records identified from the sources (after duplicate removal): 16,544
- Number of records identified from other strategies: 6
- Total number of records to undergo literature screening: 16,550

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on [Substance x]:

- Title and abstract screen
- Full text screen

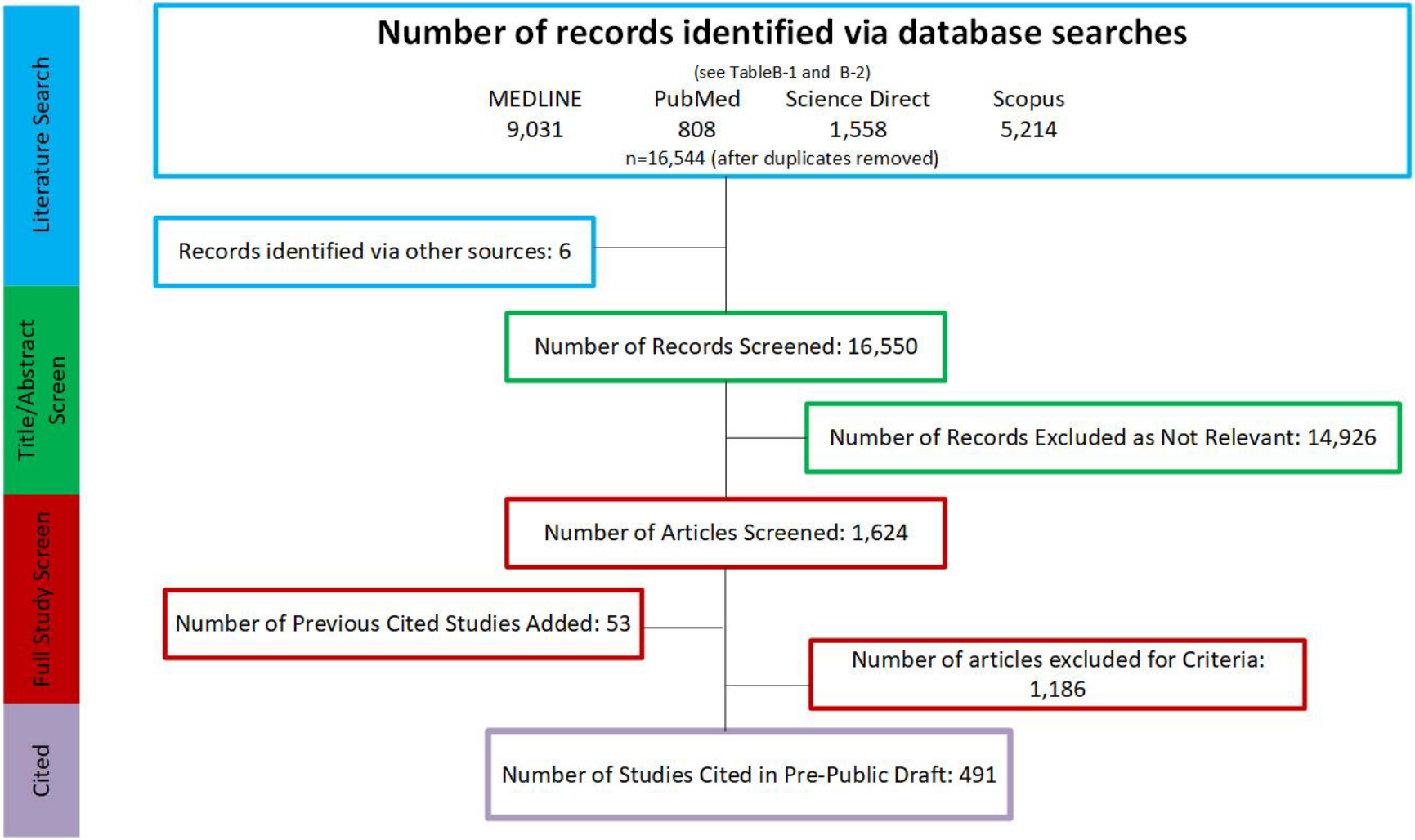
Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 16,550
- Number of studies considered relevant and moved to the next step: 1,624

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 1,624
- Number of studies cited in the pre-public draft of the toxicological profile: 491
- Total number of studies cited in the profile: 544

Figure B-1. May 2020 Literature Search Results and Screen for Cobalt



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR COBALT

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to cobalt, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to cobalt:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to cobalt. The inclusion criteria used to identify relevant studies examining the health effects of cobalt are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of cobalt. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the literature search to update the existing toxicological profile for cobalt (ATSDR 2004) was restricted to studies published between 2002 to 2020. See Appendix B for the databases searched and the search strategy.

A total of 16,550 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of cobalt.

Title and Abstract Screen. In the Title and Abstract Screen step, 16,550 records were reviewed; 438 studies were considered to meet the health effects inclusion criteria in Table B-1 and were moved to the next step in the process.

Full Text Screen. In November 2020, ATSDR received 27 studies that were relevant to cobalt toxicity and included into the full text screening. In the second step in the literature screening process for the systematic review, a full text review of the 438 health effects studies identified in the Title and Abstract Screen was performed. Among these studies, 411 studies did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanism of action or were relevant to other sections of the toxicological profile. Additionally, 53 health effects studies from the 2004 profile were included for review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-1. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

A summary of the extracted data for each study is presented in the Supplemental Documents for cobalt and overviews of the results of the inhalation, oral and dermal exposure studies are presented in Sections 2.2-2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Table 2-1, Table 2-2, and Table 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for cobalt identified in human and animal studies are presented in Table C-2 and Table C-3, respectively. These tables present the number of studies examining a given endpoint and then the number of studies that reported a treatment-related outcome. The available human toxicity studies primarily evaluated the respiratory and hematological endpoints including in controlled-exposure studies. Observational and controlled-exposure cohort studies and population level studies have primarily examine respiratory, cardiovascular, gastrointestinal, and hematological endpoints. Animal studies have examined all endpoints following oral and inhalation exposure to cobalt. The respiratory and hematological endpoints were the most examined in animal studies. Animal studies have also examined body weight, renal, hepatic, and reproductive effects in oral animal studies. A very limited number of animal studies examined toxicity following dermal exposure. Respiratory and hematological effects were considered sensitive outcomes of cobalt exposure, as effects were observed at low doses, and are commonly reported in case studies. Studies examining these two potential outcomes were carried through to Steps 4–8 of the systematic review.

Table C-2. Overview of the Health Outcomes for Cobalt Evaluated in Human Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Cohort		3 2	3 1		2 1		2 0	2 0			1 0						8 0
Case Control					1 1												1 0
Population		4 4	3 2		1 0				1 1		1 0			1 1			
Case Series		1 1															
Oral Studies																	
Cohort				4 4	5 4		1 0		1 1		3 2				1 0		
Case Control																	
Population																	
Case Series																	
Dermal Studies																	
Cohort																	
Case Control																	
Population																	
Case Series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

Table C-3. Overview of the Health Outcomes for Cobalt Evaluated in Experimental Animal Studies

	Body Weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation Studies																	
Acute-duration	2	3	2				2	2			2	2	2	2			
	2	3	1				2	1			0	2	2	0			
Intermediate-duration	10	15	7	5	9	4	7	7	4	5	4	8	5	7			5
	8	14	2	0	7	0	3	3	0	2	1	4	2	5			5
Chronic-duration	5	9	2	2		2	3	2	2	2	3	2	2	2		1	5
	2	8	0	0		0	1	0	0	0	1	2	0	2		0	5
Oral Studies																	
Acute-duration	4	1	5	2	4		4	6				3	7	2	3	1	
	2	0	5	2	4		2	5				2	6	2	2	1	
Intermediate-duration	21	2	9	2	17	1	13	8			3	8	11	10		3	
	12	1	6	0	11	0	8	6			1	7	9	9		3	
Chronic-duration																	
Dermal Studies																	
Acute-duration									1			3					
									1			3					
Intermediate-duration									1								
									1								
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

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C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Table C-4, Table C-5, and Table C-6, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (–)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C4. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-5. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of cobalt health effects studies: observational epidemiology, controlled-exposure human studies and animal experimental studies are presented in Table C-7, Table C-8, and Table C-9, respectively.

Table C-7. Summary of Risk of Bias Assessment for Cobalt- Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects							
Cohort studies							
Linna et al. 2003	+	+	+	+	+	+	First
Deng et al. 1991	-	-	+	-	+	+	Second
Gennart and Lauwerys 1990	+	-	-	-	+	-	Second
Kusaka et al. 1986	+	-	+	+	+	+	Second
Case-Control							
Sauni et al. 2010	-	+	+	-	+	+	Second
Cross-Sectional							
Walters et al. 2012	+	-	+	-	+	+	Second
Hamzah et al. 2014	+	-	+	+	+	+	Second
Nemery et al. 1992	+	-	+	+	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-8. Summary of Risk of Bias Assessment for Cobalt–Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Hematological effects								
Oral acute exposure								
Davis & Fields, 1958	-	+	+	+	-	+	+	First
Oral intermediate exposure								
Davis & Fields, 1958	-	+	+	+	-	+	+	First
Duckham &Lee 1976	-	+	+	+	-	+	+	First
Holly et al. 1955	-	+	+	+	-	+	+	First
Taylor et al. 1977	-	+	+	+	-	+	-	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

Table C-9. Summary of Risk Bias Assessment for Cobalt–Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Respiratory effects									
Inhalation acute exposure									
Camner et al 1993 (guinea pigs)	-	+	-	-	+	-	+	+	Second
Palmes et al. 1959 (rats)	-	+	+	-	+	-	-	+	Second
Inhalation intermediate exposure									
Kerfoot 1974 (mini pigs)	-	+	++	-	++	-	+	+	First
Johansson et al. 1987 (rabbits)	-	+	++	-	++	-	+	+	First
Johansson et al. 1991 (rabbits)	-	+	++	-	++	-	+	+	First
Johansson et al. 1992 (rabbits)	-	+	++	-	++	-	+	+	First
NTP 2014 (rats, mice)	+	+	++	-	++	++	+	++	First
NTP 1991 (rats, mice)	+	+	++	-	++	++	+	++	First

Table C-9. Summary of Risk Bias Assessment for Cobalt–Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Palmes et al. 1959 (rats, guinea pigs)	-	+	+	-	+	-	-	+	Second
Inhalation chronic exposure									
NTP 2014 (rats, mice)	+	+	++	-	+	++	+	++	First
NTP 1998 (rats, mice)	+	+	++	+	++	++	+	++	First
Wehner et al. 1977 (hamster)	+	+	++	-	++	-	+	++	First
Outcome: Hematological effects									
Inhalation intermediate exposure									
Kerfoot 1974 (mini pigs)	-	+	++	-	++	-	+	+	Second
NTP 2014 (rats)	+	+	++	-	++	++	+	++	First
NTP 2014 (mice)	+	+	++	-	++	++	+	++	First
NTP 1991 (rats)	+	+	++	-	++	++	+	++	First
NTP 1991 (mice)	+	+	++	-	++	++	+	++	First
Palmes et al. 1959 (rats)	-	+	+	-	+	-	+	+	First

Table C-9. Summary of Risk Bias Assessment for Cobalt–Experimental Animal Studies

Reference	Risk of bias criteria and ratings								Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Palmes et al. 1959 (guinea pigs)	-	+	+	-	+	-	+	+	First
Inhalation chronic exposure									
NTP 2014 (rats, mice)	+	+	++	-	+	++	+	++	First
Oral acute exposure									
Awoyemi et al. 2017 (rats)	+	+	++	-	+	+	+	++	First
Shrivastava et al 2010 (rats)	+	+	++	+	+	+	+	++	First
Bryan and Bright, 1973 (mice)	-	+	++	+	-	-	+	++	First
Domingo and Llobet 1984 (rats)	-	+	++	+	+	+	+	+	First
Oral intermediate exposure									
Glucheva et al. 2020 (mice)	-	+	+	-	+	-	+	++	First
Glucheva et al. 2014 (mice)	-	+	+	-	-	-	+	++	Second
Chetty et al. 1979 (rats)	-	+	+	+	+	-	+	++	First

Table C-9. Summary of Risk Bias Assessment for Cobalt–Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Corrier et al. 1985 (rats)	+	+	+	+	-	-	+	++	First
Bryan and Bright, 1973 (mice)	-	+	++	+	-	-	+	++	First
Domingo et al. 1984 (rats)	-	+	++	+	-	-	-	++	Second
Danzeisen et al. 2020 (rats)	+	+	++	-	+	++	+	++	First
Haga et al. 1996 (rats)	+	+	++	+	-	-	-	++	Second
Krasovskii & Fridlyand 1971	-	-	-	-	-	-	-	-	Third
Pedigo and Vernon 1993 (mice)	-	+	++	+	-	+	-	+	Second
Pehrsson et al. 1991(rats)	-	+	++	+	-	-	-	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to cobalt and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to cobalt and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Table C-10, Table C-11, and Table C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory and hematological health effects observed in the observational epidemiology, controlled-exposure human studies and animal experimental studies are presented in Table C-13, Table C-14, and Table C-15, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table C-16. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence.

Table C-13. Presence of Key Features of Study Design for Cobalt- Observational

Reference	Key Features				
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects					
Cohort studies					
Linna et al. 2003	Yes	Yes	Yes	Yes	High
Deng et al. 1991	No	Yes	Yes	Yes	Moderate
Gennart and Lauwerys 1990	No	Yes	No	Yes	Low
Kusaka et al. 1986	Yes	Yes	Yes	Yes	High
Case-control studies					
Sauni et al. 2010	No	Yes	Yes	No	Low
Cross-sectional studies					
Walters et al. 2012	No	Yes	Yes	Yes	Moderate
Hamzah et al. 2014	Yes	Yes	Yes	Yes	High
Nemery et al. 1992	Yes	Yes	Yes	Yes	High

Table C-14. Presence of Key Features of Study Design for Cobalt- Human-Controlled Exposure Studies

Reference	Key Features				
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	Initial study confidence
Outcome: Hematological effects					
Oral Acute Exposure					
Davis & Fields 1958	Yes	No	Yes	Yes	Moderate
Oral Intermediate Exposure					
Davis & Fields 1958	Yes	No	Yes	Yes	Moderate
Duckham & Lee 1976	Yes	No	Yes	No	Low
Holly et al. 1955	Yes	No	Yes	No	Low
Taylor et al. 1977	Yes	No	No	Yes	Low

Table C-15. Presence of Key Features of Study Design for Cobalt- Experimental Animal Studies

Reference	Key Features				
	Controlled Exposure	Exposure prior to outcome	Outcome assessed on individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects					
Inhalation Acute Exposure					
Camner et al 1993 (gn pig)	Yes	Yes	Yes	Yes	High
NTP 2014 (rats)	Yes	Yes	Yes	Yes	High
NTP 2014 (mice)	Yes	Yes	Yes	Yes	High
NTP 1991 (rats)	Yes	Yes	Yes	Yes	High
NTP 1991 (mice)	Yes	Yes	Yes	Yes	High
Inhalation Intermediate Exposure					
Kerfoot, 1974 (mini pigs)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1987 (rabbits)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1991 (rabbits)	Yes	No	Yes	Yes	Moderate
Johansson et al. 1992 (rabbits)	Yes	No	Yes	Yes	Moderate
NTP 2014 (rats)	Yes	Yes	Yes	Yes	High
NTP 2014 (mice)	Yes	Yes	Yes	Yes	High
NTP 1991 (rats)	Yes	Yes	Yes	Yes	High
NTP 1991 (mice)	Yes	Yes	Yes	Yes	High
Palmes et al. 1959 (rats)	Yes	Yes	Yes	Yes	High
Inhalation Chronic Exposure					
NTP 2014 (rats)	Yes	Yes	Yes	Yes	High
NTP 2014 (mice)	Yes	Yes	Yes	Yes	High
NTP 1998 (rats)	Yes	Yes	Yes	Yes	High
NTP 1998 (mice)	Yes	Yes	Yes	Yes	High
Wehner et al. 1998 (hamster)	Yes	Yes	Yes	Yes	High
Outcome: Hematological effects					
Oral Acute Exposure					
Awoyemi et al. 2017 (rats)	Yes	Yes	Yes	Yes	High
Shrivastava et al. 2010 (rats)	Yes	Yes	Yes	Yes	High
Bryan and Bright 1973 (mice)	Yes	No	Yes	Yes	Moderate
Domingo and Llobet 1984 (rats)	Yes	Yes	Yes	Yes	High
Oral Intermediate Exposure					
Glucheva et al. 2020 (rats)	Yes	No	Yes	Yes	Moderate
Glucheva et al. 2014 (rats)	Yes	No	Yes	Yes	Moderate
Bryan and Bright 1973 (mice)	Yes	No	Yes	Yes	Moderate
Chetty et al. 1979 (rats)	Yes	Yes	Yes	Yes	High
Corrier et al. 1985 (rats)	Yes	No	Yes	Yes	Moderate

Domingo et al. 1984 (rats)	Yes	No	Yes	Yes	Moderate
Danzeisen et al. 2020 (rats)	Yes	Yes	Yes	Yes	High
Haga et al. 1996 (rats)	Yes	No	No	Yes	Low
Krasovskii and Fridlyand 1971 (mice)	Yes	No	Yes	No	Low
Pedigo and Vernon, 1993 (mice)	Yes	Yes	No	Yes	Moderate
Pehrsson et al 1991 (rats)	Yes	Yes	No	Yes	Moderate

Table C-16. Initial Confidence Rating for Cobalt Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Inhalation Acute Exposure		
Animal Studies		
Camner et al 1993 (gn pig)	High	High
NTP 2014 (rats)	High	
NTP 2014 (mice)	High	
NTP 1991 (rats)	High	
NTP 1991 (mice)	High	
Inhalation Intermediate Exposure		
Animal Studies		
Kerfoot, 1974 (mini pigs)	Moderate	High
Johansson et al. 1987 (rabbits)	Moderate	
Johansson et al. 1991 (rabbits)	Moderate	
Johansson et al. 1992 (rabbits)	Moderate	
NTP 2014 (rats)	High	
NTP 2014 (mice)	High	
NTP 1998 (rats)	High	
NTP 1998 (mice)	High	
Palmes et al. 1959	High	
Inhalation Chronic Exposure		
Animal Studies		
NTP 2014 (rats)	High	High
NTP 2014 (mice)	High	
NTP 1998 (rats)	High	
NTP 1998 (mice)	High	
Wehner et al. 1998 (hamster)	High	
Human Studies		
Linna et al. 2003	High	High
Deng et al. 1991	Moderate	
Gennart and Lauwerys 1990	Low	
Kusaka et al. 1986	High	

Table C-16. Initial Confidence Rating for Cobalt Health Effects Studies

Reference	Initial study confidence	Initial confidence rating
Sauni et al. 2010	Low	
Walters et al. 2012	Moderate	
Hamzah et al. 2014	High	
Nemery et al. 1992	High	
Outcome: Hematological effects		
Oral Acute Exposure		
Animal Studies		
Awoyemi et al. 2017 (rats)	High	
Shrivastava et al. 2010 (rats)	High	High
Bryan and Bright 1973 (mice)	Moderate	
Domingo and Llobet 1984 (rats)	High	
Human Studies		
Davis & Fields 1958	Moderate	Moderate
Oral Intermediate Exposure		
Animal Studies		
Glucheva et al. 2020 (rats)	Moderate	
Glucheva et al. 2014 (rats)	Moderate	
Bryan and Bright 1973 (mice)	Moderate	
Chetty et al. 1979 (rats)	High	
Corrier et al. 1985 (rats)	Moderate	
Domingo et al. 1984 (rats)	High	High
Danzeisen et al. 2020 (rats)	Moderate	
Haga et al. 1996 (rats)	Low	
Krasovskii and Fridlyand 1971 (mice)	Low	
Pedigo and Vernon, 1993 (mice)	Moderate	
Pehrsson et al 1991 (rats)	Moderate	
Human Studies		
Davis & Fields 1958	Moderate	
Duckham & Lee 1976	Low	Moderate
Holly et al. 1955	Low	
Taylor et al. 1977	Low	

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory and hematological effects are presented in Table C-17.

If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with cobalt exposure is presented in Table C-18.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Table C-7, Table C-8, and Table C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier
- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect
- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for

absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions
- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias
- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies
- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., “healthy worker” effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect
- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

The results of this assessment are presented in Table C-17, and the final confidence in the body of literature for the respiratory and hematological endpoints are presented in Table C-18.

Table C-17. Adjustments to the Initial Confidence in the Body of Evidence

	Initial Confidence	Adjustments to the initial confidence rating	Final Confidence Rating
Outcome: Respiratory effects			
Animal Studies	High	-1 Risk of Bias, -1 Indirectness, +1 Consistency in body of evidence	Moderate
Human Studies	High	+1 Consistency in body of evidence	High
Outcome: Hematological effects			
Animal Studies	High	-1 Risk of Bias, +1 Consistency in body of evidence	High
Human Studies	Moderate	-1 Risk of Bias, -1 Imprecision, +1 Consistency in body of evidence	Low

Table C-18. Confidence in the Body of Evidence for Cobalt

Outcome	Confidence in Body of Evidence	
	Human studies	Animal Studies
Respiratory Effects	High	Moderate
Hematological Effects	Low	High

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for cobalt, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome

- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for cobalt, is presented in Table C-19.

Table C-19. Level of Evidence of Health Effects for Cobalt

Outcome	Confidence in Body of Evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory Effects	High	Health Effect	High
Hematological Effects	Low	Health Effect	Low
Animal studies			
Respiratory Effects	Moderate	Health Effect	Moderate
Hematological Effects	High	Health Effect	High

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

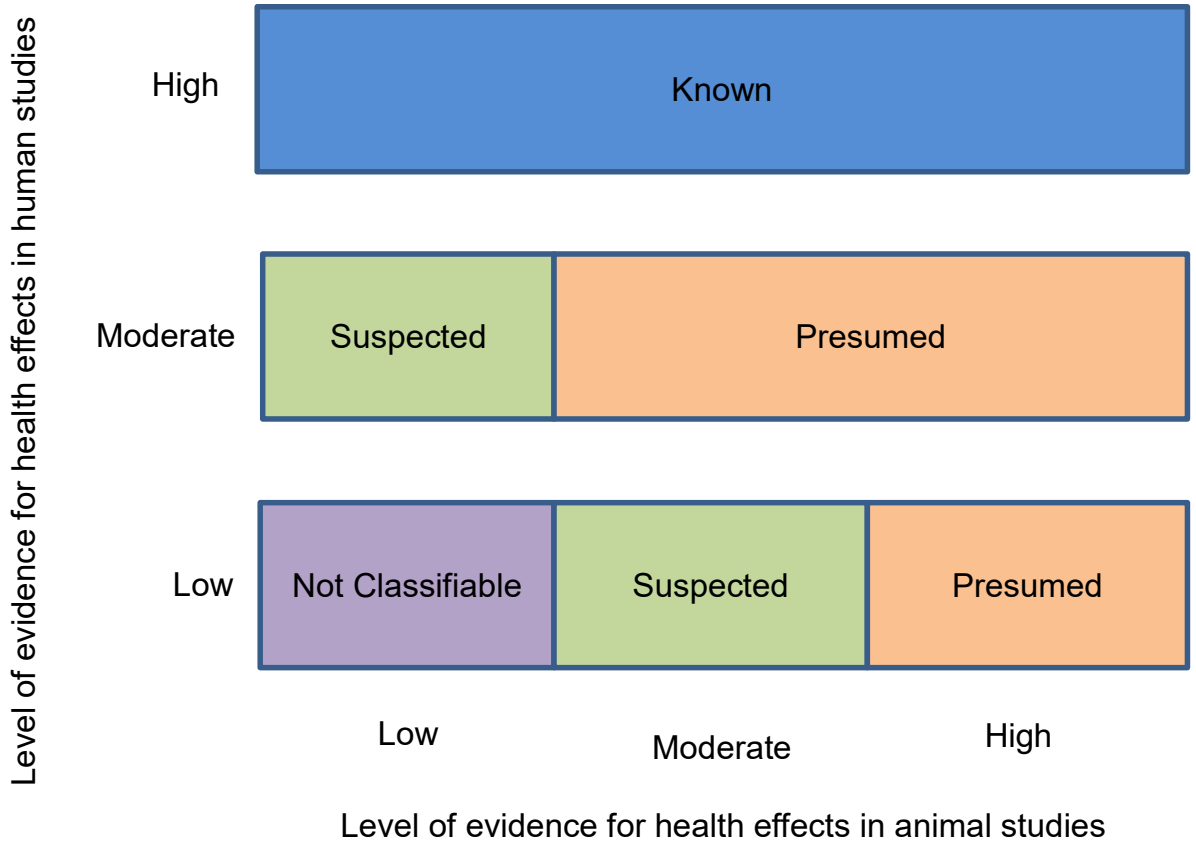
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known**: A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:

  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected**: A health effect in this category would have
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - High level of evidence for health effects in human studies AND a high, moderate, or low level of evidence in animal studies.
  - Low level of evidence in human studies AND high level of evidence in animal studies
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used.

The hazard identification conclusions for cobalt are listed below and summarized in Table C-20.

Known Health Effects

- Respiratory effects
  - High level of evidence in epidemiological studies exists where humans were occupationally exposed to cobalt by inhalation. The exposed workers showed altered spirometry and increased evidence of pulmonary irritation and dyspnea (Deng et al. 1991; Gennart and Lauwerys 1990; Kusaka et al. 1986).
  - No controlled-exposure studies for exposure to cobalt in humans were identified.
  - Moderate level of evidence of effects in mice, rats, and Guinea pigs to cobalt and its compounds showed health effects. Acute-duration exposure to cobalt increased inflammation, edema, and necrosis in the lungs (NTP 1991, 2014; Palmes et al. 1959). Intermediate-duration exposure caused an increase in lung weight and inflammation; chronic exposure increased neoplasms and hyperplasia along with lung inflammation (NTP 1991, 2014; Wehner et al. 1977).
  - No respiratory effects were observed in animal models after oral and dermal exposure to cobalt.
  - Based on high evidence from human studies and moderate evidence from animal studies, the respiratory end points of changes in spirometry should be classified as known health effect.

Presumed Health Effects

- Hematological effects
  - High level of evidence in animal studies were observed after intermediate- and chronic-duration inhalation exposure to cobalt sulfate and cobalt metal in rats and mice where a decrease in hemoglobin, hematocrit and platelet counts (NTP 1991, 2014) and an increase in erythrocytes and hematocrit were observed (NTP 2014).
  - High level of evidence in animal studies were observed after oral exposure to cobalt and its compounds. Acute- and intermediate-duration exposure in rats and mice caused an increase in hematocrit, hemoglobin, and erythrocytes (Domingo and Llobet 1984; Gluhcheva et al. 2014; Holly 1955; Shrivastava et al. 2008).
  - Low level evidence in human studies showed polycythemia after acute- and intermediate-duration oral exposure to cobalt (Davis and Fields 1958; Duckham and Lee 1976; Holly 1955).
  - Based on low level of evidence from human studies and high level of evidence from animal studies, an increase in erythrocytes should be classified as a presumed health effect.

Table C-20. Hazard Identification Conclusions for Cobalt

Outcome	Hazard identification
Respiratory Effects	Known
Hematological Effects	Presumed

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-

specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

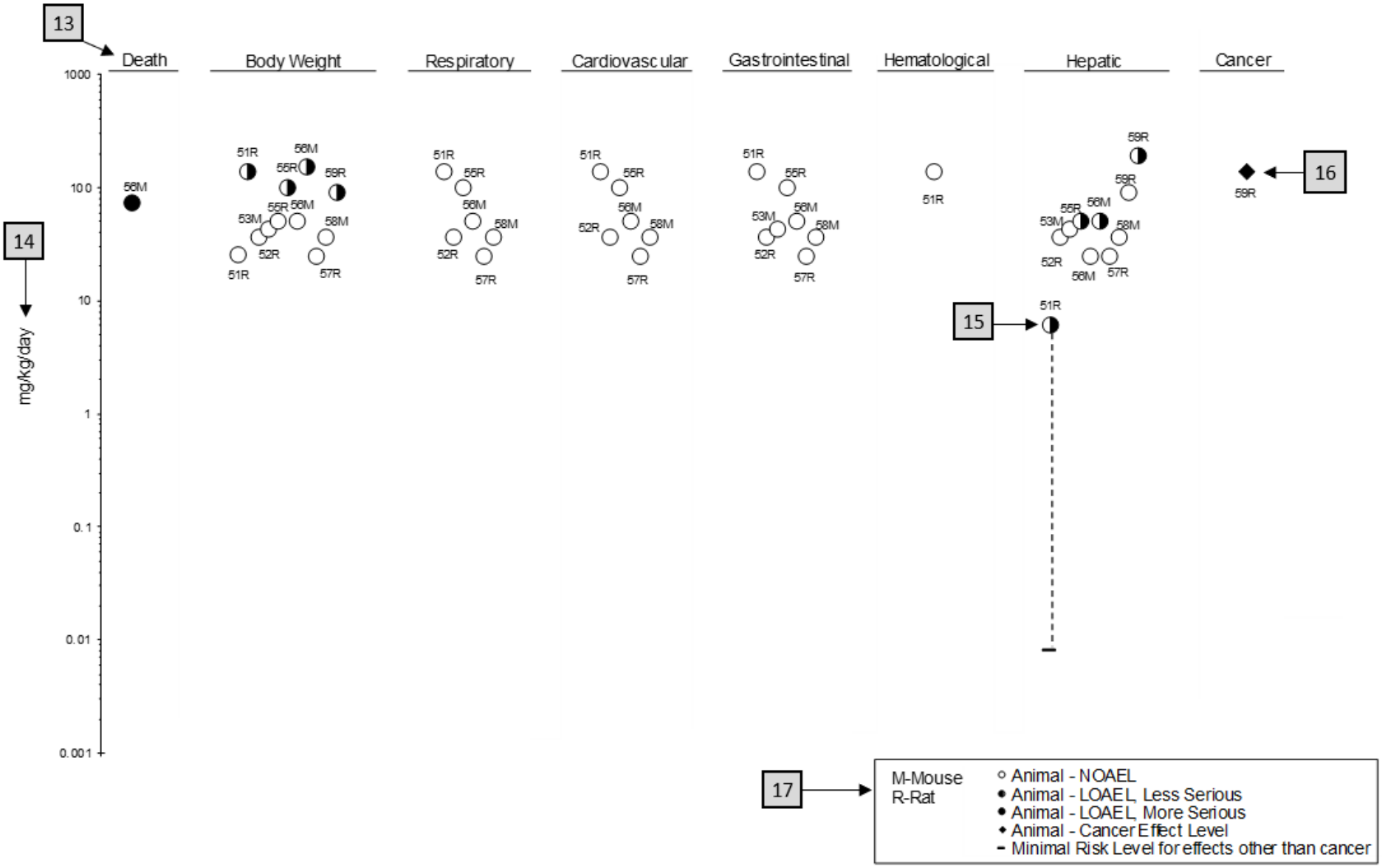
Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials. *Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

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Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at https://www.pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA

22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (Koc)—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD10 would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and in utero death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration(LO) (LCLO)—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC50)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(LO) (LDLO)—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose(50) (LD50)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time(50) (LT50)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (Kow)—The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAX	Bcl-2-associated X protein
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMDX	dose that produces a X% change in response rate of an adverse effect
BMDLX	95% lower confidence limit on the BMDX
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
COX2	Cyclooxygenase
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram

EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FEV, FEV1	Forced expiratory volume, Forced Expiratory Volume in 1 second
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPG	DNA-formamidopyrimidine glycosylase
FR	Federal Register
FSH	follicle stimulating hormone
FVC	Forced Vital Capacity
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
hOGG1	Human 8-Oxoguanine glycosylase
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
Koc	organic carbon partition coefficient
Kow	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC50	lethal concentration, 50% kill
LCLo	lethal concentration, low
LD50	lethal dose, 50% kill
LDLo	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT50	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter

mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error

SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q1*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result