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## ACM Public Meeting Records - Winneshiek County Sanitary Landfill (Permit No. 96-SDP-01-74P)

1 message

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Wilming, Gina M <Gina.Wilming@foth.com>

Thu, Nov 20, 2025 at 11:41 AM

To: "Mike Smith (Mike.Smith@dnr.iowa.gov)" <Mike.Smith@dnr.iowa.gov>

Cc: TJ Schissel <tj.schissel@co.winneshiek.ia.us>, "Oelkers, Chris G" <Chris.Oelkers@foth.com>, "Dubbs, Hannah E" <Hannah.Dubbs@foth.com>, Becky Jolly <becky.jolly@dnr.iowa.gov>

Mike –

The Groundwater Assessment of Corrective Measures public meeting for Winneshiek County Sanitary Landfill (Permit No. 96-SDP-01-74P) was held on Monday, October 13, 2025. The meeting records provided in this email and in the attachments are submitted per 567 IAC 113.10(7)d. These records will also be maintained in the facility's operating record.

The ACM public meeting was held in conjunction with the Winneshiek County Area Solid Waste Agency's October meeting. The Agency's meeting minutes are attached.

The following questions were asked following the Groundwater ACM presentation:

- **Question: Were any other parameters analyzed that would determine the source of the cobalt?** Wilming reviewed the Appendix I and II constituents included in the groundwater monitoring program, reviewed the semiannual monitoring results (noting none of the other II parameters have been detected at concentrations above the groundwater protection standards), and reviewed the landfill gas and leachate investigation measures conducted (leachate collection system inspection/survey, methane monitoring, additional landfill gas and leachate indicator parameter sampling, etc.). Wilming also discussed the ACM results regarding the reducing to oxidizing subsurface conditions caused by (1) the leachate joint leak near MW-31A and (2) reductions in infiltration/groundwater level impacts east of Cells 4 and 5 due to cell capping, placement of abutment liner, and construction of the leachate lagoons.
- **Question: If you were to pump and treat, would the pumps have a membrane filter?** For cobalt, a reverse osmosis or membrane filter would be an effective option for aboveground treatment; other filters and treatment methods would be evaluated if a pump and treat alternative were further considered.
- **Question: Do you see an increase in cobalt with an above-average rain event?** Yes, heavy rain can leach naturally occurring cobalt in soil and bedrock into groundwater. In addition, increases in precipitation can increase reducing conditions, mobilizing naturally occurring cobalt in soil and bedrock into groundwater.
- **Question: Do you have graphs that show this data historically?** MW-29A, MW-31A, and MW-35 have been monitored since November 2019. We have trend graphs depicting the stable or decreasing cobalt trends between November 2019 and June 2025.
- **Question: What are the health effects of cobalt on humans and cattle?** This was not included in the presentation. Wilming offered to follow up with the homeowner regarding this question. Bob Sersland was contacted by phone on November 13. A follow-up letter was sent to Bob Sersland (via mail) and Keith Sersland (via email). A copy of the follow-up letter is attached to this email.

- **Question: What is considered a shallow well?** Discussion ensued with the neighbor regarding the depth of their well and the gradient from the landfill. Also discussed shale layers in bedrock that limit the vertical movement of groundwater and potential contaminants.

No objections to the recommended Monitored Natural Attenuation remedy were expressed during the meeting. No written or verbal comments were received after the meeting.

### Gina Wilming

Senior Project Manager



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#### 2 attachments



**WCASWA 101325.pdf**  
128K



**LR-Sersland Cobalt Follow-Up.pdf**  
4749K



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November 20, 2025

Bob Sersland  
800 Clearview Drive  
Decorah, IA 52101

Re: Cobalt Health Effects  
October 13, 2025 Public Meeting: Groundwater Assessment of Corrective Measures  
Winneshiek County Sanitary Landfill

Dear Bob Sersland:

This letter is submitted as a follow-up to your question regarding health effects from exposure to cobalt at the October 13, 2025 public meeting and our phone conversation on November 11. Attached to this letter are two fact sheets developed by the United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) for cobalt. These are the fact sheets that I referred to during our phone conversation. I am providing a high-level summary in the paragraph below; however, please refer to these fact sheets for more detailed information.

Oral exposure (i.e., ingestion of cobalt through drinking water, food, etc.) may cause adverse hematological (blood), thyroid, and gastrointestinal effects. Cancer studies are underway with limited published data at this time. However, the fact sheets indicate cobalt may be a possible human carcinogen and that studies on mice and rats demonstrated an increased incidence of lung tumors, adrenal gland cancer, and hematopoietic (i.e., blood cell formation) cancer in rats and mice. The potential cancer effects were primarily associated with cobalt exposure from inhalation or breathing. Figure 1-2 on page 4 of the attached *Toxicological Profile for Cobalt* lists effects in humans and animals following oral exposure to cobalt based on varying concentration levels of cobalt.

As a reminder, current groundwater and surface water monitoring at the Winneshiek County Sanitary Landfill shows that cobalt is not migrating beyond the site. There are no immediate risks to drinking water or the environment. We will continue to monitor on-site cobalt concentrations to provide ongoing confirmation that cobalt concentrations remain stable or declining and that cobalt is not migrating off-site.

Please do not hesitate to contact me, Gina Wilming, at 312-485-6882 if you have any further questions. You may also share comments or questions with the Winneshiek County Area Solid Waste Agency at 563-382-4073 or [tj.schissel@co.winneshiek.ia.us](mailto:tj.schissel@co.winneshiek.ia.us).

Sincerely,

Foth Infrastructure & Environment, LLC



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cc: Keith Sersland

Enclosures

Attachment 1      Cobalt Fact Sheets

**Attachment 1**  
**Cobalt Fact Sheets**

# Cobalt - ToxFAQs™



## What is cobalt?

Cobalt (Co) is a naturally occurring element found in rocks, soils, water, and air. Alloys produced with cobalt metal are used in the manufacture of aircraft engines, magnets, grinding and cutting tools, and medical devices and prosthetics. Cobalt is used in the manufacturing processes for some forms of plastic. Cobalt compounds are used to color glass, ceramics, paints, and cosmetics. Cobalt is also used as a drier for porcelain enamel and paints. The general population is exposed to low levels of cobalt in air, water, food, and cosmetics. Vitamin B<sub>12</sub>, which is essential for good health at low levels, contains cobalt. Therefore, everyone has trace levels of cobalt in their body. Several radioactive isotopes of cobalt exist. Radioactive cobalt is used for commercial and medical purposes. <sup>60</sup>Co (read as cobalt sixty) is used for sterilizing medical equipment and consumer products, radiation therapy for treating cancer patients, manufacturing plastics, and irradiating food to increase shelf life. <sup>57</sup>Co is used in medical and scientific research.

## What happens to cobalt in the environment?

- Cobalt enters the environment from natural sources, during burning coal or oil, and through the production and use of cobalt alloys.
- In the air, cobalt combines with particles that then settle to the ground within a few days.
- Cobalt released into water or soil will stick to other particles. Some cobalt compounds may dissolve.
- Radioactive cobalt decays or changes into a stable non-radioactive substance. Half of <sup>60</sup>Co decays in 5.27 years and half of <sup>57</sup>Co decays in 272 days.

**Cobalt is beneficial to human health in minimal quantities but can be harmful in large amounts. It is a part of vitamin B<sub>12</sub>, which is crucial to human health at recommended levels.**

## How can I be exposed to cobalt?

- Food is a primary source through which you can be exposed to low levels of cobalt. You can also be exposed to cobalt by breathing air or drinking water. Very small amounts of cobalt may leach into food or water stored in certain types of plastic containers. A small portion of the cobalt is in vitamin B<sub>12</sub> as an essential trace element important to health. Some exposure is possible from medical devices and prosthetics.
- You can also be exposed to low levels of cobalt in cosmetics if the product you use (some eye shadows, face paints, lipsticks, and skin creams) contains cobalt as an ingredient. There is no evidence that living near agricultural areas that use sewage sludge, fertilizers, or amendments that contain cobalt would expose you to higher than normal levels of cobalt.
- Occupational exposure can happen by working in industries that make or use cutting or grinding tools; mine, smelt, refine, or process cobalt metal or ores; or produce cobalt alloys or use cobalt.
- The general population is rarely exposed to radioactive cobalt. Some radiation therapy patients may be exposed to radiation from cobalt located inside a therapy machine. Workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be exposed to small amounts of radioactive cobalt.

## How can cobalt affect my health?

Breathing cobalt particles can cause breathing difficulty and cause damage to your nose, throat, and lungs over time. Oral exposure to cobalt may cause adverse effects in the blood and thyroid. Skin contact with cobalt particles may cause skin irritation and discoloration. Exposure to radiation from any radioactive material or radiation exposure device can damage cells in your body. The health effects of ionizing radiation from cobalt are addressed in the [ToxFAQs for Ionizing Radiation](#).

# Cobalt

## Can cobalt cause cancer?

Several agencies and organizations, both in the United States and internationally, have reviewed studies and have assessed whether cobalt and cobalt compounds are carcinogens (substance causing cancer).

The National Toxicology program 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. Vitamin B<sub>12</sub> is not included since it is not one of these substances.

The [U.S. Environmental Protection Agency \(EPA\)](#) is currently conducting a cancer risk assessment for cobalt and cobalt compounds.

The [International Agency for Research on Cancer \(IARC\)](#) has classified soluble cobalt salts as probably carcinogenic, cobalt oxide as possibly carcinogenic, and cobalt tetroxide, cobalt sulfide, and other cobalt compounds as not classifiable as to their carcinogenicity to humans.

Cancer from exposure to ionizing radiation released from radioactive cobalt is addressed in the [ToxFAQs for Ionizing Radiation](#).

## Can I get a medical test to check for cobalt?

Cobalt levels can be tested in the urine, feces, and blood within a couple of days of exposure. It is not known if breath samples are useful. Your doctor can take samples, but must send them to a laboratory to be tested.

Tests are available to determine if you have been exposed to very high doses of ionizing radiation or if you have radioactive material in your body. These tests are not available at your doctor's office. For more information, please see the [ToxFAQs for Ionizing Radiation](#). The amount of cobalt in your urine, feces, or blood can be used to estimate how much cobalt you were exposed to. However, these tests cannot predict whether you will experience any health effects.

## How can I protect my family from cobalt exposure?

Children should avoid playing in soils near hazardous waste sites where cobalt may be present. Safely store cobalt powders, crystals, or dusts away from children, pets, or other adults. Monitor your cobalt intake if you are adding more cobalt to your diet, such as from dietary supplements like vitamin B<sub>12</sub>, which contains cobalt, to make sure you are not eating too much. Talk to your doctor, nurse, or clinic to figure out if you are taking the proper amount of cobalt. If you work with cobalt, it is important to wear the necessary protective clothing and equipment, and always follow safety procedures. Shower and change your clothes before going home each day if that is indicated by employers or safety data sheets. Additionally, workers exposed to radioactive cobalt should also be checked for contamination.

## For more information:

Call **CDC-INFO** at 1-800-232-4636, or submit your question online at <https://wwwn.cdc.gov/dcs/ContactUs/Form>

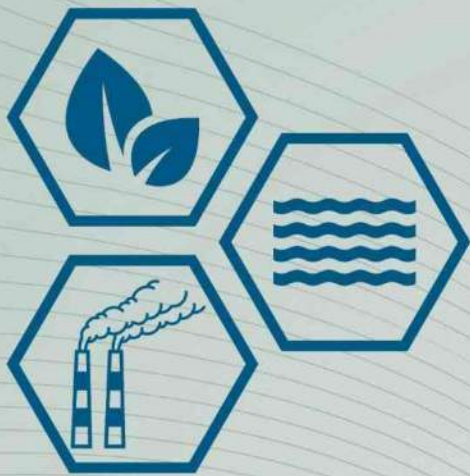
Go to ATSDR's Toxicological Profile for Cobalt: <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=373&tid=64>

Go to ATSDR's Toxic Substances Portal: <http://www.atsdr.cdc.gov/substances/index.asp>

Find & contact your ATSDR Regional Representative at [http://www.atsdr.cdc.gov/DRO/dro\\_org.html](http://www.atsdr.cdc.gov/DRO/dro_org.html)







# Toxicological Profile for Cobalt

October 2024



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

CS274127-A



## **DISCLAIMER**

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

## 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.

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

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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Christopher M. Reh, Ph.D.

Associate Director

Agency for Toxic Substances and Disease Registry  
Centers for Disease Control and Prevention

## VERSION HISTORY

| Date         | Description                                             |
|--------------|---------------------------------------------------------|
| October 2024 | Final toxicological profile released                    |
| January 2023 | Draft for public comment toxicological profile released |
| April 2004   | Final toxicological profile released                    |
| July 1992    | Final toxicological profile released                    |

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Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

#### Additional reviews for science and/or policy:

ATSDR, Office of Community Health Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Sciences; NCEH, Division of Environmental Health Science and Practice; EPA, Office of Research and Development; EPA, Office of Water.

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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 many cobalt compounds are naturally occurring. Cobalt is a ferromagnetic element and has similar physical and chemical properties to those of iron and nickel. Cobalt is the central essential element of vitamin B<sub>12</sub>; therefore, it will always be present in the human body at low levels. The largest use of metallic cobalt is now in rechargeable batteries, followed by uses as super alloys in gas turbine aircraft engines and hard metal tools. Additionally, the usage of cobalt in rechargeable batteries is expected to increase considerably over the next few decades to support electric vehicle battery production and recycling in response to the U.S. mandate to phase out fossil fueled activities from 2023 to 2050. Due to this, the U.S. Department of Energy (DOE) considers cobalt a “critical” commodity. Cobalt forms compounds with several other elements including chloride, sulfur, and oxygen. These compounds are used as pigments, colorants, paint driers, and catalysts in the various industries (e.g., the manufacture of polyethylene terephthalate [PET]). Cobalt and cobalt compounds are also used as trace element additives in animal feed, agricultural soil-amendments, and medicinal products.

Cobalt can be released to the environment by human activities or natural sources. Cobalt may be dispersed in the environment through weathering of rocks, windblown soil, seawater spray, volcanic eruptions, and forest fires. 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 (e.g., hard metal industry, lithium-cobalt battery production or recycling). 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<sub>12</sub>, also known as cyanocobalamin, which plays a crucial role in maintaining optimal health in humans and animals.

## 1. RELEVANCE TO PUBLIC HEALTH

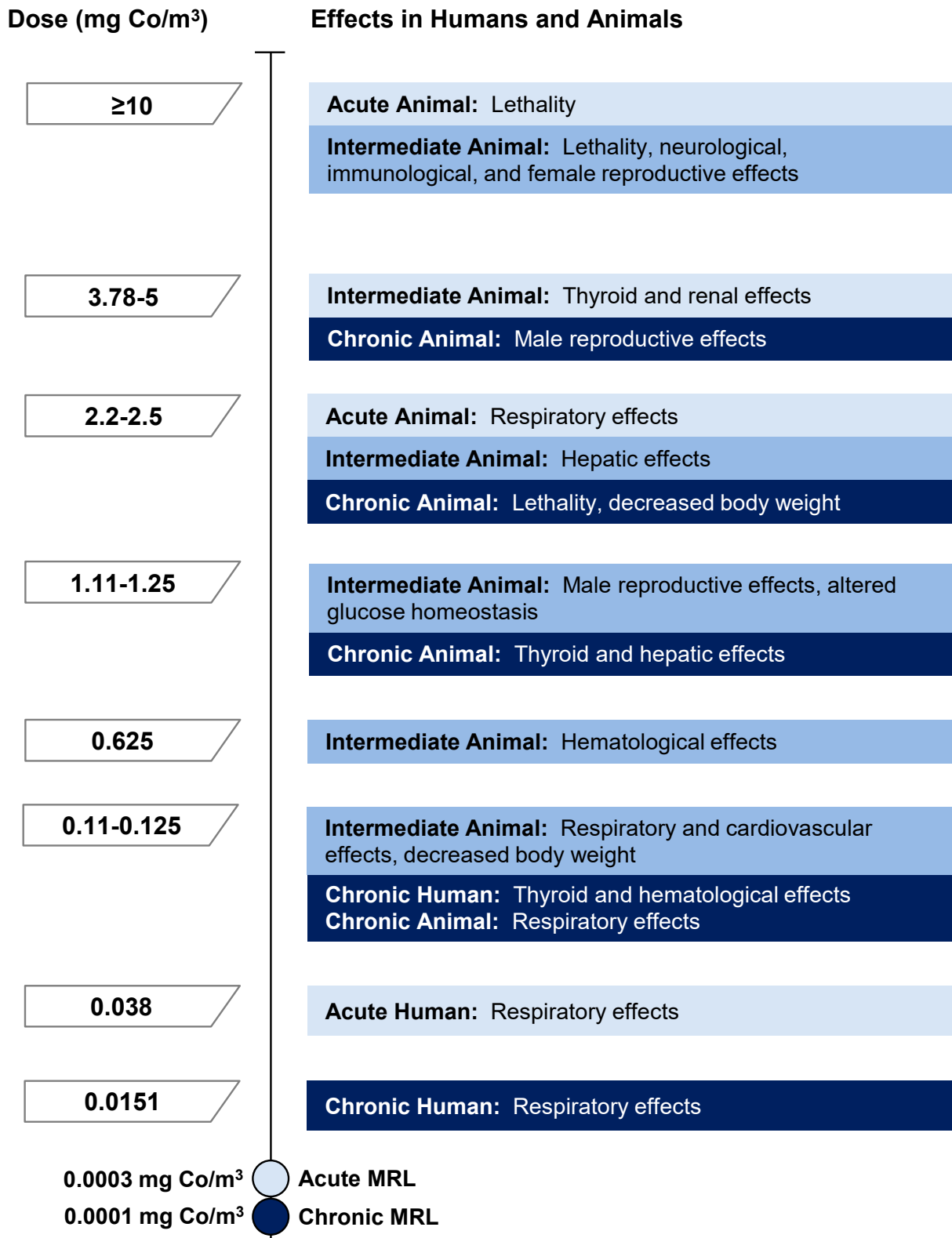
The general population can be exposed to low levels of cobalt by breathing air, eating food, or drinking water with food being the largest source of exposure. Small amounts of cobalt may migrate into beverages or food stored in plastic bottles or food packaging that contain cobalt, especially under high temperatures. Some exposure is also possible from medical devices (e.g., dental implants, joint replacements) 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  $^{60}\text{Co}$  decays in 5.27 years and half of  $^{57}\text{Co}$  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  $^{60}\text{Co}$ . 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**

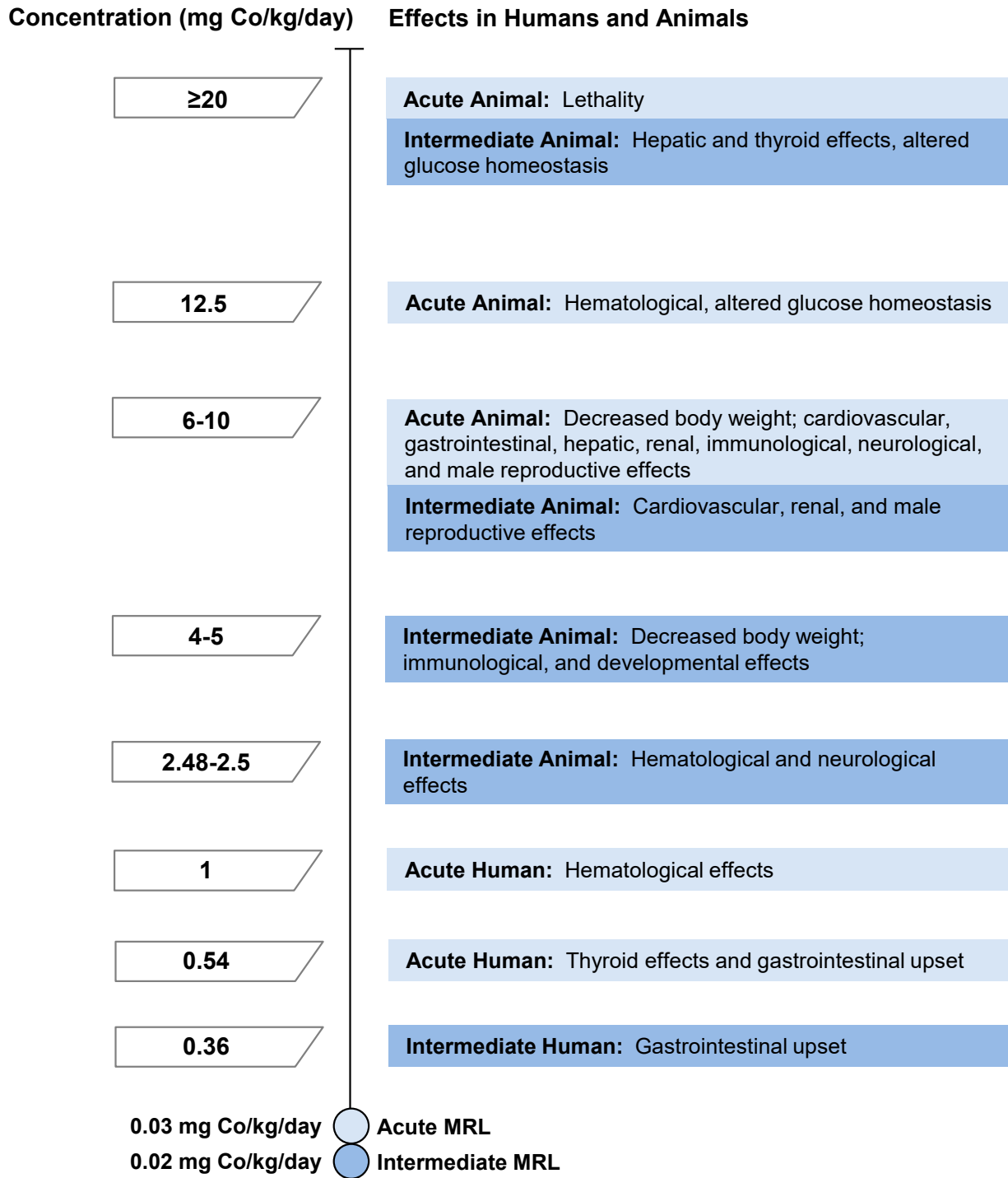
Information on the toxicity of cobalt and cobalt compounds comes predominantly from inhalation and oral studies in humans and laboratory animals. Inhalation data are available following acute ( $\leq 14$  days), intermediate (15–364 days), and chronic ( $\geq 365$  days) durations; oral data are only available following acute- and intermediate-duration exposures. Dermal exposure studies are limited; however, some skin and eye effects noted in human and animal inhalation studies are presumably due to direct contact with cobalt particles in the air rather than systemic toxicity. It is noted that as an essential trace element in vitamin B<sub>12</sub>, small amounts cobalt are beneficial for human health.

As illustrated in Figure 1-1, the respiratory tract is clearly the most sensitive target of toxicity in humans following acute- and chronic-duration inhalation exposure and in animals following inhalation exposure for any duration; no intermediate-duration inhalation studies in humans were identified. Figure 1-2 illustrates that sensitive effects following oral exposure to cobalt include gastrointestinal upset, thyroid effects, and hematological effects following acute- and intermediate-duration exposure in humans.

## 1. RELEVANCE TO PUBLIC HEALTH

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

## 1. RELEVANCE TO PUBLIC HEALTH

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



## 1. RELEVANCE TO PUBLIC HEALTH

Hematological effects are also the most sensitive effect following intermediate-duration oral exposure in animals; the acute-duration animals database showed that numerous systems were affected in the low-dose range such that the most sensitive of these could not be determined. No chronic-duration oral studies were identified. A systematic review of these endpoints (Appendix C) resulted in the following hazard identification conclusions:

- Respiratory effects are a known health effect for humans following inhalation exposure to cobalt.
- Gastrointestinal effects are not classifiable as health effects for humans following oral exposure to cobalt.
- Hematological effects are a presumed health effect for humans following oral exposure to cobalt.
- Thyroid effects are a suspected health effect for humans following oral 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 associated with increased respiratory symptoms (e.g., cough, phlegm, wheezing) and impaired lung function in workers following chronic occupational exposure; this association is more pronounced in workers who smoke cigarettes (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a; Linna et al. 2003; Meyer-Bisch et al. 1989; Nemery et al. 1992; Swennen et al. 1993; Verougstraete et al. 2004). Some occupational studies reported increased risk of asthma in cobalt-exposed workers (Kusaka et al. 1986b; Linna et al. 2003; Roto 1980; Walters et al. 2012). There is also limited evidence of impaired lung function after acute-duration inhalation exposure in humans (Kusaka et al. 1986a). Evidence from animal studies consistently shows that the respiratory tract is a sensitive target of cobalt following inhalation exposure for any duration. Both absorption and observed effects depend upon the solubility of the administered cobalt compound; however, both soluble and insoluble compounds have been shown to cause toxic effects in the respiratory tracts of laboratory animals. Acute-duration exposure is associated with inflammatory responses at low concentrations (Burzlaff et al. 2022a; Viegas et al. 2022a) and severe lung damage at lethal concentrations (Viegas et al. 2022a; Palmes et al. 1959). Widespread respiratory damage was consistently observed in rats and mice following intermittent intermediate- or chronic-duration inhalation exposure, with severity of lesions increasing in a dose- and duration-dependent manner (Burzlaff et al. 2022a; NTP 1991, 1998, 2014). In other species, intermediate-duration inhalation exposure resulted in inflammatory changes in rabbit lungs (Johansson et al. 1987) and decreased respiratory compliance, a metric of mechanical ventilation, in pigs (Kerfoot 1974).

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***Gastrointestinal Effects.*** Adverse gastrointestinal effects, including nausea, vomiting, and constipation, were reported in humans following oral exposure to cobalt as a potential treatment for anemia or hyperthyroidism (Duckham and Lee 1976; Holly 1955; Paley et al. 1958). In some cases, effects were severe enough for patients to drop out of the medical trial. Data from animal studies are limited. Alterations to the structure of the walls of the small intestine and delays in gastric emptying time were found in rats following acute-duration exposure to cobalt (Akinrinde et al. 2016c; Salami et al. 2023). However, intermediate-duration studies did not observe any damage to the gastrointestinal tract in rats following oral exposure to cobalt (Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955).

***Hematological Effects.*** A few human studies and several laboratory animal studies lend support to hematological effects being a sensitive endpoint following oral exposure to cobalt. Acute- or intermediate-duration oral exposure to cobalt in humans resulted in increased erythrocyte numbers, hematocrit, and hemoglobin that has been characterized as polycythemia (Davis and Fields 1958).

When addressed in this toxicological profile, polycythemia refers to absolute polycythemia, which is an increase in red cell mass from exposure to a substance, such as cobalt. This toxicological profile does not address other forms or causes of polycythemia. Davis and Fields (1958) reported an increase in erythrocyte levels following exposure to sufficiently high cobalt doses that returned to normal upon cessation of cobalt exposure. Other human studies did not observe polycythemia at lower cobalt doses (Finley et al. 2013; Hoffmeister et al. 2018; Tvermoes et al. 2014). Available animal studies corroborated the effects seen in the limited human database. Increased erythrocytes, hematocrit, and/or hemoglobin were observed in rats following acute-duration exposure (Domingo and Llobet 1984; Paternain and Domingo 1988; Shrivastava et al. 2008, 2010) and intermediate-duration oral exposure (Corrier et al. 1985; Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955; Murdock 1959; Stanley et al. 1947).

***Thyroid Effects.*** The thyroid has been investigated as a potential target of cobalt toxicity after development of goiter in some patients taking cobalt as a treatment for anemia associated with sickle-cell anemia, pregnancy, or chronic renal disease (Chamberlain 1961; Duckham and Lee 1976; Gross et al. 1955; Kriss et al. 1955; Little and Sunico 1958; Washburn and Kaplan 1964). A limited number of controlled human studies have reported transient impairments in thyroid function following acute- or intermediate-duration oral exposure to cobalt (Paley et al. 1958; Roche and Layrisse 1956), while others reported no effects (Finley et al. 2013; Holly 1955; Tvermoes et al. 2014). Data from animal studies are limited but show evidence of histopathological changes in the thyroid of mice following intermediate-

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duration exposure to high cobalt doses (Shrivastava et al. 1996). No evidence of thyroid damage was reported in rodents in other oral exposure studies (Danzeisen et al. 2020a; Holly 1955).

**Cancer Effects.** Most available occupational studies did not observe clear associations between cobalt exposure and increase risk of cancer incidence or death from cancer (see Section 2.19). Most studies are from the hard metal industry in which workers were exposed to a variety of metals. Based on available human data, meta-analyses do not indicate an increased overall cancer risk associated with occupational exposure to cobalt (Holy et al. 2022; Zhang et al. 2021). Chronic-duration inhalation studies reported increased incidence of lung tumors in rats and mice, pheochromocytomas in the adrenal glands of rats, and hematopoietic cancers in rats (Behl et al. 2015; Bucher et al. 1999; NTP 1998, 2014).

The International Agency for Research on Cancer (IARC) classified cobalt metal (without tungsten carbide or other metal alloys) and soluble cobalt (II) salts (cobalt chloride, cobalt sulfate) as probably carcinogenic to humans and cobalt (II) oxide as possibly carcinogenic to humans (IARC 2023). Metal mixtures containing cobalt, including cobalt metal with tungsten carbide and weapons-grade tungsten (with nickel and cobalt) are classified as probably and possibly carcinogenic to humans, respectively (IARC 2006, 2023). IARC (2023) determined that cobalt (II, III) oxide (cobalt tetraoxide), cobalt (II) sulfide, and other cobalt (II) compounds are not classifiable as to their carcinogenicity to humans. The National Toxicology Program (NTP) determined that cobalt and cobalt compounds that release cobalt ions *in vivo* are reasonably anticipated to be human carcinogens (NTP 2021). The Integrated Risk Information System (EPA 2022a) is currently conducting a cancer risk assessment for cobalt and cobalt compounds.

### 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 system is the most sensitive target of cobalt toxicity for all exposure durations. MRLs were derived for both acute- and chronic-duration inhalation exposure to cobalt; the inhalation database was considered inadequate for the derivation of an MRL for intermediate-duration inhalation exposure to cobalt. The endocrine, gastrointestinal, and hematological systems appear to be the most 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; therefore, the derivation of a chronic-duration oral MRL was not possible. MRLs derived for both the inhalation and

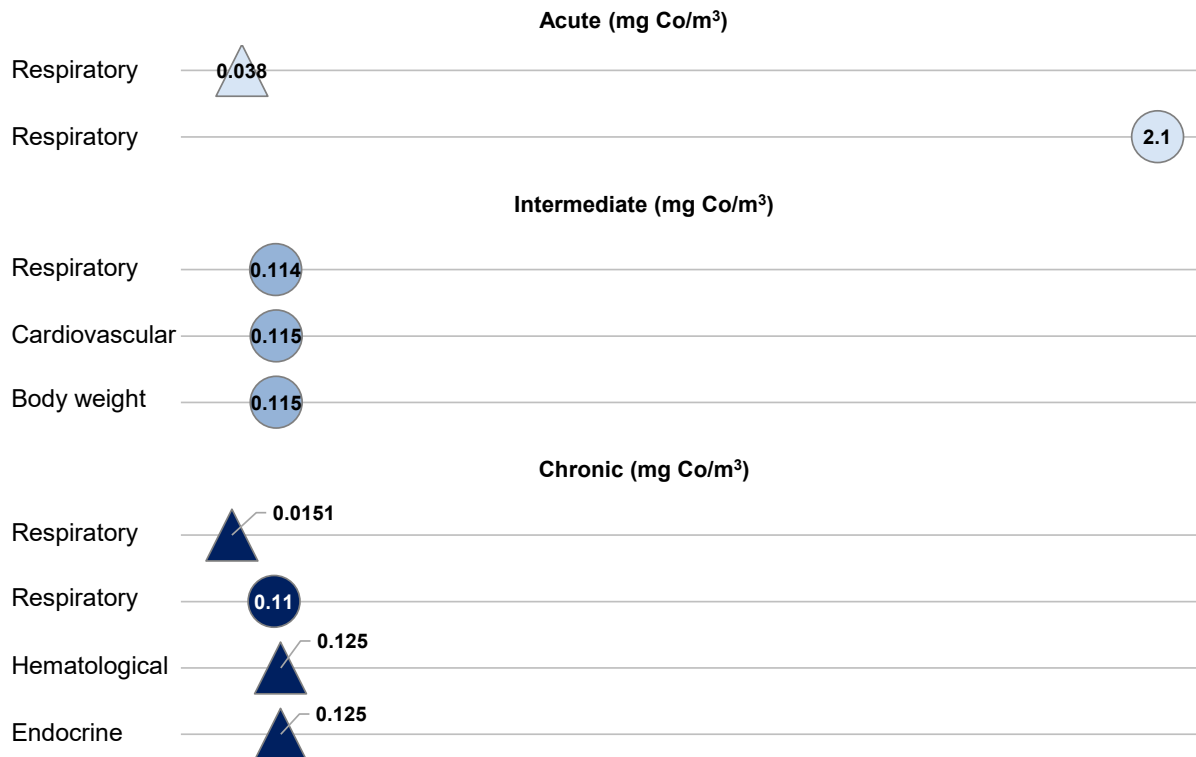
## 1. RELEVANCE TO PUBLIC HEALTH

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**

**Available data indicate that the respiratory system is the sensitive target of cobalt toxicity following inhalation exposure.**

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



## 1. RELEVANCE TO PUBLIC HEALTH

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

**Available data indicate that the gastrointestinal, endocrine, and hematological endpoints are the most sensitive targets of cobalt toxicity following oral exposure.**

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



## 1. RELEVANCE TO PUBLIC HEALTH

**Table 1-1. Minimal Risk Levels (MRLs) for Cobalt<sup>a</sup>**

| Exposure route | Exposure duration | MRL                                                      | Critical effect                                                      | POD type             | POD value                   | Uncertainty/modifying factor | Reference                  |
|----------------|-------------------|----------------------------------------------------------|----------------------------------------------------------------------|----------------------|-----------------------------|------------------------------|----------------------------|
| Inhalation     | Acute             | <b><math>3 \times 10^{-4}</math> mg Co/m<sup>3</sup></b> | Increased neutrophils in bronchoalveolar lavage fluid in female rats | NOAEL <sub>HEC</sub> | 0.01 mg Co/m <sup>3</sup>   | UF: 30                       | Viegas et al. 2022a, 2022b |
|                | Intermediate      | None                                                     | –                                                                    | –                    | –                           | –                            | –                          |
|                | Chronic           | <b><math>1 \times 10^{-4}</math> mg Co/m<sup>3</sup></b> | Reduced spirometry parameter values in workers                       | NOAEL <sub>ADJ</sub> | 0.0013 mg Co/m <sup>3</sup> | UF: 10                       | Nemery et al. 1992         |
| Oral           | Acute             | <b>0.03 mg Co/kg/day</b>                                 | Production of polycythemia in human volunteers <sup>b</sup>          | LOAEL                | 1.0 mg Co/kg/day            | UF: 30                       | Davis and Fields 1958      |
|                | Intermediate      | <b>0.02 mg Co/kg/day</b>                                 | Elevated red blood cell count in male rats                           | BMDL <sub>1SD</sub>  | 1.95 mg Co/kg/day           | UF: 100                      | Danzeisen et al. 2020a     |
|                | Chronic           | None                                                     | –                                                                    | –                    | –                           | –                            | –                          |

<sup>a</sup>See Appendix A for additional information.

<sup>b</sup>Polycythemia is the classification term used in cited literature, meaning absolute polycythemia only (increased hemoglobin, erythrocyte count, or hematocrit that can result from exposure to a substance).

1SD = 1 standard deviation; ADJ = adjusted from occupational to continuous exposure; BMDL = 95% lower confidence limit on the benchmark dose; Co = cobalt; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

## 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 ( $\leq 14$  days), intermediate (15–364 days), and chronic ( $\geq 365$  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. As discussed in *Prioritization of Human Data* in Appendix C, epidemiological studies included in the profile are focused on known environmental exposures to cobalt (e.g., occupational studies). There is a vast literature of general population studies that measure cobalt (and other trace essential elements) in the blood or urine and health outcomes. Studies of this nature without information on sources of environmental exposure above background levels are not included in this document. Additionally, studies evaluating kinetics and potential toxic effects associated with medical applications of cobalt (e.g., implantable medical devices, hydroxocobalamin for treatment of cyanide poisoning) are not included in the profile, as the profile is concerned with environmental exposures via inhalation, oral, or dermal routes.

## 2. HEALTH EFFECTS

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. Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” “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). “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. 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.

This section provides information regarding potential adverse health effects of cobalt and cobalt compounds. In order to appropriately compare doses following exposures to various cobalt compounds, inhalation exposures are expressed throughout the profile as mg Co/m<sup>3</sup> and oral and dermal exposures are expressed as mg Co/kg/day, when possible. This allows for evaluation of relative toxicities and determination of whether certain chemical properties (e.g., solubility) impact toxicity. When available, information pertaining to relative toxicity of different cobalt compounds is discussed throughout Chapter 2.

Cobalt salts (e.g., cobalt sulfate, cobalt chloride) can exist in anhydrous and hydrated forms. Since hydration status does not impact the toxicity of cobalt salts, it is not discussed throughout Chapter 2 in the health



## 2. HEALTH EFFECTS

effects sections (e.g., both anhydrous and hydrated forms of cobalt sulfate are referred to as “cobalt sulfate”). However, hydration status impacts conversion into mg Co/m<sup>3</sup> or mg Co/kg/day; therefore, hydration status is provided in the LSE tables. In cases for which hydration status of a salt was not explicitly reported (e.g., study authors report test substance as “cobalt chloride” without clearly specifying “anhydrous cobalt chloride” or “cobalt chloride hexahydrate”), dose conversions were based on the available information in the study. That is, the molecular weight of the salt (e.g., cobalt chloride) was used, without any assumptions regarding the degree of hydration. Test compounds, exactly as reported by study authors, are reported in the LSE tables. Hydration status is particularly important for inhalation studies with cobalt sulfate heptahydrate, which will convert to cobalt sulfate hexahydrate when air humidity levels are <70% (Redhammer et al. 2007). Behl et al. (2015) confirmed that predominant hydration species in inhalation chambers during the NTP (1991) studies of cobalt sulfate heptahydrate was actually cobalt sulfate hexahydrate. Therefore, the dose conversions listed in the LSE table for NTP (1991) are based on the molecular weight of cobalt hexahydrate. Additionally, based on the information provided by Behl et al. (2015) and information regarding relative humidity (Viegas 2024), the dose conversions for other inhalation studies of cobalt sulfate heptahydrate reported in the LSE tables were also based on the molecular weight of cobalt sulfate hexahydrate (e.g., Burzlaff et al. 2022a; Viegas et al. 2022a).

The health effects of cobalt and cobalt compounds have been evaluated in 75 human and 118 animal studies. As illustrated in Figure 2-1, most of the health effects data come from oral exposure studies in animals and inhalation (occupational) exposure studies in humans.

Human studies predominantly focused on respiratory endpoints following inhalation exposure and hematological and endocrine (thyroid) effects following oral exposure. Animal studies examined a comprehensive set of endpoints following inhalation and oral exposure. For inhalation studies, the most well-studied system in animals is also the respiratory system. For oral studies, the most well-studied effects (after survival) include body weight, reproductive endpoints, and hematological effects. Data from dermal exposure are very limited.

As outlined in Chapter 1, the most sensitive effects following exposure to cobalt appear to be respiratory effects following inhalation exposure and gastrointestinal, hematological, and thyroid effects following oral exposure. A systematic review was conducted on the available human and animal studies for these endpoints. The information in these studies indicate the following on the potential targets of cobalt toxicity:

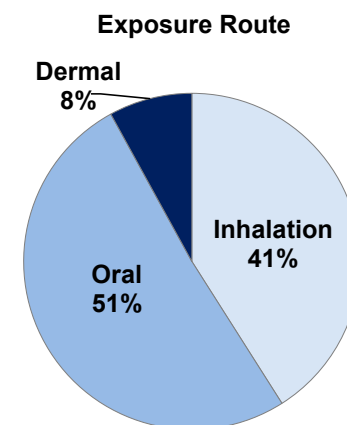
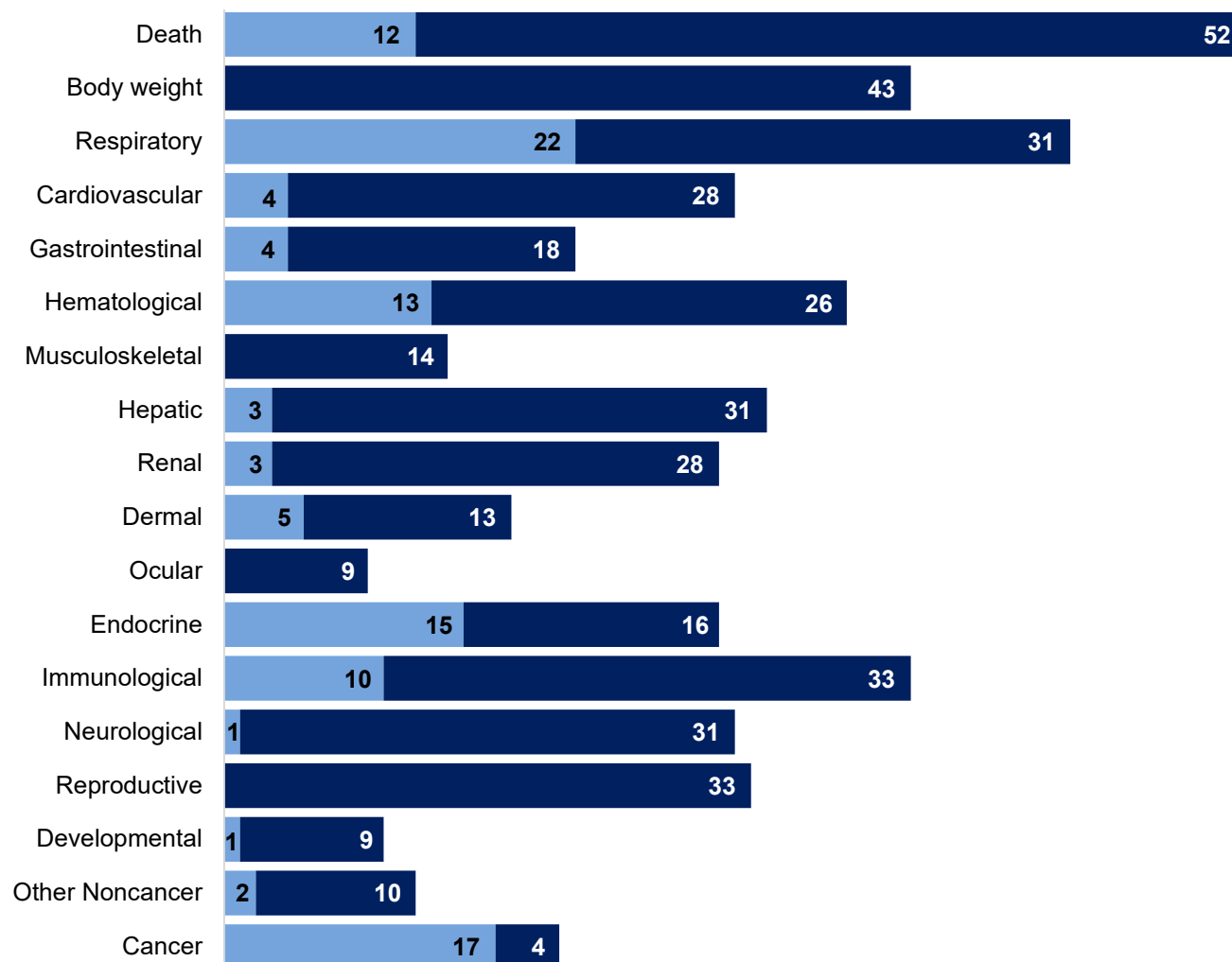
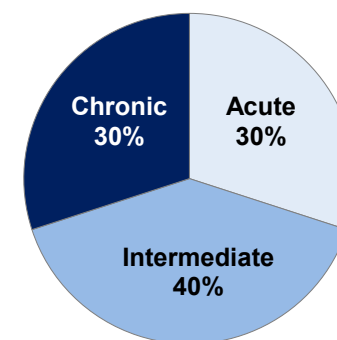
## 2. HEALTH EFFECTS

- **Respiratory Endpoints.** Respiratory effects are a known health effect for humans following inhalation exposure to cobalt based on a high level of evidence in humans and animals. In humans, occupational exposure has been associated with increased respiratory symptoms, impaired lung function, and asthma. In animals, inhalation exposure is consistently associated with inflammatory changes throughout the upper and lower respiratory tract progressing to widespread lesions with increasing concentration and duration in multiple species. At high exposure levels, severe pulmonary damage was the cause of death in rodents.
- **Gastrointestinal Endpoints.** Gastrointestinal effects are not classifiable as health effects for humans following oral exposure to cobalt due to inadequate data in humans and a low level of evidence in animals. Findings in humans are limited to complaints of gastrointestinal distress in some humans following oral exposure to cobalt potential treatment for anemia or hyperthyroidism. Animal data are limited to a few acute-duration oral studies in rats reporting damage to the small intestine and delays in gastric emptying; however, no histopathological changes were found throughout the gastrointestinal tract in intermediate-duration oral studies in rats.
- **Hematological Endpoints.** Hematological effects are a presumed health effect for humans following oral exposure to cobalt based on a moderate level of evidence in humans and a high level of evidence in animals. One study reported an increase in red blood cell concentration (defined as polycythemia by the study authors) in healthy humans following acute- or intermediate-duration oral exposure to cobalt. Cobalt supplementation has also been shown to elevate red blood cell count when given to anemic patients. Polycythemia was not observed in healthy individuals in two additional studies with exposure to lower-dose cobalt exposure. Findings in humans are supported by numerous acute- and intermediate-duration rat studies that reported elevated erythrocytes, hematocrit, and/or hemoglobin following exposure to cobalt. Mechanistic data indicate that cobalt mimics hypoxic conditions, stimulating erythropoiesis.
- **Thyroid Endpoints.** Thyroid effects are a suspected health effect for humans following oral exposure to cobalt based on a low level of evidence in humans and a moderate level of evidence in animals. There is limited evidence from case reports of goiter or impaired thyroid function in some patients taking cobalt as a treatment for anemia associated with sickle cell anemia, pregnancy, or chronic renal disease. Transient impairments in thyroid function were observed following acute- or intermediate-duration oral exposure to cobalt in some controlled human studies. Only a limited number of animal studies were identified, but they provide evidence of severe histopathological damage to the thyroid at high oral exposure doses in mice. A proposed mechanism of action is organic blocking of iodine by cobalt.

## 2. HEALTH EFFECTS

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

**Most studies examined the potential lethal, body weight, respiratory, immunological, and hematological effects of cobalt**  
 Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)

**Exposure Duration**

\*Includes studies discussed in Chapter 2. A total of 193 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                          | Species (strain) No./group | Exposure parameters | Doses                                         | Parameters monitored | Endpoint   | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------|-----------------------------------------------|----------------------|------------|-------|--------------------|---------------|-------------------------------------------------------------------------------------------------------------------------|
| <b>ACUTE EXPOSURE</b>                                                                                                            |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| <b>Kusaka et al. 1986a</b>                                                                                                       |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| 1                                                                                                                                | Human                      | 6 hours             | 0, 0.038                                      | CS, OF               | Resp       |       | 0.038              |               | Subjective complaints of respiratory irritation; decreased FVC                                                          |
|                                                                                                                                  | 15 M                       |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| <b>Burzlaff et al. 2022a</b>                                                                                                     |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| 2                                                                                                                                | Rat (Wistar)               | 14 days             | 0, 9.86,                                      | LE, BW, BI,          | Bd wt      | 160.9 |                    |               |                                                                                                                         |
|                                                                                                                                  | 5 M, 5 F                   | 6 hours/day (N)     | 33.87, 160.90                                 | OW, GN, HP           | Resp       | 9.86  | 33.87              |               | Increased BALF levels of LDH and polymorphonuclear neutrophils                                                          |
| <b>Palmes et al. 1959</b>                                                                                                        |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| 3                                                                                                                                | Rat (Albino)               | 30 minutes (WB)     | 0, 7, 28, 47, 68, 78, 113, 191, 215, 222, 408 | CS, LE               | Death Resp | 68    |                    | 165 78        | LC <sub>50</sub><br>Labored or disturbed respiration; severe pulmonary irritation                                       |
|                                                                                                                                  | 5–10 M                     |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| Exposure was to cobalt hydrocarbonyl plus oxide/carbonate decomposition products due to instability of test substance in oxygen. |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| <b>Palmes et al. 1959</b>                                                                                                        |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| 4                                                                                                                                | Rat (Albino)               | 30 minutes (WB)     | 0, 7, 26, 83, 90, 106, 116, 137, 179, 236     | GN, OW               | Resp       | 26    |                    | 83            | Gross lung lesions (hemorrhage, edema, consolidation, congestion, pleuritis, bronchiectasis, emphysema, or atelectasis) |
|                                                                                                                                  | 1–33 M                     |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| Exposure was to cobalt hydrocarbonyl plus oxide/carbonate decomposition products due to instability of test substance in oxygen. |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| <b>Viegas et al. 2022a, 2022b</b>                                                                                                |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| 5                                                                                                                                | Rat (Sprague-Dawley)       | 4 hours (N)         | 50, 500, 1,000, 5,000                         | LE, CS, HP           | Death      |       |                    | 50            | 100% mortality                                                                                                          |
|                                                                                                                                  | 3–5 M, 3–5 F               |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| <b>Viegas et al. 2022a, 2022b</b>                                                                                                |                            |                     |                                               |                      |            |       |                    |               |                                                                                                                         |
| 6                                                                                                                                | Rat (Sprague-Dawley)       | 4 hours (N)         | 32, 320, 3,200                                | LE, CS, HP           | Death      |       |                    | 32            | 100% mortality                                                                                                          |
|                                                                                                                                  | 3–5 M, 3–5 F               |                     |                                               |                      |            |       |                    |               |                                                                                                                         |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                    | Species (strain) No./group        | Exposure parameters                                               | Doses                             | Parameters monitored               | Endpoint  | NOAEL            | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------|-----------------------------------|------------------------------------|-----------|------------------|--------------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Viegas et al. 2022a, 2022b</b> <span style="float: right;"><b>Cobalt Carbonate</b></span>                               |                                   |                                                                   |                                   |                                    |           |                  |                    |               |                                                                                                                                                                                             |
| 7                                                                                                                          | Rat (Sprague-Dawley) 3–5 M, 3–5 F | 4 hours (N)                                                       | 32, 320, 3,200                    | LE, CS, HP                         | Death     |                  |                    | 3,200         | LC <sub>50</sub>                                                                                                                                                                            |
| <b>Viegas et al. 2022a, 2022b</b> <span style="float: right;"><b>Cobalt Oxide</b></span>                                   |                                   |                                                                   |                                   |                                    |           |                  |                    |               |                                                                                                                                                                                             |
| 8                                                                                                                          | Rat (Sprague-Dawley) 3–5 M, 3–5 F | 4 hours (N)                                                       | 39, 79, 390, 790, 3,900           | LE, CS, HP                         | Death     |                  |                    | 47            | LC <sub>50</sub>                                                                                                                                                                            |
| <b>Viegas et al. 2022a, 2022b; Viegas 2024</b> <span style="float: right;"><b>Cobalt Sulfate Heptahydrate</b></span>       |                                   |                                                                   |                                   |                                    |           |                  |                    |               |                                                                                                                                                                                             |
| 9                                                                                                                          | Rat (Sprague-Dawley) 5 F          | 4 hours (WB)                                                      | 0, 0.02, 0.07, 0.2, 2.2, 6.7      | LE, CS, HP, BI                     | Resp      | 0.2 <sup>b</sup> | 2.2                |               | Increased BALF neutrophils, decreased BALF cell viability                                                                                                                                   |
| Test substance was likely converted to cobalt sulfate hexahydrate in the inhalation chamber due to relative humidity <70%. |                                   |                                                                   |                                   |                                    |           |                  |                    |               |                                                                                                                                                                                             |
| <b>INTERMEDIATE EXPOSURE</b>                                                                                               |                                   |                                                                   |                                   |                                    |           |                  |                    |               |                                                                                                                                                                                             |
| <b>Bucher et al. 1990; NTP 1991, 2023</b> <span style="float: right;"><b>Cobalt Sulfate Heptahydrate</b></span>            |                                   |                                                                   |                                   |                                    |           |                  |                    |               |                                                                                                                                                                                             |
| 10                                                                                                                         | Rat (F344/N) 10 M, 10 F           | 13 weeks 5 days/week 6 hours + 12 minutes (T90 time) per day (WB) | 0, 0.114, 0.376, 1.11, 3.78, 11.4 | BC, BW, CS, GN, HE, HP, LE, OW, RX | Bd wt     | 11.4 F 3.78 M    | 11.4 M 0.114       | 3.78          | 14% decrease in final body weight<br>LOAEL: Minimal-to-mild squamous metaplasia of the larynx<br>SLOAEL: Lung fibrosis in females; laryngeal ulceration, necrosis, and polyps in both sexes |
|                                                                                                                            |                                   |                                                                   |                                   |                                    | Resp      |                  |                    |               |                                                                                                                                                                                             |
|                                                                                                                            |                                   |                                                                   |                                   |                                    | Cardio    | 11.4             |                    |               |                                                                                                                                                                                             |
|                                                                                                                            |                                   |                                                                   |                                   |                                    | Gastro    | 11.4             |                    |               |                                                                                                                                                                                             |
|                                                                                                                            |                                   |                                                                   |                                   |                                    | Hemato    | 1.11 F 0.376 M   | 3.78 F 1.11 M      |               | Polycythemia, decreased platelet count<br>Polycythemia                                                                                                                                      |
|                                                                                                                            |                                   |                                                                   |                                   |                                    | Musc/skel | 11.4             |                    |               |                                                                                                                                                                                             |
|                                                                                                                            |                                   |                                                                   |                                   |                                    | Hepatic   | 11.4             |                    |               |                                                                                                                                                                                             |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                                     | Species (strain)<br>No./group | Exposure parameters           | Doses                    | Parameters monitored                     | Endpoint        | NOAEL                    | Less serious<br>LOAEL | Serious<br>LOAEL | Effects                                                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------|--------------------------|------------------------------------------|-----------------|--------------------------|-----------------------|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                             |                               |                               |                          |                                          | Renal           | 11.4                     |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Dermal          | 11.4                     |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Endocr          | 1.11 F<br>3.78 M         | 3.78 F<br>11.4 M      |                  | Decreased serum T3<br>Decreased serum TSH                                                                                                                                                         |
|                                                                                                                                             |                               |                               |                          |                                          | Immuno          | 11.4                     |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Neuro           | 11.4                     |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Repro           | 11.4                     |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Other noncancer | 11.4                     |                       |                  |                                                                                                                                                                                                   |
| Exposure chamber analysis showed that under test conditions, the test substance converted to cobalt sulfate hexahydrate (Behl et al. 2015). |                               |                               |                          |                                          |                 |                          |                       |                  |                                                                                                                                                                                                   |
| <b>Burzlaff et al. 2022a</b>                                                                                                                |                               |                               |                          |                                          |                 | <b>Cobalt Tetraoxide</b> |                       |                  |                                                                                                                                                                                                   |
| 11                                                                                                                                          | Rat (Wistar)<br>10 M, 10 F    | 28 days<br>6 hours/day<br>(N) | 0, 3.76,<br>15.05, 59.31 | CS, FI, WI,<br>BW, BC, BI,<br>HE, UR, HP | Bd wt<br>Resp   | 59.31<br>3.76            | 15.05                 | 59.31            | LOAEL: Alveolar lipoproteinosis,<br>increased LDH and<br>polymorphonuclear neutrophils in<br>BALF<br>SLOAEL: Moderate interstitial<br>fibrosis and interstitial inflammatory<br>cell infiltration |
|                                                                                                                                             |                               |                               |                          |                                          | Cardio          | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Gastro          | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Hemato          | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Musc/skel       | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Hepatic         | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Renal           | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Endocr          | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Immuno          | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Neuro           | 59.31                    |                       |                  |                                                                                                                                                                                                   |
|                                                                                                                                             |                               |                               |                          |                                          | Repro           | 59.31                    |                       |                  |                                                                                                                                                                                                   |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                                           | Species (strain)<br>No./group | Exposure parameters                                                                | Doses                                  | Parameters monitored             | Endpoint                                                                                                           | NOAEL                                                    | Less serious<br>LOAEL | Serious<br>LOAEL                               | Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|------------------------------------------------------------------------------------|----------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Burzlauff et al. 2022a, 2022b</b>                                                                                                              |                               |                                                                                    |                                        |                                  |                                                                                                                    | <b>Cobalt Sulfate Heptahydrate</b>                       |                       |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 12                                                                                                                                                | Rat (Wistar)<br>10 M, 10 F    | 28 days<br>6 hours/day<br>(N)                                                      | 0, 0.46                                | CS, WI, BW,<br>BC, BI, HE,<br>HP | Bd wt<br>Resp                                                                                                      | 0.46                                                     | 0.46                  |                                                | Slight focal squamous metaplasia and inflammatory changes in larynx in both sexes; increased BALF LDH levels and polymorphonuclear neutrophils in males                                                                                                                                                                                                                                                                                                    |
| Based on findings in other studies (Behl et al. 2015), the test substance likely converted to cobalt sulfate hexahydrate in the exposure chamber. |                               |                                                                                    |                                        |                                  |                                                                                                                    |                                                          |                       |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>NTP 1991, 2023</b>                                                                                                                             |                               |                                                                                    |                                        |                                  |                                                                                                                    | <b>Cobalt Sulfate Heptahydrate</b>                       |                       |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 13                                                                                                                                                | Rat<br>(F344/N)<br>5 M, 5 F   | 16 days<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per<br>day<br>(WB) | 0, 0.035,<br>0.19, 1.80,<br>19.0, 75.7 | BW, CS,<br>GN, HP, LE,<br>OW     | Death<br>Bd wt<br>Resp<br>Cardio<br>Gastro<br>Musc/skel<br>Hepatic<br>Renal<br>Dermal<br>Endocr<br>Immuno<br>Neuro | 1.8<br>1.8<br>75.7<br>75.7<br>75.7<br>75.7<br>1.8<br>1.8 |                       | 75.7 F<br>19 M<br>19<br>19<br>75.7<br>19<br>19 | 5/5 died<br>2/5 died<br>Decrease in final body weight in males (47%) and females (23%)<br>Lesions throughout the respiratory tract (inflammation, necrosis, hyperplasia, metaplasia, acanthosis, fibrosis, histiocytic infiltration)<br>Congestion and necrosis of liver (in rats that died)<br>Necrosis of thymus (in rats that died); decreased absolute and relative thymus weights<br>Congestion of vessels in brain (in rats that died); hypoactivity |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                                     | Species (strain) No./group | Exposure parameters                                              | Doses                 | Parameters monitored       | Endpoint            | NOAEL           | Less serious LOAEL | Serious LOAEL                | Effects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|------------------------------------------------------------------|-----------------------|----------------------------|---------------------|-----------------|--------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                             |                            |                                                                  |                       |                            | Repro               | 75.7 F<br>1.8 M |                    | 19 M                         | Testicular atrophy; decreased cellularity of the seminiferous tubules and atypical germinal epithelial cells in the epididymal ducts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Exposure chamber analysis showed that under test conditions, the test substance converted to cobalt sulfate hexahydrate (Behl et al. 2015). |                            |                                                                  |                       |                            |                     |                 |                    |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>NTP 2014</b>                                                                                                                             |                            |                                                                  |                       |                            | <b>Cobalt Metal</b> |                 |                    |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 14                                                                                                                                          | Rat (F344/N) 5 M, 5 F      | 16 days 5 days/week 6 hours + 12 minutes (T90 time) per day (WB) | 0, 2.5, 5, 10, 20, 40 | BW, CS, GN, HP, LE, OW, UR | Death Bd wt         | 5 F<br><br>5 M  | 10 F<br><br>2.5    | 20<br>20 F<br><br>10 M<br>20 | 5/5 males and 3/5 females died<br>LOAEL: 12% decrease in final body weight<br>SLOAEL: 45% decrease in final body weight<br>20% decrease in final body weight<br>LOAEL: Minimal cytoplasmic vacuolization of bronchiolar epithelium; minimal-to-mild atrophy and necrosis of olfactory epithelium<br>SLOAEL: Abnormal breathing; histiocytic infiltrates in the lungs; lung hemorrhage and acute inflammation in male; nasal respiratory epithelium necrosis in females<br>Decreased absolute liver weight<br>Decreased absolute and relative liver weight<br>Increased urinary creatinine levels, decreased urine volume<br>Increased urinary creatinine levels, decreased urine volume<br>Decreased relative thymus weight |
|                                                                                                                                             |                            |                                                                  |                       |                            | Hepatic             | 2.5 F           | 5 F<br>2.5 M       |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                             |                            |                                                                  |                       |                            | Renal               | 10 F<br><br>5 M | 20 F<br><br>10 M   |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|                                                                                                                                             |                            |                                                                  |                       |                            | Immuno              | 10 F<br>40 M    | 20 F               |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |



## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup> | Species (strain)<br>No./group | Exposure parameters                                                                 | Doses                     | Parameters monitored                                  | Endpoint        | NOAEL          | Less serious LOAEL | Serious LOAEL | Effects                                                                                             |
|-------------------------|-------------------------------|-------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------------|-----------------|----------------|--------------------|---------------|-----------------------------------------------------------------------------------------------------|
|                         |                               |                                                                                     |                           |                                                       | Neuro           | 20 F<br>10 M   | 40 F<br>20 M       |               | Lethargy<br>Lethargy                                                                                |
| <b>NTP 2014</b>         |                               |                                                                                     |                           |                                                       |                 |                |                    |               | <b>Cobalt Metal</b>                                                                                 |
| 15                      | Rat (F344/N)<br>10 M, 10 F    | 14 weeks<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per<br>day<br>(WB) | 0, 0.625,<br>1.25, 2.5, 5 | BC, BW, CS, Bd wt<br>GN, HE, HP,<br>LE, OW, RX,<br>UR |                 | 5              | 0.625              |               | Chronic active inflammation in lung, pulmonary alveolar proteinosis, increased relative lung weight |
|                         |                               |                                                                                     |                           |                                                       | Cardio          | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Gastro          | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Hemato          | 0.625 F        | 1.25 F             |               | Increased hematocrit, hemoglobin, and red blood cell counts; decreased platelets                    |
|                         |                               |                                                                                     |                           |                                                       |                 |                | 0.625 M            |               | Increased hemoglobin and red blood cell count                                                       |
|                         |                               |                                                                                     |                           |                                                       | Musc/skel       | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Hepatic         | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Renal           | 2.5 F<br>2.5 M | 5 F<br>5 M         |               | Increased relative kidney weight<br>Increased serum creatinine                                      |
|                         |                               |                                                                                     |                           |                                                       | Dermal          | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Ocular          | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Endocr          | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Immuno          | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Neuro           | 5              |                    |               |                                                                                                     |
|                         |                               |                                                                                     |                           |                                                       | Repro           | 5 F<br>1.25 M  | 2.5 M              |               | Decreased sperm motility, increased relative testes weight                                          |
|                         |                               |                                                                                     |                           |                                                       | Other noncancer | 5 F<br>0.625 M | 1.25 M             |               | Decreased serum glucose                                                                             |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                          | Species (strain) No./group | Exposure parameters                                               | Doses                             | Parameters monitored               | Endpoint     | NOAEL         | Less serious LOAEL                 | Serious LOAEL | Effects                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------|-----------------------------------|------------------------------------|--------------|---------------|------------------------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Palmes et al. 1959</b>                                                                                                        |                            |                                                                   |                                   |                                    |              |               | <b>Cobalt Hydrocarbonyl</b>        |               |                                                                                                                                                                    |
| 16                                                                                                                               | Rat (Albino) 34–57 M       | 3 months 5 days/week 6 hours/day (WB)                             | 0, 9                              | BW, CS, GN, HE, HP, LE             | Bd wt Hemato | 9             | 9                                  |               | Increased hemoglobin levels; decreased percent monocytes and increased percent basophils                                                                           |
| Exposure was to cobalt hydrocarbonyl plus oxide/carbonate decomposition products due to instability of test substance in oxygen. |                            |                                                                   |                                   |                                    |              |               |                                    |               |                                                                                                                                                                    |
| <b>Bucher et al. 1990; NTP 1991, 2023</b>                                                                                        |                            |                                                                   |                                   |                                    |              |               | <b>Cobalt Sulfate Heptahydrate</b> |               |                                                                                                                                                                    |
| 17                                                                                                                               | Mouse (B6C3F1) 10 M, 10 F  | 13 weeks 5 days/week 6 hours + 12 minutes (T90 time) per day (WB) | 0, 0.114, 0.376, 1.11, 3.78, 11.4 | BC, BW, CS, GN, HE, HP, LE, OW, RX | Death Bd wt  | 3.78          |                                    | 11.4 M        | 2/10 died                                                                                                                                                          |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Resp         |               | 11.4 M 0.114                       |               | 22% decrease in final body weight 14% decrease in final body weight Squamous metaplasia of the larynx in both sexes; histiocytic infiltrates in the lungs in males |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Cardio       | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Gastro       | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Hemato       | 3.78 F 11.4 M | 11.4 F                             |               | Decreased platelets                                                                                                                                                |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Musc/skel    | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Hepatic      | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Renal        | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Dermal       | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Endocr       | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Immuno       | 3.78          | 11.4                               |               | Lymphoid hyperplasia in mediastinal lymph nodes                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Neuro        | 11.4          |                                    |               |                                                                                                                                                                    |
|                                                                                                                                  |                            |                                                                   |                                   |                                    | Repro        | 3.78 F        | 11.4 F 1.11 M                      | 11.4 M        | Increased estrous cycle length SLOAEL: Testicular atrophy; 3-fold increase in percent abnormal sperm LOAEL: Decreased sperm motility                               |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**

[illegible]

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup> | Species (strain)<br>No./group | Exposure parameters                                                                | Doses                    | Parameters monitored             | Endpoint       | NOAEL               | Less serious<br>LOAEL | Serious<br>LOAEL | Effects                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------|-------------------------------|------------------------------------------------------------------------------------|--------------------------|----------------------------------|----------------|---------------------|-----------------------|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>NTP 2014</b>         |                               |                                                                                    |                          |                                  |                | <b>Cobalt Metal</b> |                       |                  |                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 19                      | Mouse<br>(B6C3F1)<br>5 M, 5 F | 17 days<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per<br>day<br>(WB) | 0, 2.5, 5, 10,<br>20, 40 | BW, CS,<br>GN, HP, LE,<br>OW, UR | Death<br>Bd wt | 10 F                | 20 F                  | 40 F             | 3/5 males and 3/5 females died<br>SLOAEL: 38% decrease in final<br>body weight<br>LOAEL: 16% decrease in final<br>body weight                                                                                                                                                                                                                                                                                        |
|                         |                               |                                                                                    |                          |                                  | Resp           | 20 M                | 2.5                   | 40 M<br>20       | 27% decrease in final body weight<br>LOAEL: Minimal-to-mild nasal<br>lesions (atrophy of olfactory<br>epithelium; vacuolization of<br>respiratory epithelium); minimal<br>cytoplasmic vacuolization of<br>bronchiolar epithelium with<br>histiocytic infiltrates in males<br>SLOAEL: Pulmonary fibrosis,<br>olfactory epithelial necrosis,<br>respiratory epithelial metaplasia,<br>alveolar/bronchiolar karyomegaly |
|                         |                               |                                                                                    |                          |                                  | Hepatic        |                     | 2.5                   |                  | Decreased absolute and relative<br>liver weight                                                                                                                                                                                                                                                                                                                                                                      |
|                         |                               |                                                                                    |                          |                                  | Renal          | 20                  |                       |                  |                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                         |                               |                                                                                    |                          |                                  | Endocr         | 40                  |                       |                  |                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                         |                               |                                                                                    |                          |                                  | Immuno         | 40                  |                       |                  |                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                         |                               |                                                                                    |                          |                                  | Neuro          | 5 F                 | 10 F                  |                  | Lethargy                                                                                                                                                                                                                                                                                                                                                                                                             |
|                         |                               |                                                                                    |                          |                                  |                | 10 M                | 20 M                  |                  | Lethargy                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>NTP 2014</b>         |                               |                                                                                    |                          |                                  |                | <b>Cobalt Metal</b> |                       |                  |                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 20                      | Mouse<br>(B6C3F1)             | 14 weeks<br>5 days/week                                                            |                          | BC, BW, CS,<br>GN, HE, HP,       | Bd wt          | 5                   | 10                    |                  | 13–14% decrease in final body<br>weight                                                                                                                                                                                                                                                                                                                                                                              |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup> | Species (strain) No./group | Exposure parameters                          | Doses                      | Parameters monitored | Endpoint        | NOAEL  | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                     |
|-------------------------|----------------------------|----------------------------------------------|----------------------------|----------------------|-----------------|--------|--------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         | 10 M, 9–10 F               | 6 hours + 12 minutes (T90 time) per day (WB) | 0, 0.625, 1.25, 2.5, 5, 10 | LE, OW, RX, UR       | Resp            |        | 0.625              | 5             | LOAEL: Squamous metaplasia of the larynx; cytoplasmic vacuolization of bronchiole epithelium and alveolar histiocytic cellular infiltration<br>SLOAEL: Pulmonary hemorrhage |
|                         |                            |                                              |                            |                      | Cardio          | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Gastro          | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Hemato          | 5      | 10                 |               | Increased red blood cell count in both sexes, increased hemoglobin in males                                                                                                 |
|                         |                            |                                              |                            |                      | Musc/skel       | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Hepatic         | 1.25 F | 2.5 F              |               | Decreased absolute and relative liver weight                                                                                                                                |
|                         |                            |                                              |                            |                      |                 | 5 M    | 10 M               |               | Decreased absolute and relative liver weight                                                                                                                                |
|                         |                            |                                              |                            |                      | Renal           | 2.5    | 5                  |               | Decreased absolute and relative kidney weight                                                                                                                               |
|                         |                            |                                              |                            |                      | Dermal          | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Ocular          | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Endocr          | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Immuno          | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Neuro           | 10     |                    |               |                                                                                                                                                                             |
|                         |                            |                                              |                            |                      | Repro           | 5 F    | 10 F               |               | Prolonged estrous cycle                                                                                                                                                     |
|                         |                            |                                              |                            |                      |                 | 1.25 M | 2.5 M              |               | Decreased percent motile sperm                                                                                                                                              |
|                         |                            |                                              |                            |                      | Other noncancer | 10     |                    |               |                                                                                                                                                                             |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>      | Species (strain) No./group | Exposure parameters                     | Doses           | Parameters monitored | Endpoint                                                                | NOAEL                                            | Less serious LOAEL      | Serious LOAEL | Effects                                                                                                                                                            |
|------------------------------|----------------------------|-----------------------------------------|-----------------|----------------------|-------------------------------------------------------------------------|--------------------------------------------------|-------------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Johansson et al. 1987</b> |                            |                                         |                 |                      |                                                                         |                                                  |                         |               | <b>Cobalt Metal</b>                                                                                                                                                |
| 21                           | Rabbit (NS) 8 M            | 17 weeks, 5 days/week, 6 hours/day (WB) | 0, 0.4, 2.0     | CS, HP, OF, OW       | Resp                                                                    |                                                  | 0.4                     | 2             | LOAEL: Moderate lung inflammation and accumulation of macrophages<br>SLOAEL: Severe lung inflammation and accumulation of macrophages; lung edema (lower lobe)     |
| <b>Johansson et al. 1991</b> |                            |                                         |                 |                      |                                                                         |                                                  |                         |               | <b>Cobalt Chloride</b>                                                                                                                                             |
| 22                           | Rabbit (NS) 8 M            | 4 months, 5 days/week, 6 hours/day (WB) | 0, 0.5          | BI, CS, GN, HP       | Resp                                                                    | 0.5                                              |                         |               |                                                                                                                                                                    |
| <b>Johansson et al. 1992</b> |                            |                                         |                 |                      |                                                                         |                                                  |                         |               | <b>Cobalt Chloride</b>                                                                                                                                             |
| 23                           | Rabbit (NS) 8 M            | 4 months, 5 days/week, 6 hours/day (WB) | 0, 0.6          | BI, CS, GN, HP       | Resp                                                                    |                                                  | 0.6                     |               | Inflammatory lesions in the lung; increased cellularity of BALF, with decreased percent macrophages and increased percent monocytes                                |
| <b>Kerfoot 1974</b>          |                            |                                         |                 |                      |                                                                         |                                                  |                         |               | <b>Cobalt Metal</b>                                                                                                                                                |
| 24                           | Pig 5 NS                   | 3 months, 5 days/week, 6 hour/day       | 0, 0.115, 0.991 | CS, GN, HE, HP, UR   | Bd wt<br>Resp<br><br>Cardio<br><br>Hemato<br>Hepatic<br>Renal<br>Immuno | <br><br><br><br>0.991<br>0.991<br>0.991<br>0.991 | 0.115<br>0.115<br>0.115 |               | 16% decrease in final body weight<br>Decreased lung compliance (a metric of mechanical ventilation)<br>Increased heart rate, EKG changes (decreased QRS amplitude) |
| <b>Palmer et al. 1959</b>    |                            |                                         |                 |                      |                                                                         |                                                  |                         |               | <b>Cobalt Hydrocarbonyl</b>                                                                                                                                        |
| 25                           |                            | 3 months                                | 0, 9            |                      | Bd wt                                                                   | 9                                                |                         |               |                                                                                                                                                                    |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                          | Species (strain) No./group | Exposure parameters                                                   | Doses                  | Parameters monitored   | Endpoint | NOAEL               | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------|----------------------------|-----------------------------------------------------------------------|------------------------|------------------------|----------|---------------------|--------------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                  | Guinea pig (NS) 6–32 M     | 5 days/week<br>6 hours/day<br>(WB)                                    |                        | BW, CS, GN, HE, HP, LE | Hemato   |                     | 9                  |               | Increased hemoglobin levels; decreased percent lymphocytes and increased percent basophils                                                                  |
| Exposure was to cobalt hydrocarbonyl plus oxide/carbonate decomposition products due to instability of test substance in oxygen. |                            |                                                                       |                        |                        |          |                     |                    |               |                                                                                                                                                             |
| <b>CHRONIC EXPOSURE</b>                                                                                                          |                            |                                                                       |                        |                        |          |                     |                    |               |                                                                                                                                                             |
| <b>Deng et al. 1991</b>                                                                                                          |                            |                                                                       |                        |                        |          |                     |                    |               |                                                                                                                                                             |
| 26                                                                                                                               | Human 362–1,370 B          | 21 years (occupational)                                               | 0, 0.0175              | CS                     | Resp     | 0.0175              |                    |               | <b>Cobalt Metal</b>                                                                                                                                         |
| <b>Kusaka et al. 1986a</b>                                                                                                       |                            |                                                                       |                        |                        |          |                     |                    |               |                                                                                                                                                             |
| 27                                                                                                                               | Human 34–68 M, 8–16 F      | 3 years (occupational)                                                | 0, 0.126               | CS, OF                 | Resp     |                     | 0.126              |               | <b>Cobalt Metal</b><br>Decreased FEV <sub>1</sub>                                                                                                           |
| <b>Nemery et al. 1992</b>                                                                                                        |                            |                                                                       |                        |                        |          |                     |                    |               |                                                                                                                                                             |
| 28                                                                                                                               | Human 212 M, 41 F          | Current employees; duration of employment not reported (occupational) | 0.0004, 0.0053, 0.0151 | CS, OF, UR             | Resp     | 0.0053 <sup>c</sup> | 0.0151             |               | <b>Cobalt Metal</b><br>Decreased FEV <sub>1</sub> and FVC; increased cough, wheezing, and upper airway irritation                                           |
| <b>Prescott et al. 1992</b>                                                                                                      |                            |                                                                       |                        |                        |          |                     |                    |               |                                                                                                                                                             |
| 29                                                                                                                               | Human 34–36 F              | 14.6 years (occupational)                                             | 0.05                   | BI, CS, EA, OW         | Endocr   | 0.05                |                    |               | <b>Cobalt Aluminate</b>                                                                                                                                     |
| <b>Swennen et al. 1993</b>                                                                                                       |                            |                                                                       |                        |                        |          |                     |                    |               |                                                                                                                                                             |
| 30                                                                                                                               | Human 82 M                 | 8 years (occupational)                                                | 0, 0.125               | BC, CS, HE, UR         | Resp     |                     | 0.125              |               | <b>Hard Metal</b><br>Increased self-reported dyspnea and wheezing in smoking workers, compared to unexposed smokers, without changes in lung function tests |
|                                                                                                                                  |                            |                                                                       |                        |                        | Hemato   |                     | 0.125              |               | Decreased red blood cell counts, hemoglobin, and hematocrit levels; increase in white blood cell count                                                      |
|                                                                                                                                  |                            |                                                                       |                        |                        | Endocr   |                     | 0.125              |               | Decreased T3 levels                                                                                                                                         |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                                                                                                     | Species (strain)<br>No./group | Exposure parameters                                                                  | Doses                  | Parameters monitored  | Endpoint                                                                                                                                                                         | NOAEL                                                                                    | Less serious LOAEL                 | Serious LOAEL  | Effects                                                                                                                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------|------------------------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Behl et al. 2015; Bucher et al. 1999, 2022; NTP 1998, 2023</b>                                                                           |                               |                                                                                      |                        |                       |                                                                                                                                                                                  |                                                                                          | <b>Cobalt Sulfate Heptahydrate</b> |                |                                                                                                                                                                                       |
| 31                                                                                                                                          | Rat<br>(F344/N)<br>50 M, 50 F | 105 weeks<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per<br>day<br>(WB) | 0, 0.12, 0.39,<br>1.11 | BW, CS,<br>GN, HP, LE | Bd wt<br><br>Resp<br><br><br>Cardio<br><br>Gastro<br><br>Musc/skel<br><br>Hepatic<br><br>Renal<br><br>Dermal<br><br>Endocr<br><br>Immuno<br><br>Neuro<br><br>Repro<br><br>Cancer | 1.11<br><br><br><br><br><br><br><br><br><br><br><br><br><br><br><br><br><br><br><br><br> |                                    | 0.12           | Hyperplasia and metaplasia of upper and lower respiratory tract tissues; pulmonary fibrosis; inflammatory changes in lungs                                                            |
|                                                                                                                                             |                               |                                                                                      |                        |                       |                                                                                                                                                                                  |                                                                                          |                                    | 0.39 F         | CEL: Alveolar/bronchiolar neoplasms                                                                                                                                                   |
|                                                                                                                                             |                               |                                                                                      |                        |                       |                                                                                                                                                                                  |                                                                                          |                                    | 0.39 M         | CEL: Benign, complex, or malignant pheochromocytoma                                                                                                                                   |
| Exposure chamber analysis showed that under test conditions, the test substance converted to cobalt sulfate hexahydrate (Behl et al. 2015). |                               |                                                                                      |                        |                       |                                                                                                                                                                                  |                                                                                          |                                    |                |                                                                                                                                                                                       |
| <b>Behl et al. 2015; NTP 2014</b>                                                                                                           |                               |                                                                                      |                        |                       |                                                                                                                                                                                  |                                                                                          | <b>Cobalt Metal</b>                |                |                                                                                                                                                                                       |
| 32                                                                                                                                          | Rat<br>(F344/N)<br>50 M, 50 F | 105 weeks<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per<br>day<br>(WB) | 0, 1.25, 2.5,<br>5     | BW, CS,<br>GN, HP, LE | Death<br><br>Bd wt                                                                                                                                                               | 1.25                                                                                     | 2.5                                | 2.5 F<br><br>5 | 22% decrease in survival<br><br>LOAEL: Final body weights decreased by 11% in males and 16% in females<br><br>SLOAEL: Final body weights decreased by 29% in males and 30% in females |



## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup> | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint  | NOAEL        | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                                   |
|-------------------------|----------------------------|---------------------|-------|----------------------|-----------|--------------|--------------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         |                            |                     |       |                      | Resp      |              |                    | 1.25          | Pulmonary lesions (alveolar epithelium hyperplasia and proteinosis, bronchiole epithelium hyperplasia) and nasal lesions (hyperplasia, metaplasia, necrosis, and atrophy of the olfactory epithelium and nasal turbinate) |
|                         |                            |                     |       |                      | Cardio    | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Gastro    | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Musc/skel | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Hepatic   | 2.5 F        | 5 F<br>1.25 M      |               | Basophilic foci<br>Basophilic foci                                                                                                                                                                                        |
|                         |                            |                     |       |                      | Renal     | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Dermal    | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Ocular    | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Endocr    |              | 1.25 F             |               | Adrenal medullary hyperplasia                                                                                                                                                                                             |
|                         |                            |                     |       |                      |           | 5 M          |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Immuno    | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Neuro     | 5            |                    |               |                                                                                                                                                                                                                           |
|                         |                            |                     |       |                      | Repro     | 5 F<br>2.5 M |                    | 5 M           | Testicular infarct (complete effacement of parenchyma due to necrosis)                                                                                                                                                    |
|                         |                            |                     |       |                      | Cancer    |              |                    | 1.25          | CEL: Alveolar/bronchiolar carcinoma in both sexes; mononuclear cell leukemia in females and bilateral benign pheochromocytoma in males                                                                                    |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>                                           | Species (strain)<br>No./group   | Exposure parameters                                                                  | Doses                  | Parameters monitored  | Endpoint                                                                                                                             | NOAEL                                                                                    | Less serious<br>LOAEL              | Serious<br>LOAEL | Effects                                           |
|-------------------------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------------|------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------|------------------|---------------------------------------------------|
| <b>Behl et al. 2015; Bucher et al. 1999, 2022; NTP 1998, 2023</b> |                                 |                                                                                      |                        |                       |                                                                                                                                      |                                                                                          | <b>Cobalt Sulfate Heptahydrate</b> |                  |                                                   |
| 33                                                                | Mouse<br>(B6C3F1)<br>50 M, 50 F | 105 weeks<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per<br>day<br>(WB) | 0, 0.11, 0.39,<br>1.14 | BW, CS,<br>GN, HP, LE | Bd wt<br>Resp<br><br>Cardio<br>Gastro<br><br>Musc/skel<br>Hepatic<br>Renal<br>Dermal<br>Endocr<br>Immuno<br>Neuro<br>Repro<br>Cancer | 1.14<br><br><br>1.14<br>1.14<br><br>1.14<br>1.14<br>1.14<br>1.14<br>1.14<br>1.14<br>1.14 | 0.11                               |                  | Minimal squamous metaplasia of<br>the larynx      |
|                                                                   |                                 |                                                                                      |                        |                       |                                                                                                                                      |                                                                                          |                                    | 0.39 F           | CEL: Alveolar/bronchiolar<br>adenoma or carcinoma |
|                                                                   |                                 |                                                                                      |                        |                       |                                                                                                                                      |                                                                                          |                                    | 1.14 M           | CEL: Alveolar/bronchiolar<br>adenoma or carcinoma |

Exposure chamber analysis showed that under test conditions, the test substance converted to cobalt sulfate hexahydrate (Behl et al. 2015).

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>           | Species (strain)<br>No./group   | Exposure parameters                                                                  | Doses              | Parameters monitored  | Endpoint                   | NOAEL               | Less serious<br>LOAEL | Serious<br>LOAEL       | Effects                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------|---------------------------------|--------------------------------------------------------------------------------------|--------------------|-----------------------|----------------------------|---------------------|-----------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Behl et al. 2015; NTP 2014</b> |                                 |                                                                                      |                    |                       |                            | <b>Cobalt Metal</b> |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
| 34                                | Mouse<br>(B6C3F1)<br>50 M, 50 F | 105 weeks<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per<br>day<br>(WB) | 0, 1.25, 2.5,<br>5 | BW, CS,<br>GN, HP, LE | Death<br>Bd wt<br><br>Resp | 2.5                 |                       | 2.5 M<br>5<br><br>1.25 | 20% decrease in survival<br>Final body weights decreased by<br>24% in males and 29% in females<br>Hyperplasia and cytoplasmic<br>vacuolization of<br>alveolar/bronchiolar epithelium;<br>atrophy, hyperplasia, and<br>metaplasia of olfactory epithelium;<br>cytoplasmic vacuolization and<br>squamous metaplasia of nasal<br>respiratory epithelium; nasal<br>turbinate atrophy |
|                                   |                                 |                                                                                      |                    |                       | Cardio                     | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Gastro                     | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Musc/skel                  | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Hepatic                    | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Renal                      | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Dermal                     | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Ocular                     | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Endocr                     | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Immuno                     | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Neuro                      | 5                   |                       |                        |                                                                                                                                                                                                                                                                                                                                                                                  |
|                                   |                                 |                                                                                      |                    |                       | Repro                      | 5 F<br>2.5 M        | 5 M                   |                        | Minimal to mild germinal epithelium<br>degradation                                                                                                                                                                                                                                                                                                                               |
|                                   |                                 |                                                                                      |                    |                       | Cancer                     |                     |                       | 1.25                   | CEL: Alveolar/bronchiolar<br>carcinoma                                                                                                                                                                                                                                                                                                                                           |

## 2. HEALTH EFFECTS

**Table 2-1. Levels of Significant Exposure to Cobalt – Inhalation  
(mg Co/m<sup>3</sup>)**

| Figure key <sup>a</sup>   | Species (strain)<br>No./group | Exposure parameters                      | Doses  | Parameters monitored | Endpoint      | NOAEL | Less serious<br>LOAEL | Serious<br>LOAEL | Effects                            |
|---------------------------|-------------------------------|------------------------------------------|--------|----------------------|---------------|-------|-----------------------|------------------|------------------------------------|
| <b>Wehner et al. 1977</b> |                               |                                          |        |                      |               |       |                       |                  | <b>Cobalt Oxide</b>                |
| 35                        | Hamster<br>(ENG:ELA)<br>51 M  | Lifetime,<br>5 days/week,<br>7 hours/day | 0, 7.9 | BW, CS, LE,<br>OF    | Bd wt<br>Resp | 7.9   |                       | 7.9              | Lung Inflammation and<br>emphysema |

<sup>a</sup>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.

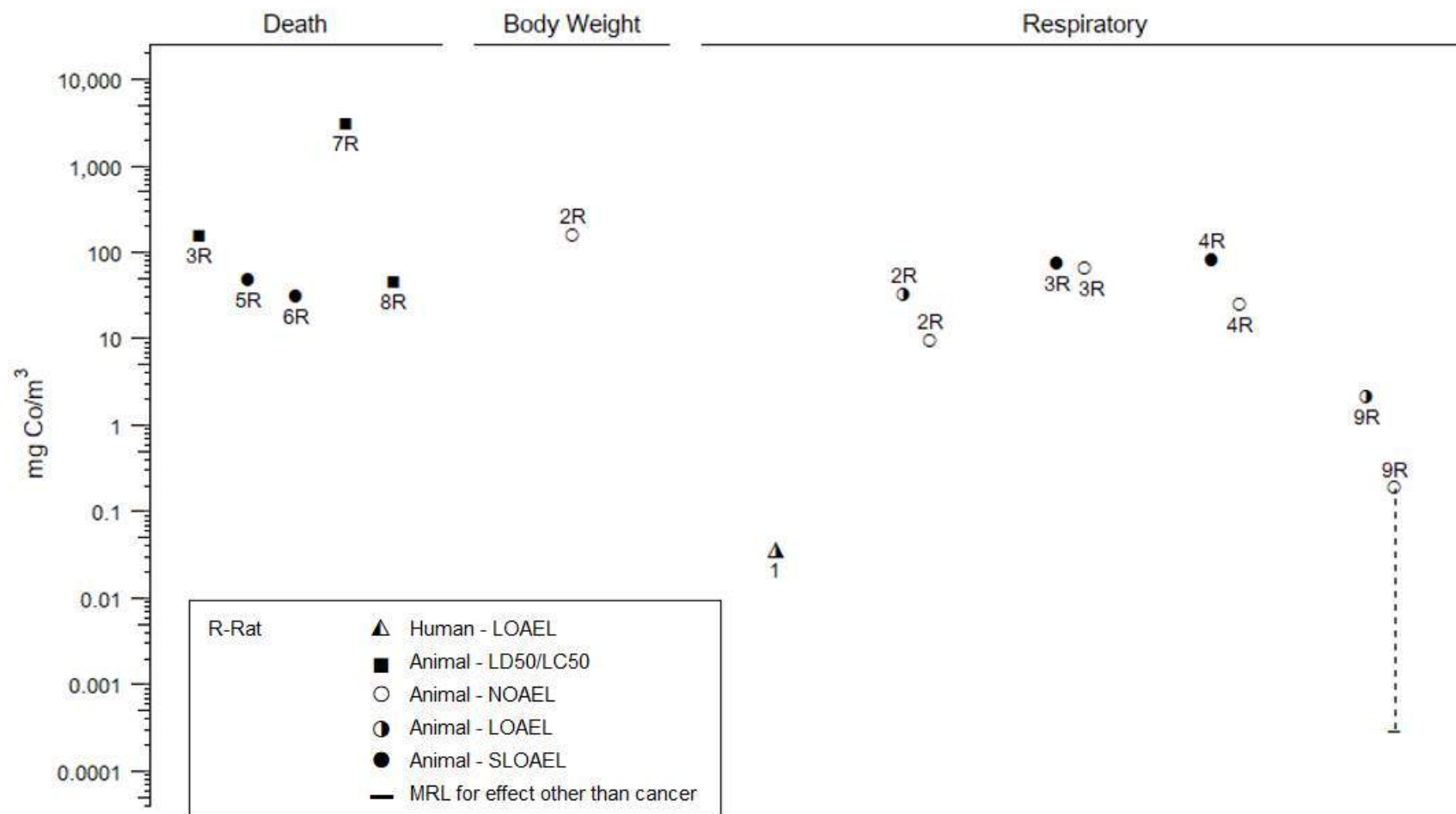
<sup>b</sup>Used to derive an acute-duration inhalation MRL of 0.0003 mg Co/m<sup>3</sup>; the NOAEL was converted into a HEC of 0.01 mg Co/m<sup>3</sup> using MPPD modeling (see Appendix A for calculations) and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

<sup>c</sup>Used to derive a chronic-duration inhalation MRL of 0.0001 mg Co/m<sup>3</sup>; concentration adjusted for intermittent exposure and divided by an uncertainty factor of 10 (for human variability).

B= both males and females; BALF = bronchoalveolar lavage fluid; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; Co = cobalt; CS = clinical signs; EKG = electrocardiogram; Endocr = endocrine; F = female(s); FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; Gastro = gastrointestinal; GN = gross necropsy; HE = hematological; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; LC<sub>50</sub> = lethal concentration, 50% kill; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MPPD = multiple-path particle dosimetry; MRL = minimal risk level; Musc/skel = musculoskeletal; (N) = nose-only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; polycythemia = author-reported term associated with increased hemoglobin or erythrocyte count; Repro = reproductive; Resp = respiratory; RX = reproductive function; SLOAEL = serious LOAEL; T3 = triiodothyronine; T90 = the time required for the inhalation chamber concentration to reach 90% of the target concentration; TSH = thyroid-stimulating hormone; UR = urinalysis; (WB) = whole-body; WI = water intake

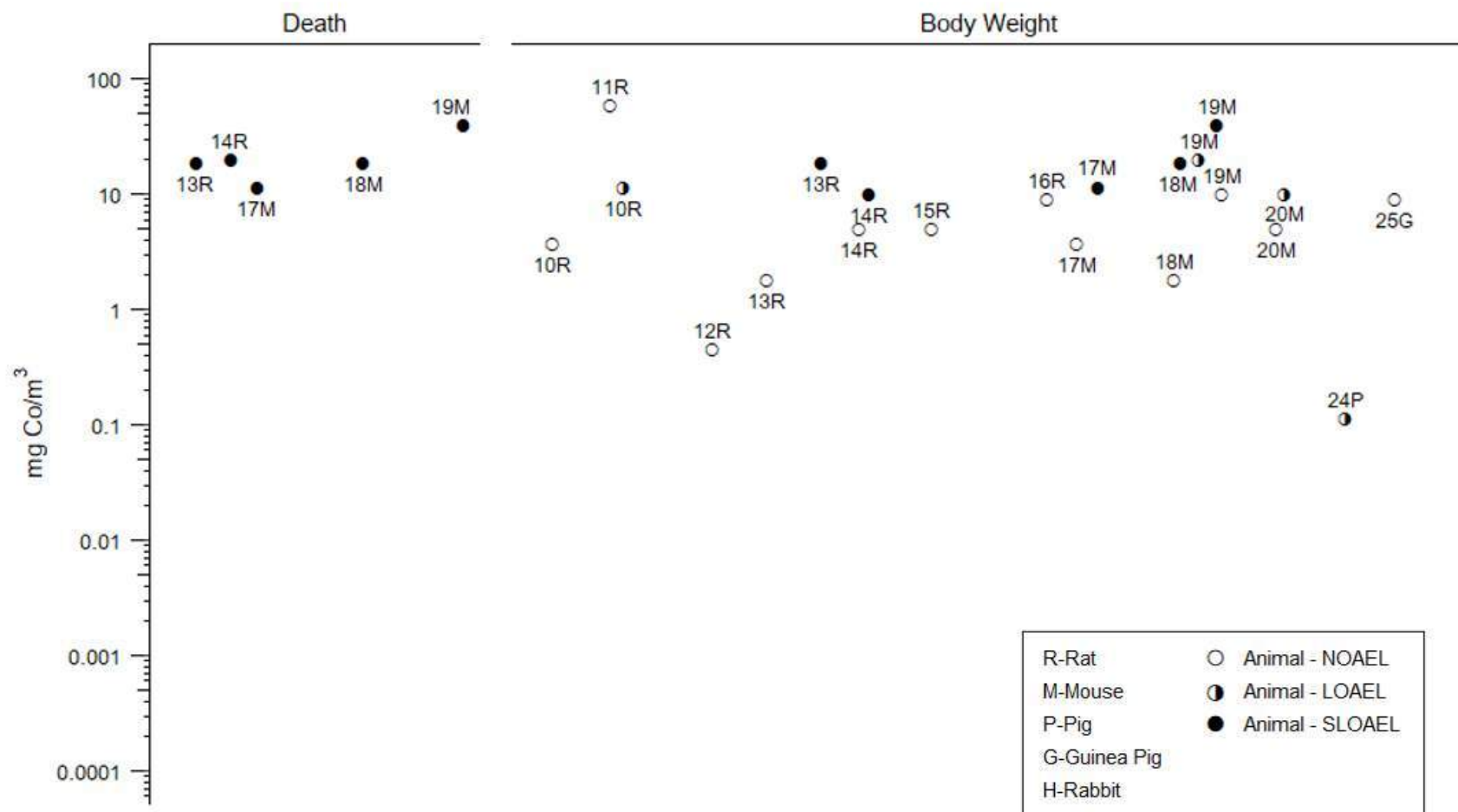
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Acute (≤14 days)



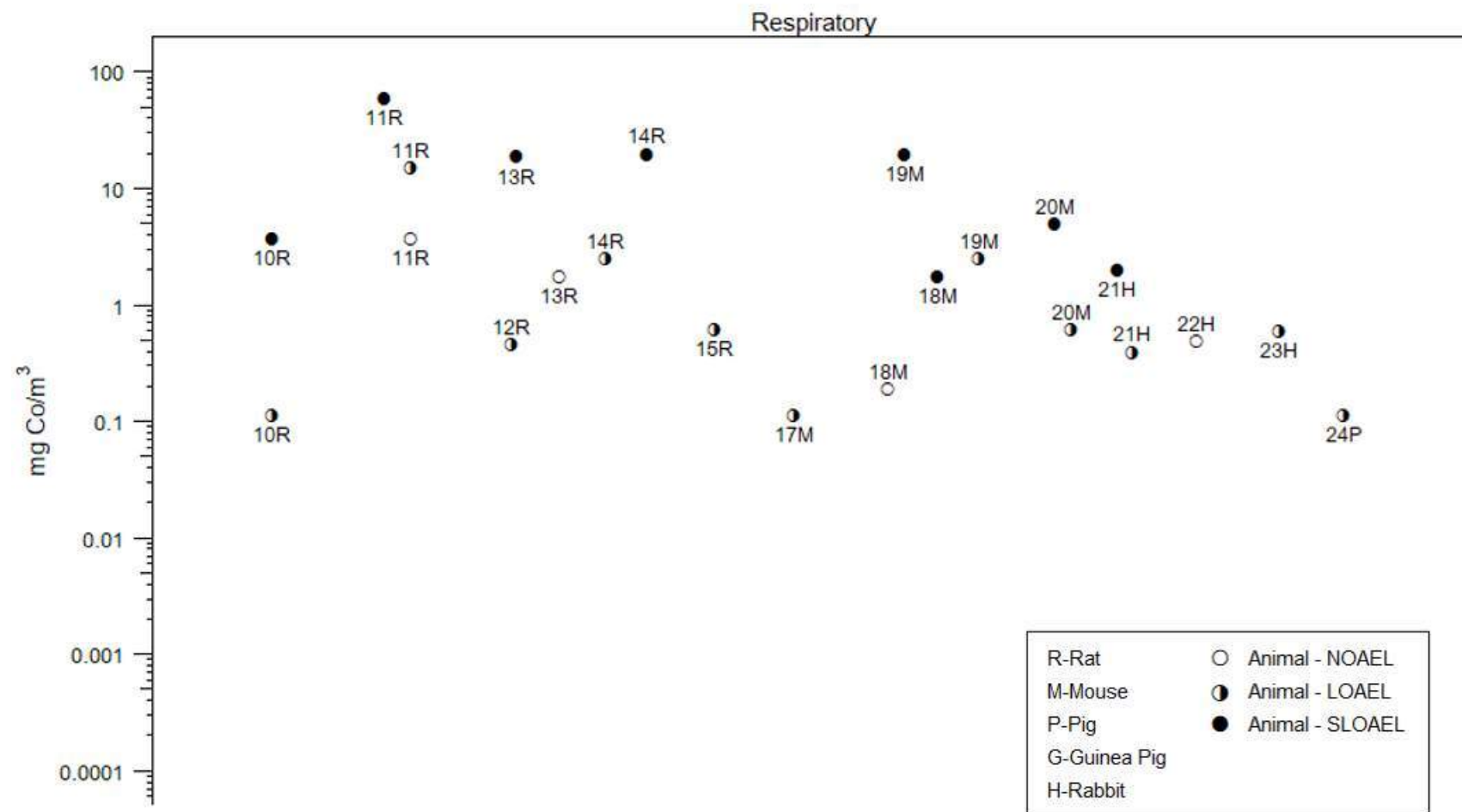
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Intermediate (15–364 days)



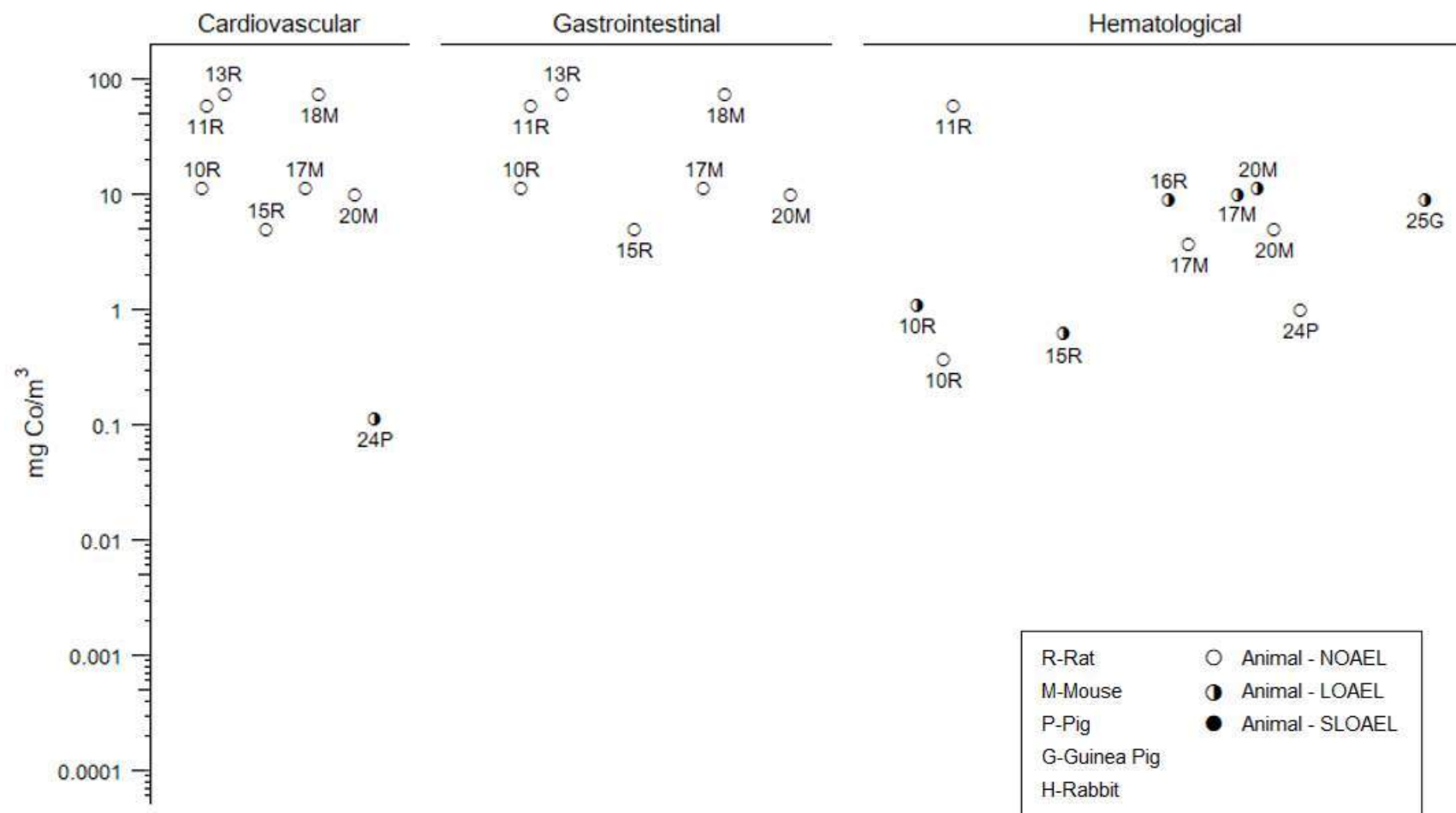
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Intermediate (15–364 days)



## 2. HEALTH EFFECTS

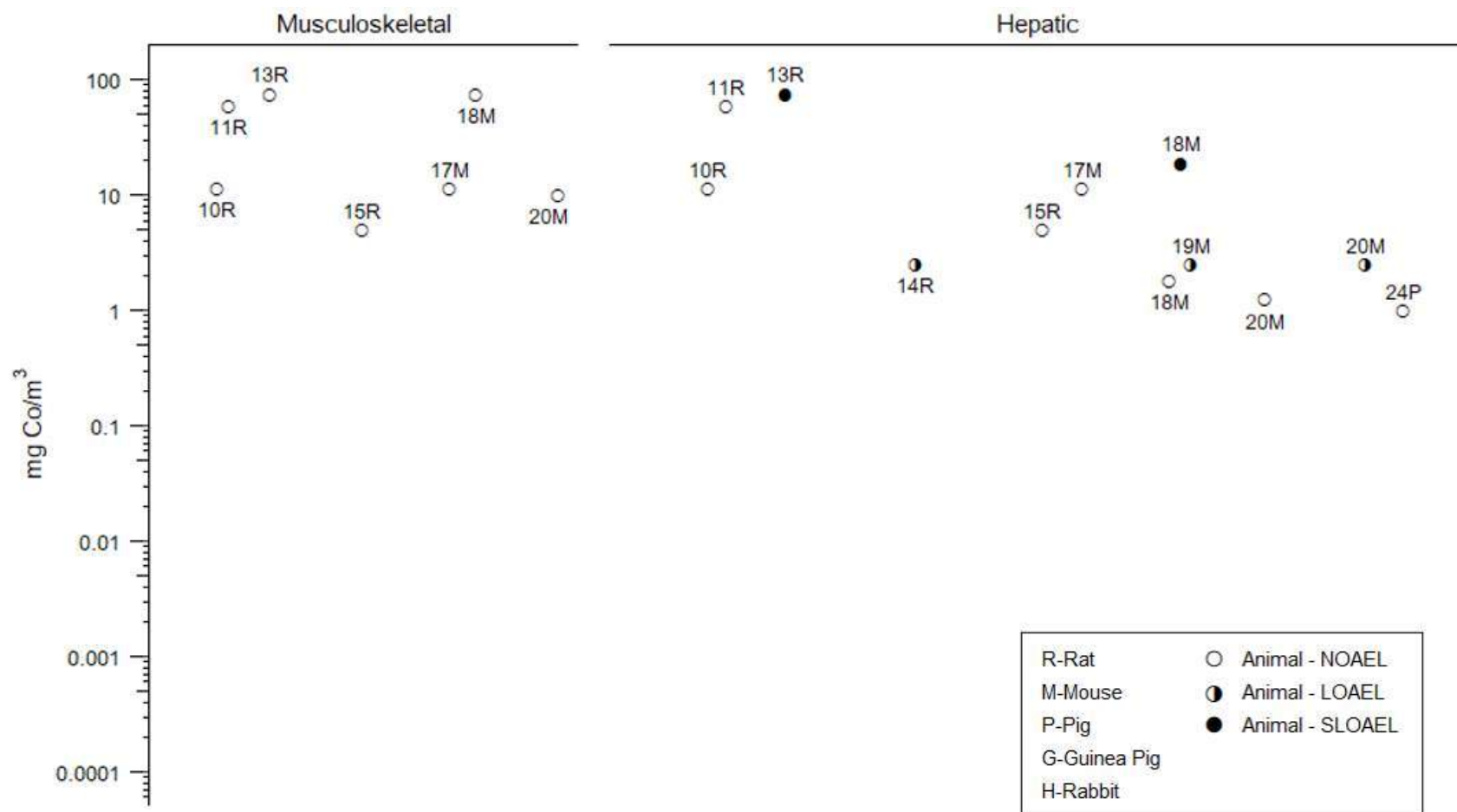
**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Intermediate (15–364 days)





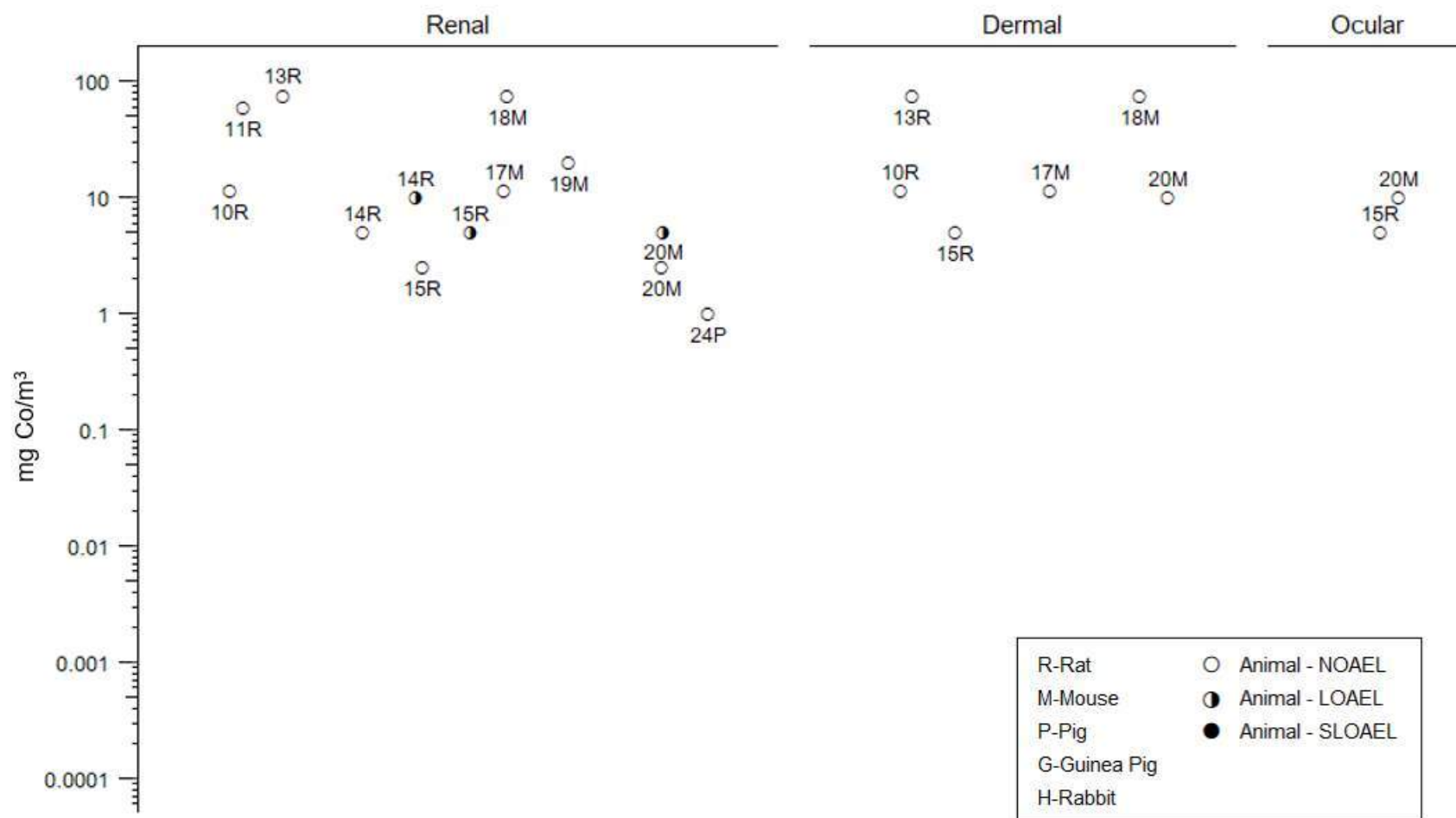
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Intermediate (15–364 days)



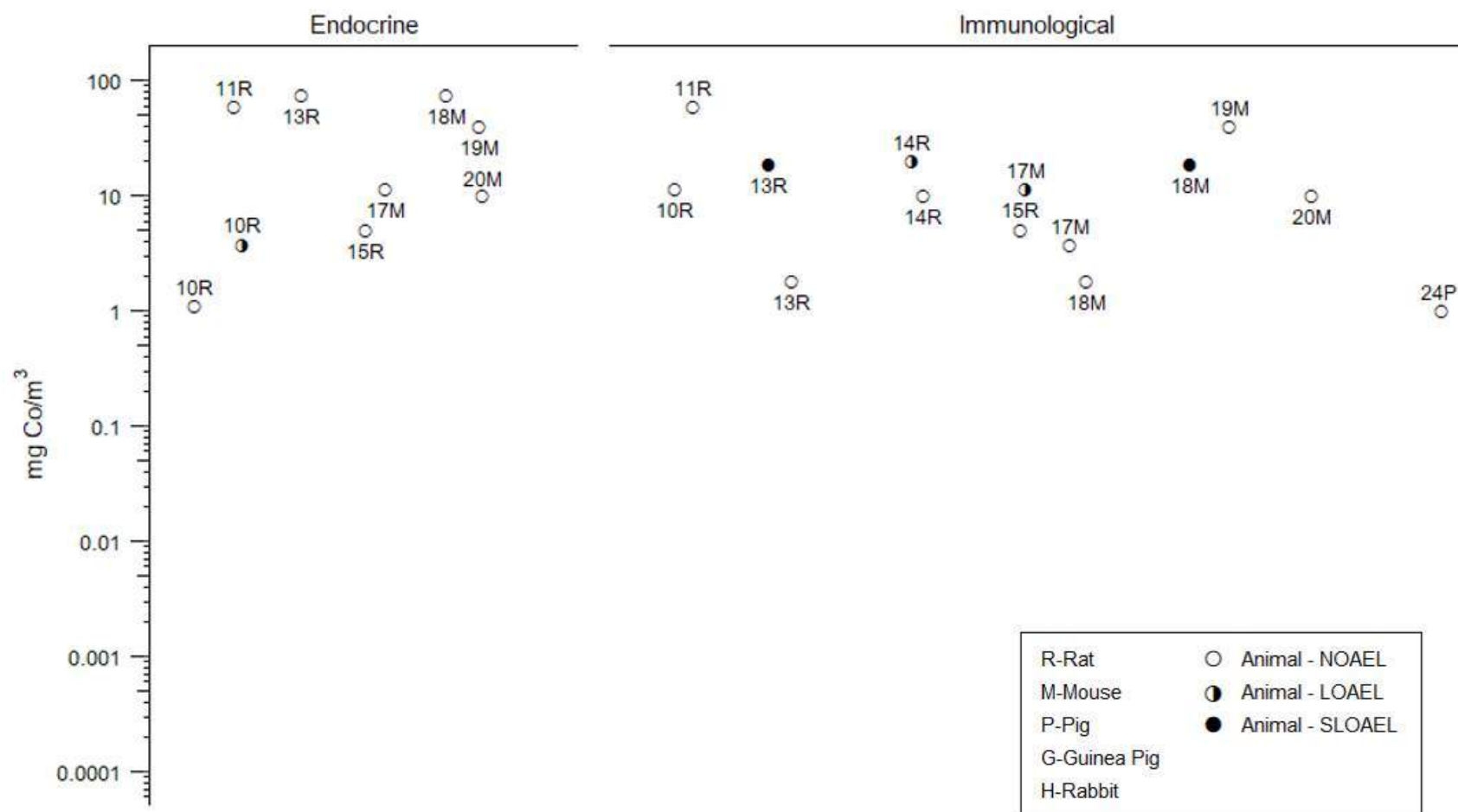
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Intermediate (15–364 days)



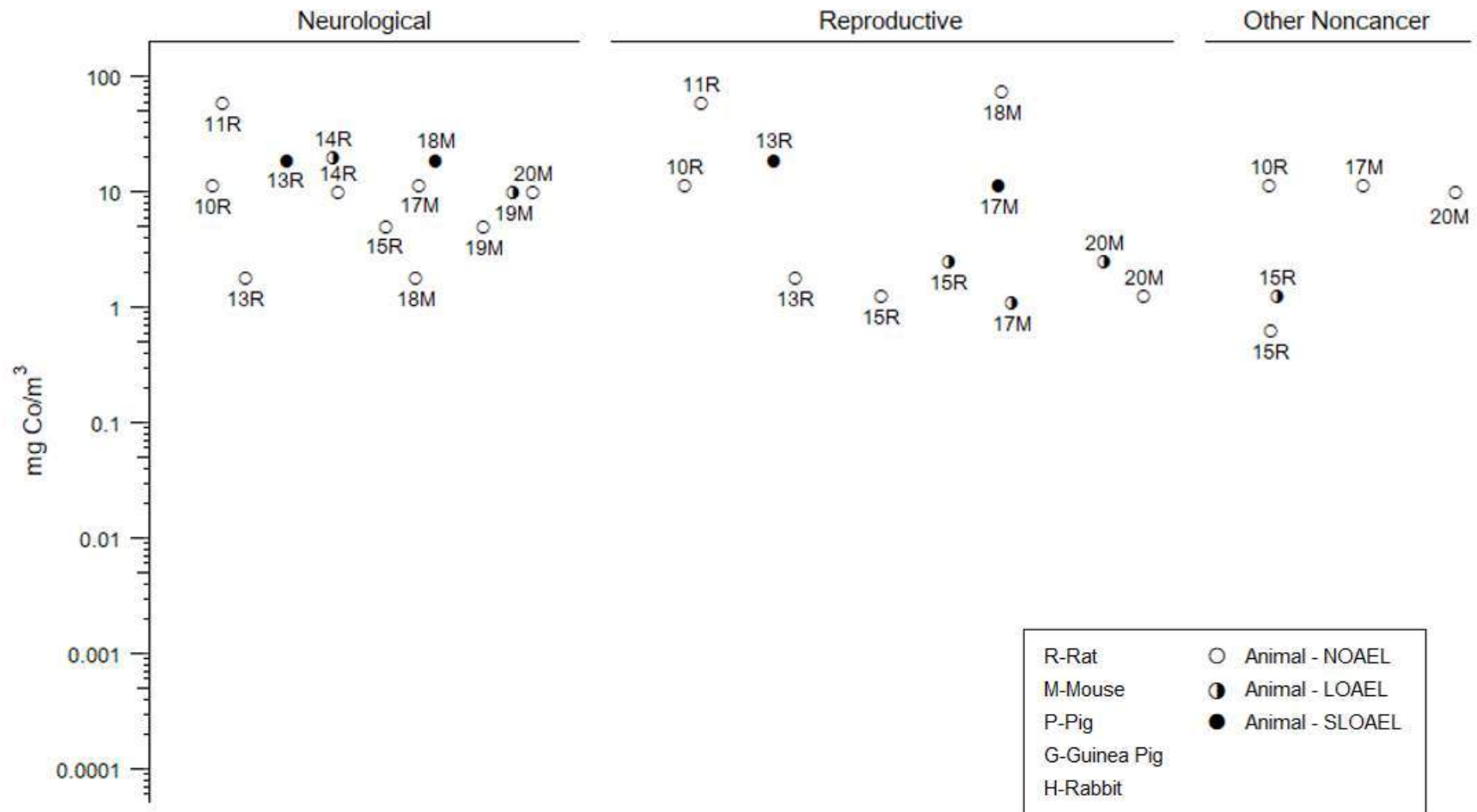
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Intermediate (15–364 days)



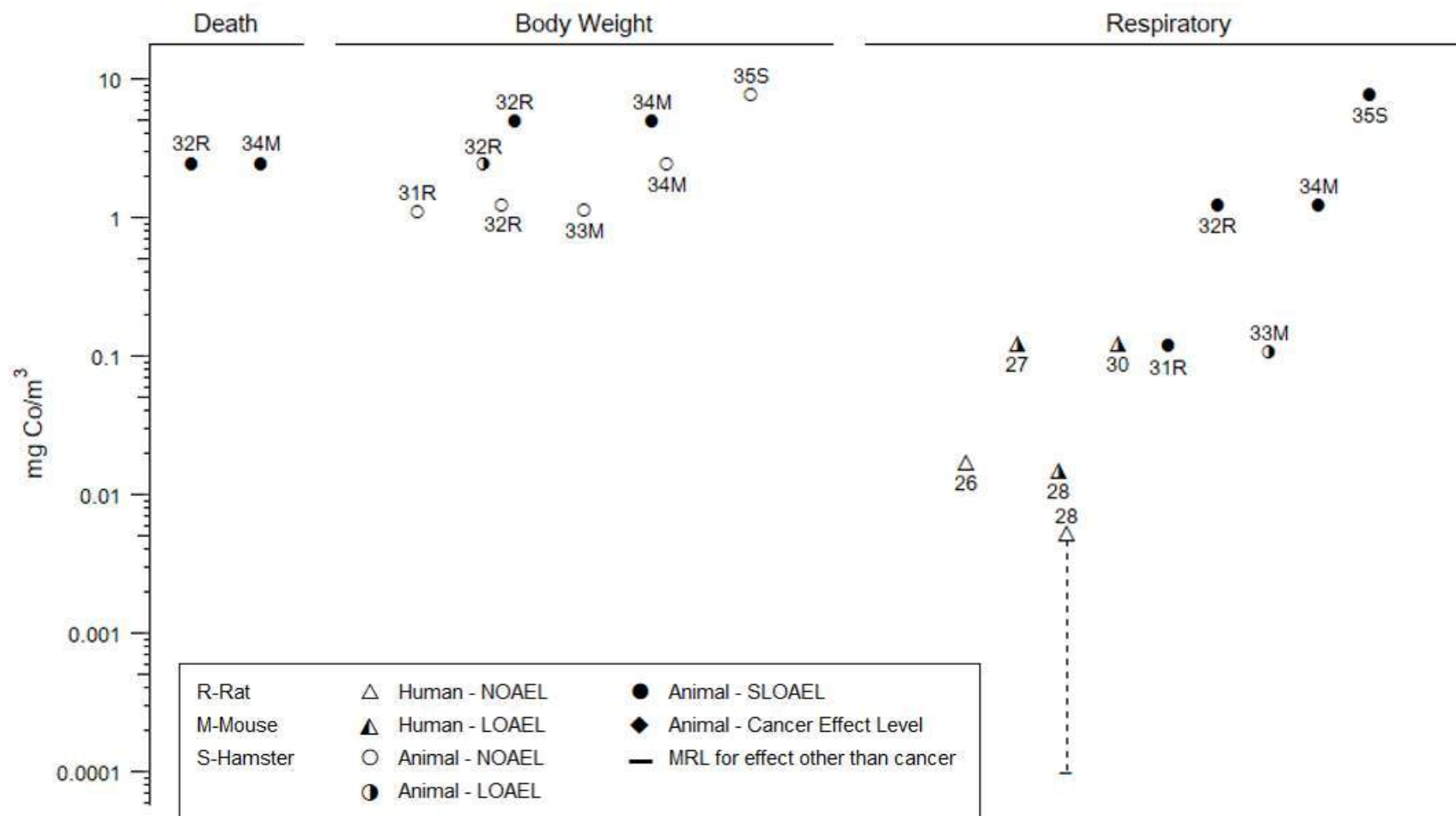
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Intermediate (15–364 days)



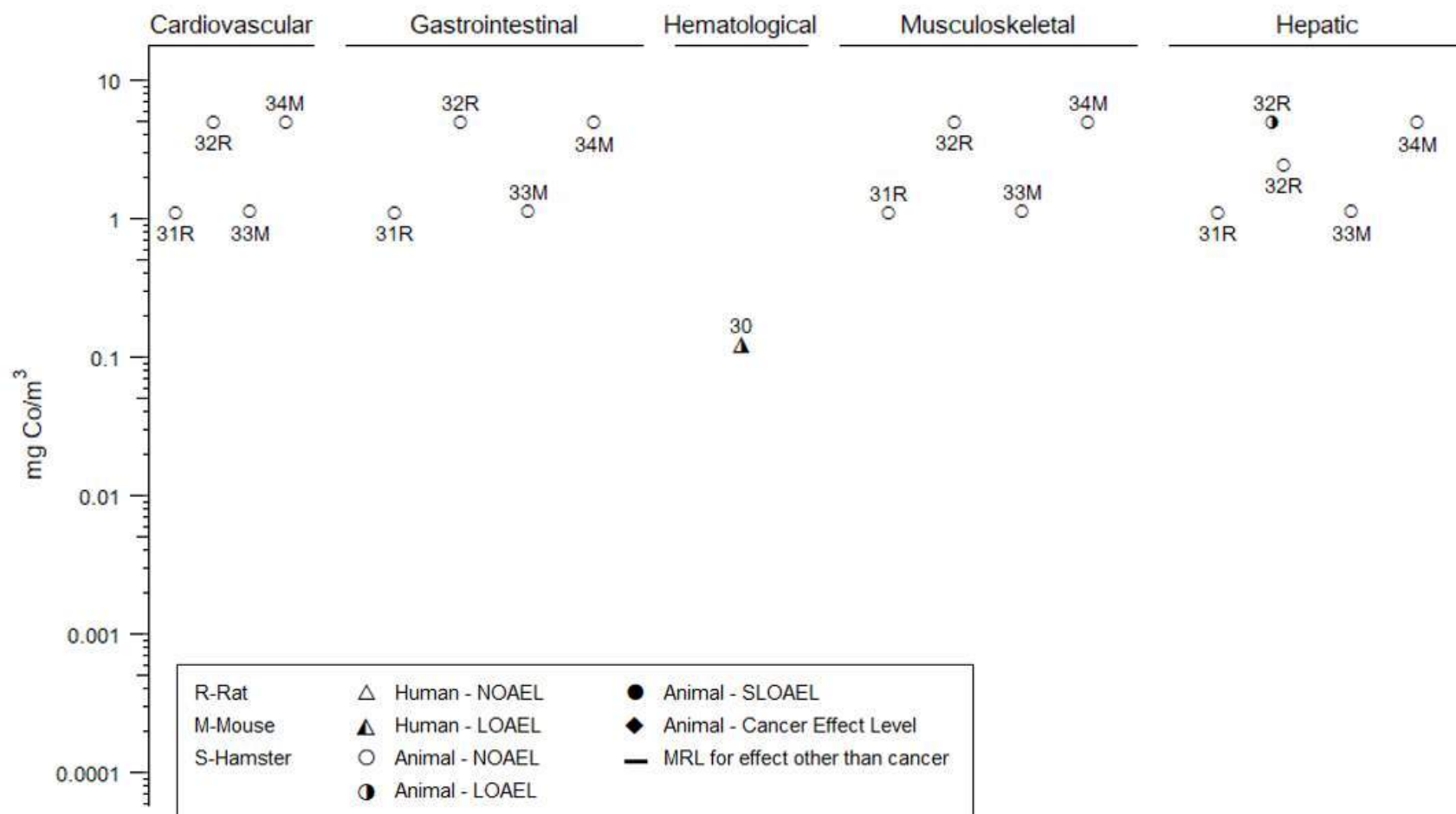
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Chronic (≥365 days)



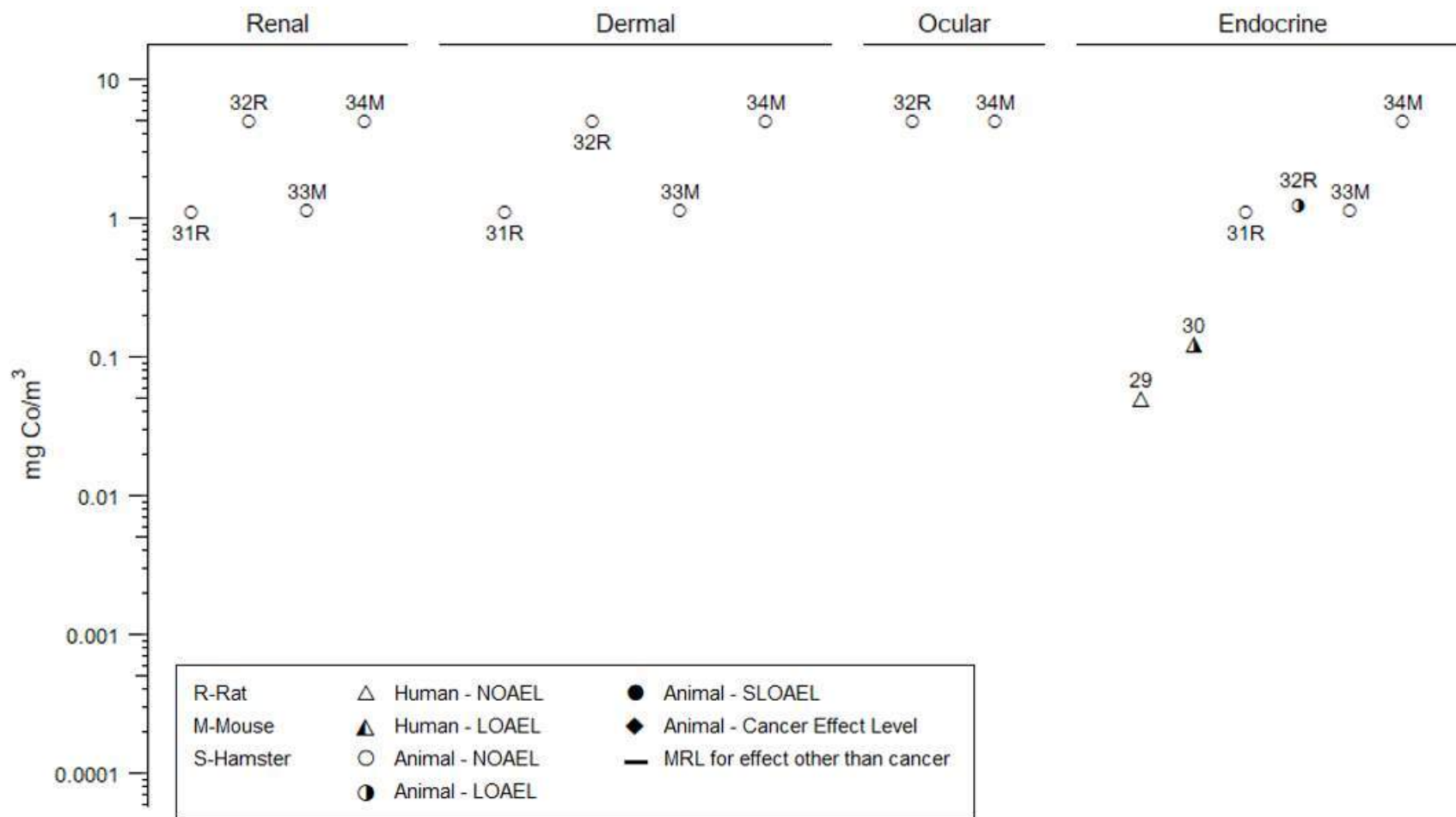
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Chronic (≥365 days)



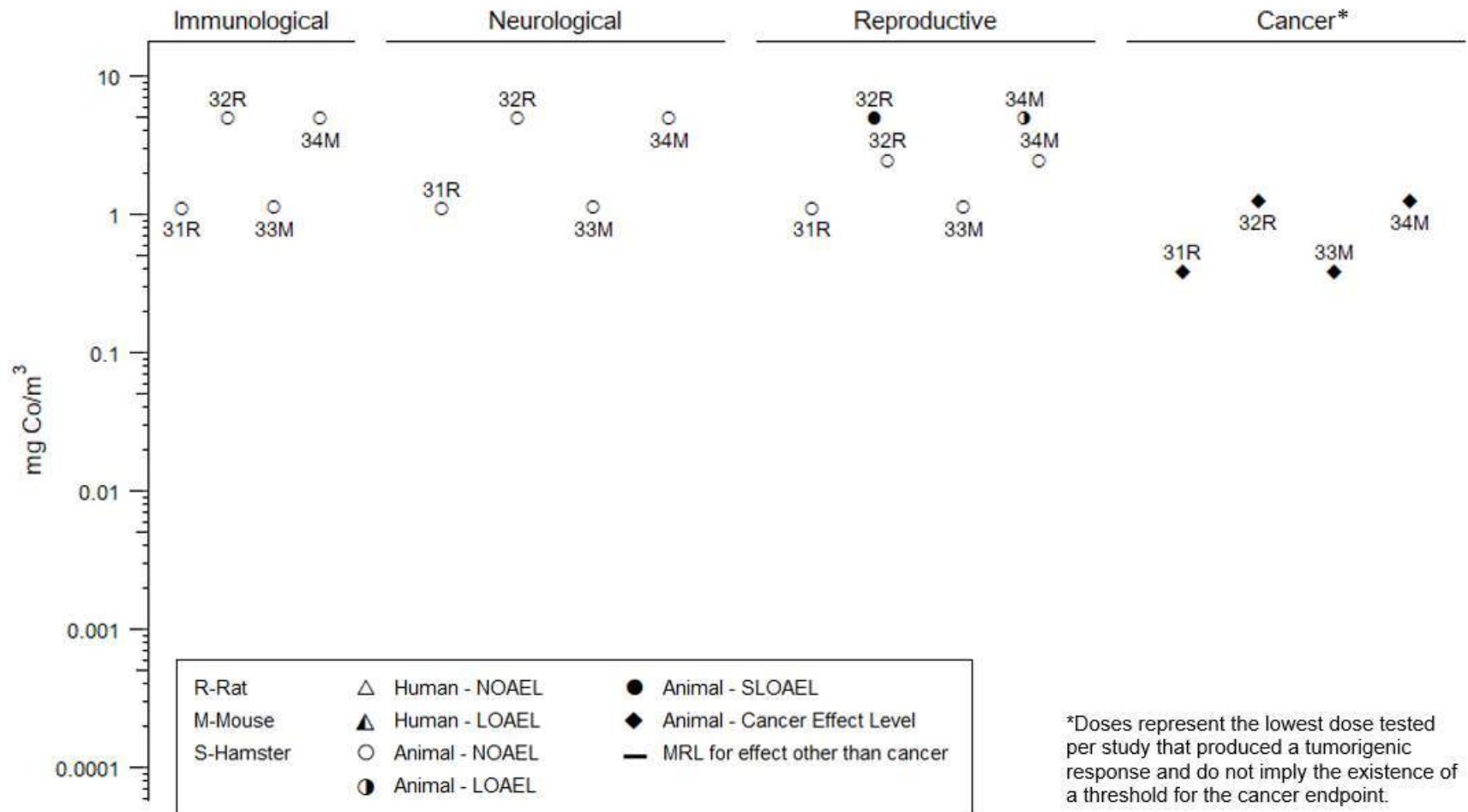
## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Chronic (≥365 days)



## 2. HEALTH EFFECTS

**Figure 2-2. Levels of Significant Exposure to Cobalt – Inhalation (mg Co/m<sup>3</sup>)**  
Chronic (≥365 days)





## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>           | Species (strain)<br>No./group | Exposure parameters        | Doses   | Parameters monitored | Endpoint            | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                                            |
|-----------------------------------|-------------------------------|----------------------------|---------|----------------------|---------------------|-------|--------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ACUTE EXPOSURE</b>             |                               |                            |         |                      |                     |       |                    |               |                                                                                                                                                                                                                                    |
| <b>Davis and Fields 1958</b>      |                               |                            |         |                      |                     |       |                    |               |                                                                                                                                                                                                                                    |
| 1                                 | Human 5 M                     | 7–14 days (C)              | 0, 1    | HE                   | Hemato              |       | 1 <sup>b</sup>     |               | <b>Cobalt Chloride</b><br>Polycythemia (clinically high red blood cell levels)                                                                                                                                                     |
| <b>Hoffmeister et al. 2018</b>    |                               |                            |         |                      |                     |       |                    |               |                                                                                                                                                                                                                                    |
| 2                                 | Human 8–16 M                  | 7–14 days (C)              | 0, 0.03 | HE                   | Hemato              | 0.03  |                    |               | <b>Cobalt (II)</b>                                                                                                                                                                                                                 |
| <b>Paley et al. 1958</b>          |                               |                            |         |                      |                     |       |                    |               |                                                                                                                                                                                                                                    |
| 3                                 | Human 3 M                     | 10–14 days (C)             | 0, 0.54 | BC, CS, OF           | Gastro<br>Endocr    |       | 0.54<br>0.54       |               | <b>Cobalt Chloride</b><br>Mild gastric distress<br>Impaired thyroid uptake of radioactive iodine-131                                                                                                                               |
| <b>Roche and Layrisse 1956</b>    |                               |                            |         |                      |                     |       |                    |               |                                                                                                                                                                                                                                    |
| 4                                 | Human 12 NS                   | 2 weeks<br>7 days/week (C) | 0, 1.0  | BC, OF               | Endocr              |       | 1                  |               | <b>Cobalt Chloride</b><br>Impaired thyroid uptake of radioactive iodine-131                                                                                                                                                        |
| <b>Ajibade et al. 2017</b>        |                               |                            |         |                      |                     |       |                    |               |                                                                                                                                                                                                                                    |
| 5                                 | Rat (Wistar) 6 M              | 2 weeks<br>7 days/week (W) | 0, 35   | BC, BI, OF, HP       | Cardio<br><br>Renal |       | 35<br><br>35       |               | <b>Cobalt Chloride</b><br>Elevated systolic, diastolic, and mean arterial blood pressure; cellular infiltration and cardiac cell swelling<br>Increased serum urea, inflammation of renal tissues                                   |
| <b>Akinrinde and Adebisi 2019</b> |                               |                            |         |                      |                     |       |                    |               |                                                                                                                                                                                                                                    |
| 6                                 | Rat (Wistar) 12 M             | 7 days (GW)                | 0, 67.5 | BC, BI, CS, NX       | Immuno<br><br>Neuro |       | 67.5               | 67.5          | <b>Cobalt (II) Chloride Hexahydrate</b><br>Increased IL-1 $\beta$ and TNF $\alpha$<br><br>Decreased motor strength, decreased activity and exploration in an open field; increased brain GFAP (reactive gliosis) and AChE activity |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>       | Species (strain)<br>No./group | Exposure parameters            | Doses           | Parameters monitored  | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                            |
|-------------------------------|-------------------------------|--------------------------------|-----------------|-----------------------|----------|-------|--------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Akinrinde et al. 2016a</b> |                               |                                |                 |                       |          |       |                    |               |                                                                                                                                                                                                                    |
| 7                             | Rat (Wistar)<br>8 M           | 2 weeks,<br>7 days/week<br>(W) | 0, 10           | BC, BI, GN,<br>HP, OF | Cardio   |       |                    | 10            | <b>Cobalt (II) Chloride Hexahydrate</b><br>Decreased systolic blood pressure; hemorrhagic lesions and congestion in the coronary blood vessels and infiltration of inflammatory cells in the myocardium and atrium |
|                               |                               |                                |                 |                       | Renal    |       | 10                 |               | Increased serum urea and creatinine; loss of normal renal cell morphology, loss of tubular and glomerular outlines, peritubular inflammatory cell infiltration                                                     |
| <b>Akinrinde et al. 2016b</b> |                               |                                |                 |                       |          |       |                    |               |                                                                                                                                                                                                                    |
| 8                             | Rat (Wistar)<br>7 M           | 7 days<br>(W)                  | 0, 10           | BI, HP, OF            | Cardio   |       |                    | 10            | <b>Cobalt (II) Chloride Hexahydrate</b><br>Decreased systolic, diastolic, and mean arterial blood pressure; Inflammation of the myocardium and areas of myocardial infarction                                      |
|                               |                               |                                |                 |                       | Renal    |       | 10                 |               | Peritubular and perivascular inflammation; focal tubular necrosis                                                                                                                                                  |
| <b>Akinrinde et al. 2016c</b> |                               |                                |                 |                       |          |       |                    |               |                                                                                                                                                                                                                    |
| 9                             | Rat (Wistar)<br>7 M           | 7 days<br>(W)                  | 0, 10           | BC, BI, HP,<br>OW     | Gastro   |       | 10                 |               | <b>Cobalt (II) Chloride Hexahydrate</b><br>Decreased relative small intestine weight; significant histopathological damage to intestine with depletion of absorptive epithelial cells                              |
|                               |                               |                                |                 |                       | Hepatic  |       | 10                 |               | Reduced relative liver weight; hepatocellular damage and areas of necrosis                                                                                                                                         |
|                               |                               |                                |                 |                       | Immuno   |       | 10                 |               | Decreased serum TNF $\alpha$ and increased serum IL-1 $\beta$                                                                                                                                                      |
| <b>Awoyemi et al. 2017</b>    |                               |                                |                 |                       |          |       |                    |               |                                                                                                                                                                                                                    |
| 10                            | Rat (Albino)<br>10 M          | 7 days<br>(W)                  | 0, 4.4, 8.9, 18 | BC, BI, HP            | Hepatic  | 4.4   | 8.9                |               | <b>Cobalt (II) Chloride Hexahydrate</b><br>Focal area of necrosis and congestion of vessels; mild infiltration by inflammatory cells                                                                               |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>              | Species (strain)<br>No./group | Exposure parameters | Doses                       | Parameters monitored | Endpoint                                               | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                                                                                 |
|--------------------------------------|-------------------------------|---------------------|-----------------------------|----------------------|--------------------------------------------------------|-------|--------------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Corrier et al. 1985</b>           |                               |                     |                             |                      |                                                        |       |                    |               |                                                                                                                                                                                                                                                                         |
| 11                                   | Rat (Sprague-Dawley) 3 M (F)  | 14 days daily       | 0, 20                       | HP, RX               | Repro                                                  | 20    |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                                                                                                 |
| <b>Domingo and Llobet 1984</b>       |                               |                     |                             |                      |                                                        |       |                    |               |                                                                                                                                                                                                                                                                         |
| 12                                   | Rat (Sprague-Dawley) 20 M     | Once (GW)           | 0, 161                      | BC, CS, HE, LE       | Death<br>Hemato<br>Hepatic<br>Renal<br>Other noncancer | 161   | 161                | 161           | <b>Cobalt (II) Chloride Hexahydrate</b><br>11/20 died<br>Increased hematocrit<br>Increased serum urea<br>Decreased serum glucose                                                                                                                                        |
| <b>Domingo et al. 1985a</b>          |                               |                     |                             |                      |                                                        |       |                    |               |                                                                                                                                                                                                                                                                         |
| 13                                   | Rat (Sprague-Dawley) 20 M     | Once (G)            | 0, 37, 61                   | LE                   | Death                                                  |       |                    | 37            | <b>Cobalt (II) Chloride Hexahydrate</b><br>10/20 died                                                                                                                                                                                                                   |
| <b>Krasovskii and Fridlyand 1971</b> |                               |                     |                             |                      |                                                        |       |                    |               |                                                                                                                                                                                                                                                                         |
| 14                                   | Rat (albino) NS               | Once (GW)           | Not reported                | LE                   | Death                                                  |       |                    | 36            | <b>Cobalt Chloride</b><br>LD <sub>50</sub>                                                                                                                                                                                                                              |
| <b>Murdock 1959</b>                  |                               |                     |                             |                      |                                                        |       |                    |               |                                                                                                                                                                                                                                                                         |
| 15                                   | Rat (NS) 10 M                 | Once (GW)           | 98, 122, 137, 150, 153, 191 | LE                   | Death                                                  |       |                    | 144           | <b>Cobalt Chloride</b><br>LD <sub>50</sub>                                                                                                                                                                                                                              |
| <b>Oria et al. 2022</b>              |                               |                     |                             |                      |                                                        |       |                    |               |                                                                                                                                                                                                                                                                         |
| 16                                   | Rat (Wistar) 15 M             | 14 days (GW)        | 0, 9.9                      | BC, HP, NX           | Immuno<br>Neuro                                        |       | 9.9                | 9.9           | <b>Cobalt (II) Chloride Hexahydrate</b><br>Increased serum IL-1 $\beta$ and TNF $\alpha$<br>Neurobehavioral effects (altered exploration, impaired memory, increased anxiety-like behaviors); ultrastructural changes in the hippocampus and amygdala; reactive gliosis |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>           | Species (strain)<br>No./group   | Exposure parameters           | Doses                 | Parameters monitored                                | Endpoint        | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                              |
|-----------------------------------|---------------------------------|-------------------------------|-----------------------|-----------------------------------------------------|-----------------|-------|--------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Oyagbemi et al. 2020</b>       |                                 |                               |                       |                                                     |                 |       |                    |               |                                                                                                                                                                                      |
| 17                                | Rat (Wistar)<br>8 M             | 8 days<br>(GW)                | 0, 37                 | BC, BI, OW,<br>HP                                   | Cardio          |       |                    | 37            | <b>Cobalt (II) Chloride Hexahydrate</b><br>Histopathological changes to cardiac muscle (atrophy and patchy degeneration of myofibers, loss of striation); distension of interstitium |
|                                   |                                 |                               |                       |                                                     | Renal           |       | 37                 |               | Mild tubular atrophy, necrotizing nephritis, inflammatory cell infiltrate                                                                                                            |
| <b>Paternian and Domingo 1988</b> |                                 |                               |                       |                                                     |                 |       |                    |               |                                                                                                                                                                                      |
| 18                                | Rat<br>(Sprague-Dawley)<br>20 F | 10 days<br>(GDs 6–15)<br>(GW) | 0, 6.2, 12.4,<br>24.8 | BC, BW, DX,<br>HE, OW                               | Bd wt           |       |                    | 6.2           | <b>Cobalt (II) Chloride Hexahydrate</b><br>23% decrease in maternal body weight gain during gestation                                                                                |
|                                   |                                 |                               |                       |                                                     | Hemato          | 12.4  | 24.8               |               | Increased hematocrit, hemoglobin, and reticulocytes                                                                                                                                  |
|                                   |                                 |                               |                       |                                                     | Develop         | 24.8  |                    |               |                                                                                                                                                                                      |
| <b>Salami et al. 2023</b>         |                                 |                               |                       |                                                     |                 |       |                    |               |                                                                                                                                                                                      |
| 19                                | Rat (Wistar)<br>5 M             | 8 days<br>(G)                 | 0, 11, 28, 68,<br>136 | BW, OW, HP                                          | Bd wt           | 28    |                    | 68            | <b>Cobalt Chloride</b><br>Body weight loss (13% loss compared to starting weight; compared to 8% gain in controls)                                                                   |
|                                   |                                 |                               |                       |                                                     | Gastro          | 28    | 68                 |               | Increased cryptal depth in small intestine, altered gut motility (increased gastric emptying time)                                                                                   |
| <b>Shrivastava et al. 2008</b>    |                                 |                               |                       |                                                     |                 |       |                    |               |                                                                                                                                                                                      |
| 20                                | Rat<br>(Sprague-Dawley) 6 M     | 7 days<br>(G)                 | 0, 12.5               | HE                                                  | Hemato          |       | 12.5               |               | <b>Cobalt (II) Chloride Hexahydrate</b><br>Increased hematocrit and hemoglobin levels                                                                                                |
|                                   |                                 |                               |                       |                                                     | Other noncancer |       | 12.5               |               | Elevated serum glucose levels                                                                                                                                                        |
| <b>Shrivastava et al. 2010</b>    |                                 |                               |                       |                                                     |                 |       |                    |               |                                                                                                                                                                                      |
| 21                                | Rat<br>(Sprague-Dawley) 8 M     | 7 days<br>(G)                 | 0, 12.5               | BC, BI, BW,<br>FI, HE, HP,<br>LE, NX, OP,<br>OW, WI | Bd wt           | 12.5  |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                              |
|                                   |                                 |                               |                       |                                                     | Resp            | 12.5  |                    |               |                                                                                                                                                                                      |
|                                   |                                 |                               |                       |                                                     | Cardio          | 12.5  |                    |               |                                                                                                                                                                                      |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>         | Species (strain)<br>No./group | Exposure parameters | Doses        | Parameters monitored | Endpoint        | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                             |
|---------------------------------|-------------------------------|---------------------|--------------|----------------------|-----------------|-------|--------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 |                               |                     |              |                      | Hemato          |       | 12.5               |               | Increased red blood cell count, hematocrit, and hemoglobin; increased percent granulocytes and monocytes                                                                                            |
|                                 |                               |                     |              |                      | Hepatic         | 12.5  |                    |               |                                                                                                                                                                                                     |
|                                 |                               |                     |              |                      | Renal           | 12.5  |                    |               |                                                                                                                                                                                                     |
|                                 |                               |                     |              |                      | Ocular          | 12.5  |                    |               |                                                                                                                                                                                                     |
|                                 |                               |                     |              |                      | Immuno          | 12.5  |                    |               |                                                                                                                                                                                                     |
|                                 |                               |                     |              |                      | Neuro           | 12.5  |                    |               |                                                                                                                                                                                                     |
|                                 |                               |                     |              |                      | Other noncancer |       | 12.5               |               | Elevated serum glucose levels                                                                                                                                                                       |
| <b>Singh and Junnarkar 1991</b> |                               |                     |              |                      |                 |       |                    |               |                                                                                                                                                                                                     |
| 22                              | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | 0, 7.8       | CS, NX               | Neuro           |       | 7.8                |               | <b>Cobalt Chloride</b><br>Moderate CNS depression (decreased spontaneous activity, muscle tone, touch response, respiratory rate, mild hypothermia; increased pentobarbitone-induced sleeping time) |
| <b>Singh and Junnarkar 1991</b> |                               |                     |              |                      |                 |       |                    |               |                                                                                                                                                                                                     |
| 23                              | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | 0, 35.2      | CS, NX               | Neuro           |       | 35.2               |               | <b>Cobalt Sulfate</b><br>Mild CNS depression (decreased spontaneous activity, muscle tone, touch response, respiratory rate, mild hypothermia; increased pentobarbitone-induced sleeping time)      |
| <b>Singh and Junnarkar 1991</b> |                               |                     |              |                      |                 |       |                    |               |                                                                                                                                                                                                     |
| 24                              | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | Not reported | LE                   | Death           |       |                    | 77.6          | <b>Cobalt Chloride</b><br>LD <sub>50</sub>                                                                                                                                                          |
| <b>Singh and Junnarkar 1991</b> |                               |                     |              |                      |                 |       |                    |               |                                                                                                                                                                                                     |
| 25                              | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | Not reported | LE                   | Death           |       |                    | 352           | <b>Cobalt Sulfate</b><br>LD <sub>50</sub>                                                                                                                                                           |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>     | Species (strain)<br>No./group | Exposure parameters | Doses                     | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                    |
|-----------------------------|-------------------------------|---------------------|---------------------------|----------------------|----------|-------|--------------------|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 26                          | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | 124, 149, 178, 214, 282   | LE, CS               | Death    |       |                    | 190           | <b>Cobalt (II) Chloride Hexahydrate</b><br>LD <sub>50</sub>                                                                                                                |
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 27                          | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | 53.9, 80.8, 121, 182, 272 | LE, CS               | Death    |       |                    | 109           | <b>Cobalt Bromide</b><br>LD <sub>50</sub>                                                                                                                                  |
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 28                          | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | 94.4, 142, 210, 315, 472  | LE, CS               | Death    |       |                    | 161           | <b>Cobalt Sulfate Heptahydrate</b><br>LD <sub>50</sub>                                                                                                                     |
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 29                          | Rat (Wistar)<br>5 M, 5 F      | Once (G)            | 43, 68, 109, 176, 280     | LE, CS, HP           | Death    |       |                    | 91            | <b>Cobalt fluoride</b><br>LD <sub>50</sub>                                                                                                                                 |
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 30                          | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | 91.1, 137, 202, 304, 455  | LE, CS               | Death    |       |                    | 140           | <b>Cobalt Nitrate Hexahydrate</b><br>LD <sub>50</sub>                                                                                                                      |
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 31                          | Rat (Wistar)<br>5 M, 5 F      | Once (G)            | 104, 156, 234, 346, 519   | LE, CS               | Death    |       |                    | 187           | <b>Cobalt Phosphate Octahydrate</b><br>LD <sub>50</sub>                                                                                                                    |
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 32                          | Rat (Wistar)<br>5 M, 5 F      | Once (G)            | 157, 236, 354, 530, 794   | LE, CS, HP           | Death    |       |                    | 159           | <b>Cobalt Oxide</b><br>LD <sub>50</sub>                                                                                                                                    |
| <b>Speijers et al. 1982</b> |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 33                          | Rat (Wistar)<br>5 M, 5 F      | Once (GW)           | 59.1, 88.7, 132, 199, 298 | LE, CS               | Death    |       |                    | 168           | <b>Cobalt Acetate Tetrahydrate</b><br>LD <sub>50</sub>                                                                                                                     |
| <b>Tanoğlu et al. 2022</b>  |                               |                     |                           |                      |          |       |                    |               |                                                                                                                                                                            |
| 34                          | Rat (Wistar)<br>6M            | 7 days (GW)         | 0, 37                     | BI, HP               | Neuro    |       |                    | 37            | <b>Cobalt (II) Chloride Hexahydrate</b><br>Moderate-to-severe sciatic nerve damage (degeneration of myelinated fibers; Schwann cell degeneration, perineurium disjunction) |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>              | Species (strain)<br>No./group   | Exposure parameters          | Doses                     | Parameters monitored | Endpoint             | NOAEL      | Less serious LOAEL | Serious LOAEL | Effects                                                                                            |                        |
|--------------------------------------|---------------------------------|------------------------------|---------------------------|----------------------|----------------------|------------|--------------------|---------------|----------------------------------------------------------------------------------------------------|------------------------|
| <b>Hassan et al. 2006</b>            |                                 |                              |                           |                      |                      |            |                    |               |                                                                                                    | <b>Cobalt Chloride</b> |
| 35                                   | Mouse (NS)<br>3 M               | 5 days<br>(NS)               | 0, 7.089,<br>14.18, 28.37 | RX                   | Repro                |            | 7.089              |               | Increased percent abnormal sperm                                                                   |                        |
| <b>Krasovskii and Fridlyand 1971</b> |                                 |                              |                           |                      |                      |            |                    |               |                                                                                                    | <b>Cobalt Chloride</b> |
| 36                                   | Mouse<br>(white) NS             | Once<br>(GW)                 | Not reported              | LE                   | Death                |            |                    | 36            | LD50                                                                                               |                        |
| <b>Seidenberg et al. 1986</b>        |                                 |                              |                           |                      |                      |            |                    |               |                                                                                                    | <b>Cobalt Chloride</b> |
| 37                                   | Mouse<br>(ICR/SIM)<br>28 F      | 5 days<br>(GDs 8–12)<br>(GW) | 0, 81                     | BW, CS, DX           | Bd wt<br><br>Develop | <br><br>81 |                    | 81            | 32% decrease in maternal body weight gain                                                          |                        |
| <b>Singh and Junnarkar 1991</b>      |                                 |                              |                           |                      |                      |            |                    |               |                                                                                                    | <b>Cobalt Sulfate</b>  |
| 38                                   | Mouse<br>(Swiss-Webster)<br>5 M | Once<br>(GW)                 | 0, 22.2                   | CS, NX               | Neuro                |            | 22.2               |               | Mild CNS excitation (elevated spontaneous activity and respiration)                                |                        |
| <b>Singh and Junnarkar 1991</b>      |                                 |                              |                           |                      |                      |            |                    |               |                                                                                                    | <b>Cobalt Chloride</b> |
| 39                                   | Mouse<br>(Swiss-Webster)<br>5 M | Once<br>(GW)                 | 0, 16                     | CS, NX               | Neuro                |            | 16                 |               | Mild CNS depression (decreased spontaneous activity, touch response, muscle tone, and respiration) |                        |
| <b>Singh and Junnarkar 1991</b>      |                                 |                              |                           |                      |                      |            |                    |               |                                                                                                    | <b>Cobalt Chloride</b> |
| 40                                   | Mouse<br>(Swiss-Webster)<br>5 M | Once<br>(GW)                 | Not reported              | LE                   | Death                |            |                    | 163           | LD <sub>50</sub>                                                                                   |                        |
| <b>Singh and Junnarkar 1991</b>      |                                 |                              |                           |                      |                      |            |                    |               |                                                                                                    | <b>Cobalt Sulfate</b>  |
| 41                                   | Mouse<br>(Swiss-Webster)<br>5 M | Once<br>(GW)                 | Not reported              | LE                   | Death                |            |                    | 222           | LD <sub>50</sub>                                                                                   |                        |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>              | Species (strain)<br>No./group | Exposure parameters       | Doses        | Parameters monitored | Endpoint                                                 | NOAEL                                              | Less serious LOAEL | Serious LOAEL | Effects                 |                        |
|--------------------------------------|-------------------------------|---------------------------|--------------|----------------------|----------------------------------------------------------|----------------------------------------------------|--------------------|---------------|-------------------------|------------------------|
| <b>Krasovskii and Fridlyand 1971</b> |                               |                           |              |                      |                                                          |                                                    |                    |               |                         | <b>Cobalt Chloride</b> |
| 42                                   | Guinea pig (NS) NS            | Once (GW)                 | Not reported | LE                   | Death                                                    |                                                    |                    | 25            | LD <sub>50</sub>        |                        |
| <b>INTERMEDIATE EXPOSURE</b>         |                               |                           |              |                      |                                                          |                                                    |                    |               |                         |                        |
| <b>Duckham and Lee 1976</b>          |                               |                           |              |                      |                                                          |                                                    |                    |               |                         | <b>Cobalt Chloride</b> |
| 43                                   | Human 6 M, 6 F                | 12 weeks, 7 days/week (C) | 0, 0.36      | BC, CS, OF           | Gastro                                                   |                                                    | 0.36 F             |               | Nausea and constipation |                        |
| <b>Finley et al. 2013</b>            |                               |                           |              |                      |                                                          |                                                    |                    |               |                         | <b>Cobalt Chloride</b> |
| 44                                   | Human 5 M, 5 F                | 31 days (IN)              | 0, 0.013     | BC, CS, HE, IX       | Hemato<br>Hepatic<br>Renal<br>Endocr<br>Immuno           | 0.013<br>0.013<br>0.013<br>0.013<br>0.013          |                    |               |                         |                        |
| <b>Hoffmeister et al. 2018</b>       |                               |                           |              |                      |                                                          |                                                    |                    |               |                         | <b>Cobalt (II)</b>     |
| 45                                   | Human 8–16 M                  | 21 days (C)               | 0, 0.03      | HE                   | Hemato                                                   | 0.03                                               |                    |               |                         |                        |
| <b>Holly 1955</b>                    |                               |                           |              |                      |                                                          |                                                    |                    |               |                         | <b>Cobalt Chloride</b> |
| 46                                   | Human 20–55 F                 | 13 weeks 7 days/week (C)  | 0, 0.57      | BC, CS, DX, HE, UR   | Gastro<br>Hepatic<br>Endocr<br>Develop                   | 0.57<br>0.57<br>0.57<br>0.57                       | 0.57               |               | Gastric intolerance     |                        |
| <b>Tvermoes et al. 2014</b>          |                               |                           |              |                      |                                                          |                                                    |                    |               |                         | <b>Cobalt Chloride</b> |
| 47                                   | Human 5 M, 5 F                | 88–91 days daily (IN)     | 0, 0.013     | BC, CS, HE, NX, OF   | Cardio<br>Hemato<br>Hepatic<br>Renal<br>Endocr<br>Immuno | 0.013<br>0.013<br>0.013<br>0.013<br>0.013<br>0.013 |                    |               |                         |                        |



## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>       | Species (strain)<br>No./group | Exposure parameters      | Doses                          | Parameters monitored   | Endpoint         | NOAEL       | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                        |
|-------------------------------|-------------------------------|--------------------------|--------------------------------|------------------------|------------------|-------------|--------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Abdel-Daim et al. 2020</b> |                               |                          |                                |                        |                  |             |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                        |
| 48                            | Rat (Sprague-Dawley) 10 M     | 4 weeks daily (W)        | 0, 8.9                         | BC, BI, BW, CS, LE, OW | Bd wt<br>Renal   |             |                    | 8.9           | 192% decrease in body weight gain (11 g body weight loss compared to 12 g body weight gain in controls)<br>Increased serum urea and creatinine                                                 |
| <b>Bourg et al. 1985</b>      |                               |                          |                                |                        |                  |             |                    |               | <b>Cobalt Chloride</b>                                                                                                                                                                         |
| 49                            | Rat (Sprague-Dawley) 8 M      | 57 days daily (W)        | 0, 20.3                        | BW, NX, WI             | Bd wt<br>Neuro   | 20.3        | 20.3               |               | Enhanced avoidance retention in passive-avoidance testing (suggestive of decreased stress tolerance)                                                                                           |
| <b>Chetty et al. 1979</b>     |                               |                          |                                |                        |                  |             |                    |               | <b>Cobalt Chloride</b>                                                                                                                                                                         |
| 50                            | Rat (Sprague-Dawley) 8–15 M   | 30 days daily (F)        | 0, 0.45, 2.2, 4.53, 8.99, 13.8 | BI, BW, HE, IX, OW     | Hemato<br>Immuno | 8.99<br>2.2 | 13.8<br>4.53       |               | Decreased hemoglobin<br>Immune suppression (decreased immune response to sheep red blood cells)                                                                                                |
| <b>Clyne et al. 1988</b>      |                               |                          |                                |                        |                  |             |                    |               | <b>Cobalt Sulfate Heptahydrate</b>                                                                                                                                                             |
| 51                            | Rat (Sprague-Dawley) 5 M      | 8 weeks, 7 days/week (F) | 0, 4.2                         | BW                     | Bd wt            |             |                    | 4.2           | 33% decrease in body weight gain                                                                                                                                                               |
| <b>Corrier et al. 1985</b>    |                               |                          |                                |                        |                  |             |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                        |
| 52                            | Rat (Sprague-Dawley) 3 M      | 98 days daily (F)        | 0, 20                          | HE, HP, RX             | Hemato<br>Repro  |             | 20                 | 20            | Increased red blood cell count, hemoglobin level, and packed cell volume<br>Marked degeneration and necrosis of germinal epithelium of seminiferous tubules; 43% decrease in spermatid reserve |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>       | Species (strain)<br>No./group         | Exposure parameters     | Doses               | Parameters monitored                       | Endpoint  | NOAEL             | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                                |
|-------------------------------|---------------------------------------|-------------------------|---------------------|--------------------------------------------|-----------|-------------------|--------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Danzeisen et al. 2020a</b> |                                       |                         |                     |                                            |           |                   |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                                                |
| 53                            | Rat<br>(Sprague-Dawley)<br>10 M, 10 F | 90 days<br>daily<br>(G) | 0, 0.74, 2.48, 7.44 | BW, FI, HE, HP, LE, NX, OP, OW, RX, UR, WI | Bd wt     | 2.48              | 7.44               |               | Decrease in body weight (11% in males at the end of exposure; 17% in males and 13% in females at the end of 4-week recovery period)                                                                                    |
|                               |                                       |                         |                     |                                            | Resp      | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Cardio    | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Gastro    | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Hemato    | 0.74 <sup>c</sup> | 2.48               |               | Increased red blood cell count, hemoglobin, and hematocrit in males; erythroid hyperplasia in the bone marrow in both sexes; BMDL <sub>1SD</sub> for increased red blood cells in males=1.95 mg Co/kg/day <sup>c</sup> |
|                               |                                       |                         |                     |                                            | Musc/skel | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Hepatic   | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Renal     | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Dermal    | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Ocular    | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Endocr    | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Immuno    | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Neuro     | 7.44              |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Repro     | 7.44              |                    |               |                                                                                                                                                                                                                        |
| <b>Danzeisen et al. 2020a</b> |                                       |                         |                     |                                            |           |                   |                    |               | <b>Cobalt Tetraoxide</b>                                                                                                                                                                                               |
| 54                            | Rat<br>(Sprague-Dawley)<br>10 M, 10 F | 90 days<br>daily<br>(G) | 0, 73.4, 220, 734   | BW, FI, HE, HP, LE, NX, OP, OW, RX, UR, WI | Resp      | 734               |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Cardio    | 734               |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Gastro    | 734               |                    |               |                                                                                                                                                                                                                        |
|                               |                                       |                         |                     |                                            | Hemato    | 220 F             | 734 F              |               | Increased red blood cell count, hemoglobin, and hematocrit                                                                                                                                                             |
|                               |                                       |                         |                     |                                            |           | 73.4 M            | 220 M              |               | Increased red blood cell count, hemoglobin, and hematocrit                                                                                                                                                             |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>       | Species (strain)<br>No./group         | Exposure parameters                                              | Doses                | Parameters monitored                     | Endpoint                                                       | NOAEL                                    | Less serious LOAEL | Serious LOAEL | Effects                                                   |
|-------------------------------|---------------------------------------|------------------------------------------------------------------|----------------------|------------------------------------------|----------------------------------------------------------------|------------------------------------------|--------------------|---------------|-----------------------------------------------------------|
|                               |                                       |                                                                  |                      |                                          | Musc/skel                                                      | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Hepatic                                                        | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Renal                                                          | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Dermal                                                         | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Ocular                                                         | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Endocr                                                         | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Immuno                                                         | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Neuro                                                          | 734                                      |                    |               |                                                           |
|                               |                                       |                                                                  |                      |                                          | Repro                                                          | 734                                      |                    |               |                                                           |
| <b>Danzeisen et al. 2020a</b> |                                       |                                                                  |                      |                                          |                                                                |                                          |                    |               | <b>Cobalt Sulfide</b>                                     |
| 55                            | Rat<br>(Sprague-Dawley)<br>10 M, 10 F | One generation<br>(2 weeks pre-mating–<br>PND 3)<br>daily<br>(G) | 0, 64.8, 194,<br>648 | BW, DX, FI,<br>RX                        | Bd wt<br>Neuro<br>Repro<br>Develop                             | 648<br>648<br>648<br>648                 |                    |               |                                                           |
| <b>Danzeisen et al. 2020a</b> |                                       |                                                                  |                      |                                          |                                                                |                                          |                    |               | <b>Cobalt Tetraoxide</b>                                  |
| 56                            | Rat<br>(Sprague-Dawley)<br>10 M, 10 F | One generation<br>(2 weeks pre-mating–<br>PND 3)<br>daily<br>(G) | 0, 73.4, 220,<br>734 | BW, DX, FI,<br>RX                        | Bd wt<br>Neuro<br>Repro<br>Develop                             | 734<br>734<br>734<br>220                 |                    | 734           | Decreased pup weight at birth (18%)<br>and on PND 4 (21%) |
| <b>Domingo et al. 1984</b>    |                                       |                                                                  |                      |                                          |                                                                |                                          |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                   |
| 57                            | Rat<br>(Sprague-Dawley)<br>20 M       | 13 weeks<br>7 days/week<br>(W)                                   | 0, 16.5              | BC, CS, FI,<br>GN, HE, HP,<br>OW, UR, WI | Resp<br>Cardio<br>Gastro<br>Hemato<br><br>Musc/skel<br>Hepatic | 16.5<br>16.5<br>16.5<br><br>16.5<br>16.5 |                    | 16.5          | Increased hematocrit and<br>hemoglobin                    |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>     | Species (strain)<br>No./group | Exposure parameters                            | Doses          | Parameters monitored                                | Endpoint         | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                                               |
|-----------------------------|-------------------------------|------------------------------------------------|----------------|-----------------------------------------------------|------------------|-------|--------------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |                               |                                                |                |                                                     | Renal            | 16.5  |                    |               |                                                                                                                                                                                                                                       |
|                             |                               |                                                |                |                                                     | Endocr           | 16.5  |                    |               |                                                                                                                                                                                                                                       |
|                             |                               |                                                |                |                                                     | Immuno           | 16.5  |                    |               |                                                                                                                                                                                                                                       |
|                             |                               |                                                |                |                                                     | Repro            |       | 16.5               |               | Decreased relative testicular weight                                                                                                                                                                                                  |
| <b>Domingo et al. 1985b</b> |                               |                                                |                |                                                     |                  |       |                    |               |                                                                                                                                                                                                                                       |
| 58                          | Rat (Wistar)<br>15 F          | 28 days<br>GD 14–PND 21<br>(G)                 | 0, 5.4, 11, 22 | DX                                                  | Develop          |       |                    | 5.4           | <b>Cobalt Chloride</b><br>PNDs 1–21: Decreased pup weight in males (17-29%) and females (12–28%); decreased pup length in males (3–9%) and females (6%)                                                                               |
| <b>Garoui et al. 2011</b>   |                               |                                                |                |                                                     |                  |       |                    |               |                                                                                                                                                                                                                                       |
| 59                          | Rat (Wistar)<br>6 F           | 28 days<br>(GD 14–<br>PND 14);<br>daily<br>(W) | 0, 20          | BC, BI, BW,<br>DX, FI, GN,<br>LE, OW, WI            | Bd wt<br>Hepatic | 20    | 20                 |               | Increased absolute liver weight; hepatic injury (infiltration of mononuclear cells and vascular congestion)                                                                                                                           |
|                             |                               |                                                |                |                                                     | Develop          |       |                    | 20            | Effects at PND 14: 40% decrease in body weight; hepatic damage (elevated plasma ALT, AST; infiltration of mononuclear cells and vascular congestion); decreased plasma glucose                                                        |
|                             |                               |                                                |                |                                                     | Other noncancer  |       | 20                 |               | Decreased plasma glucose levels; decreased maternal food intake                                                                                                                                                                       |
| <b>Garoui et al. 2012</b>   |                               |                                                |                |                                                     |                  |       |                    |               |                                                                                                                                                                                                                                       |
| 60                          | Rat (Wistar)<br>6 F           | 28 days<br>(GD 14–<br>PND 14);<br>daily<br>(W) | 0, 20          | BI, BW, CS,<br>DX, FI, GN,<br>HP, LE, OW,<br>UR, WI | Bd wt<br>Renal   | 20    | 20                 |               | <b>Cobalt Chloride</b><br>Vascular congestion, reduction of glomerular space, and infiltration of leukocyte cells between tubules; increased plasma urea, decreased urinary creatinine and urea, and decreased relative kidney weight |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>   | Species (strain) No./group | Exposure parameters               | Doses  | Parameters monitored | Endpoint                 | NOAEL          | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                  |
|---------------------------|----------------------------|-----------------------------------|--------|----------------------|--------------------------|----------------|--------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                            |                                   |        |                      | Develop                  |                |                    | 20            | Effects at PND 14: 40% decrease in body weight; renal damage (elevated plasma creatinine; decreased urinary creatinine and urea; vascular congestion and reduction of glomerular space)  |
|                           |                            |                                   |        |                      | Other noncancer          |                | 20                 |               | Decreased maternal food intake                                                                                                                                                           |
| <b>Garoui et al. 2013</b> |                            |                                   |        |                      |                          |                |                    |               | <b>Cobalt Chloride</b>                                                                                                                                                                   |
| 61                        | Rat (Wistar) 6 F           | 28 days (GD 14–PND 14); daily (W) | 0, 20  | DX, LE               | Develop                  |                |                    | 20            | Findings at PND 14: Reduced AChE and BuChE levels in cerebrum and cerebellum; altered development of cerebellar architecture (poorly differentiated layers with frequent pyknotic cells) |
| <b>Grice et al. 1969</b>  |                            |                                   |        |                      |                          |                |                    |               | <b>Cobalt Sulfate</b>                                                                                                                                                                    |
| 62                        | Rat (Wistar) 10 M          | 8 weeks 7 days/week (GW)          | 26     | LE, HP               | Death<br>Cardio          |                |                    | 26<br>26      | 50% mortality<br>Degenerative myocardial heart lesions                                                                                                                                   |
| <b>Haga et al. 1996</b>   |                            |                                   |        |                      |                          |                |                    |               | <b>Cobalt Sulfate Heptahydrate</b>                                                                                                                                                       |
| 63                        | Rat (Sprague-Dawley) 10 M  | 24 weeks 7 days/week (F)          | 0, 8.4 | BW, OF, OW           | Bd wt<br>Cardio          |                |                    | 8.4<br>8.4    | 31% decrease in final body weight<br>Impaired left ventricular function                                                                                                                  |
| <b>Haga et al. 1996</b>   |                            |                                   |        |                      |                          |                |                    |               | <b>Cobalt Sulfate Heptahydrate</b>                                                                                                                                                       |
| 64                        | Rat (Sprague-Dawley) 8 M   | 16 weeks 7 days/week (F)          | 0, 8.4 | BW, OF, OW           | Bd wt<br>Cardio          | 8.4            |                    | 8.4           | 26% decrease in final body weight                                                                                                                                                        |
| <b>Holly 1955</b>         |                            |                                   |        |                      |                          |                |                    |               | <b>Cobalt Chloride</b>                                                                                                                                                                   |
| 65                        | Rat (Wistar) 3–8 M         | 4 months 7 days/week (G)          | 0, 18  | HE, HP               | Resp<br>Cardio<br>Gastro | 18<br>18<br>18 |                    |               |                                                                                                                                                                                          |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>              | Species (strain) No./group | Exposure parameters           | Doses             | Parameters monitored | Endpoint         | NOAEL      | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                             |
|--------------------------------------|----------------------------|-------------------------------|-------------------|----------------------|------------------|------------|--------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                      |                            |                               |                   |                      | Hemato           |            | 18                 |               | Increased red blood cell count and hemoglobin levels                                                                                                                                                |
|                                      |                            |                               |                   |                      | Hepatic          | 18         |                    |               |                                                                                                                                                                                                     |
|                                      |                            |                               |                   |                      | Renal            | 18         |                    |               |                                                                                                                                                                                                     |
|                                      |                            |                               |                   |                      | Endocr           | 18         |                    |               |                                                                                                                                                                                                     |
|                                      |                            |                               |                   |                      | Immuno           | 18         |                    |               |                                                                                                                                                                                                     |
|                                      |                            |                               |                   |                      | Neuro            | 18         |                    |               |                                                                                                                                                                                                     |
| <b>Khalil et al. 2020</b>            |                            |                               |                   |                      |                  |            |                    |               |                                                                                                                                                                                                     |
| 66                                   | Rat (Sprague-Dawley) 8 M   | 4 weeks<br>7 days/week (W)    | 0, 68             | BC, CS, LE           | Hepatic          |            | 68                 |               | <b>Cobalt (II) Chloride Hexahydrate</b><br>Increased serum AST, ALT, ALP, LDH, and total bilirubin                                                                                                  |
| <b>Krasovskii and Fridlyand 1971</b> |                            |                               |                   |                      |                  |            |                    |               |                                                                                                                                                                                                     |
| 67                                   | Rat (NS) NS                | 7 months,<br>6 days/week (GW) | 0, 0.05, 0.5, 2.5 | HE, OF, IX, NX       | Hepatic<br>Neuro | 2.5<br>0.5 | 2.5                |               | <b>Cobalt Chloride</b><br>Learning impairment (altered operant behavior)                                                                                                                            |
| <b>Mathur et al. 2011</b>            |                            |                               |                   |                      |                  |            |                    |               |                                                                                                                                                                                                     |
| 68                                   | Rat (Wistar) 8 M           | 60 days<br>daily (GW)         | 0, 25             | BC, BI, BW, HP, OW   | Bd wt<br>Hepatic | 25         | 25                 |               | <b>Cobalt (II) Chloride Hexahydrate</b><br>Increased relative liver weight; increased AST and bilirubin; qualitatively reported changes in liver cells (altered morphology and atrophy)             |
| <b>Mohamed et al. 2019</b>           |                            |                               |                   |                      |                  |            |                    |               |                                                                                                                                                                                                     |
| 69                                   | Rat (Wistar) 10 M          | 60 days<br>daily (NS)         | 0, 27             | BI, CS, HP, LE       | Death<br>Neuro   |            |                    | 27<br>27      | <b>Anhydrous Cobalt Chloride</b><br>4/10 rats died<br>Decreased neurotransmitter levels in the brain (serotonin, norepinephrine, dopamine, GABA); encephalopathy; increased GFAP (reactive gliosis) |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>        | Species (strain)<br>No./group | Exposure parameters       | Doses    | Parameters monitored | Endpoint              | NOAEL    | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                         |
|--------------------------------|-------------------------------|---------------------------|----------|----------------------|-----------------------|----------|--------------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mollenhauer et al. 1985</b> |                               |                           |          |                      |                       |          |                    |               | <b>Cobalt Metal</b>                                                                                                                             |
| 70                             | Rat (Sprague-Dawley) 3 M (F)  | 98 days daily (F)         | 0, 20    | HP                   | Repro                 |          | 20                 |               | Thickening of basal lamina and collagen layer surrounding the seminiferous tubules and vessel walls; ultrastructural damage to testicular cells |
| <b>Morvai et al. 1993</b>      |                               |                           |          |                      |                       |          |                    |               | <b>Cobalt Chloride</b>                                                                                                                          |
| 71                             | Rat (CFY) 8 M                 | 3 weeks 7 days/week (G)   | 0, 22    | BW, HP, OF, OW       | Bd wt Cardio          | 22       |                    | 22            | Decrease in cardiac output and arterial blood pressure; multifocal myocytolysis and myofibril degeneration                                      |
| <b>Murdock 1959</b>            |                               |                           |          |                      |                       |          |                    |               | <b>Cobalt Chloride</b>                                                                                                                          |
| 72                             | Rat (NS) 6–30 M               | 150 days 5 days/week (GW) | 0, 10    | HE                   | Hemato                |          | 10                 |               | Increased red blood cell count, hemoglobin, and hematocrit                                                                                      |
| <b>Nation et al. 1983</b>      |                               |                           |          |                      |                       |          |                    |               | <b>Cobalt Chloride</b>                                                                                                                          |
| 73                             | Rat (Sprague-Dawley) 6 M (F)  | 69 days daily (F)         | 0, 5, 20 | CS, GN, OW, NX       | Neuro Repro           | 5<br>5   | 20                 | 20            | Impaired operant conditioning<br>Testicular atrophy, decreased testicular weight                                                                |
| <b>Pehrsson et al. 1991</b>    |                               |                           |          |                      |                       |          |                    |               | <b>Cobalt Sulfate Heptahydrate</b>                                                                                                              |
| 74                             | Rat (Sprague-Dawley) 12 M     | 8 weeks 7 days/week (F)   | 0, 8.4   | BW, OF               | Bd wt Cardio          | 8.4      |                    | 8.4           | 30% decrease in final body weight                                                                                                               |
| <b>Saker et al. 1998</b>       |                               |                           |          |                      |                       |          |                    |               | <b>Cobalt Chloride</b>                                                                                                                          |
| 75                             | Rat (Sprague-Dawley) 6 M (W)  | 12–16 days daily (W)      | 0, 18    | BC, BI, BW, CS       | Bd wt Other noncancer | 18<br>18 |                    |               |                                                                                                                                                 |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>      | Species (strain) No./group  | Exposure parameters           | Doses                  | Parameters monitored       | Endpoint                  | NOAEL        | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                              |
|------------------------------|-----------------------------|-------------------------------|------------------------|----------------------------|---------------------------|--------------|--------------------|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Stanley et al. 1947</b>   |                             |                               |                        |                            |                           |              |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                              |
| 76                           | Rat (Sprague-Dawley) 4–6 NS | 8 weeks<br>7 days/week (C)    | 0, 0.62, 2.5, 9.9      | BW, CS, HE                 | Bd wt<br>Hemato           | 9.9<br>0.62  | 2.5                |               | Increased red blood cell count and hemoglobin                                                                                                                                                        |
| <b>Umar et al. 2016</b>      |                             |                               |                        |                            |                           |              |                    |               | <b>Cobalt Chloride</b>                                                                                                                                                                               |
| 77                           | Rat (Wistar) 5 B            | 28 days daily (NS)            | 0, 23                  | CS, NX                     | Neuro                     | 23           |                    |               |                                                                                                                                                                                                      |
| <b>Anderson et al. 1992</b>  |                             |                               |                        |                            |                           |              |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                              |
| 78                           | Mouse (CD-1) 10 M           | 7–13 weeks<br>7 days/week (W) | 0, 43.4                | GN, HP, OW                 | Hepatic<br>Renal<br>Repro | 43.4<br>43.4 |                    | 43.4          | Decreased absolute testicular weight at ≥9 weeks; damage to seminiferous tubules (mild at 9 weeks progressing to extensive Sertoli and germ cell loss at ≥11 weeks); testicular atrophy at ≥11 weeks |
| <b>Anderson et al. 1993</b>  |                             |                               |                        |                            |                           |              |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                              |
| 79                           | Mouse (CD-1) 10 M           | 13 weeks<br>7 days/week (W)   | 0, 43.4                | BW, HP, OW                 | Bd wt<br>Repro            | 43.4         |                    | 43.4          | Decreased absolute testes weight; seminiferous tubule damage and degeneration and hypercellularity of the interstitial areas                                                                         |
| <b>Elbetieha et al. 2008</b> |                             |                               |                        |                            |                           |              |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                              |
| 80                           | Mouse (Swiss) 10 M          | 12 weeks<br>7 days/week (W)   | 0, 6.354, 11.62, 23.01 | BW, CS, HP, LE, OW, RX, WI | Bd wt<br>Repro            | 23.01        |                    | 6.354         | Impaired male fertility (deceased viable pregnancies when mated to unexposed females), decreased epididymal sperm count                                                                              |



## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>                           | Species (strain)<br>No./group | Exposure parameters                                                                              | Doses    | Parameters monitored | Endpoint            | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                                        |
|---------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------|----------|----------------------|---------------------|-------|--------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Gluchcheva et al. 2020</b>                     |                               |                                                                                                  |          |                      |                     |       |                    |               |                                                                                                                                                                                                                                |
| 81                                                | Mouse (ICR)<br>7–8 B          | 20–21 days;<br>GD 19 or 20–<br>PND 18<br>(W)                                                     | 0, 19    | DX                   | Develop             |       |                    | 19            | <b>Cobalt (II) Chloride Hexahydrate</b><br>Effects on PND 18: 17% decrease in body weight; elevated red blood cell count; decreased relative spleen and kidney weights; histopathological changes in spleen, liver, and kidney |
| <b>Huy et al. 2022</b>                            |                               |                                                                                                  |          |                      |                     |       |                    |               |                                                                                                                                                                                                                                |
| 82                                                | Mouse<br>(B6C3F1)<br>5 F      | 17 days<br>(GW)                                                                                  | 0, 9, 18 | BC, OW, IX           | Immuno              | 18    |                    |               | <b>Cobalt Chloride</b>                                                                                                                                                                                                         |
| <b>Legostaeva et al. 2013; Zaksas et al. 2013</b> |                               |                                                                                                  |          |                      |                     |       |                    |               |                                                                                                                                                                                                                                |
| 83                                                | Mouse<br>(BALB/c)<br>8 M, 8 F | 62–63 days;<br>GD 19 or 20–<br>PND 25 (via<br>dam) + direct<br>for 35 days<br>postweaning<br>(W) | 0, 31    | BC, BW, IX           | Bd wt<br><br>Immuno |       | 31                 | 31            | <b>Cobalt (II) Chloride Hexahydrate</b><br>33% decrease in body weight on PND 60<br>Decreased plasma IgG on PND 60                                                                                                             |
| <b>Pedigo and Vernon 1993</b>                     |                               |                                                                                                  |          |                      |                     |       |                    |               |                                                                                                                                                                                                                                |
| 84                                                | Mouse<br>(B6C3F1)<br>10 M     | 10 weeks<br>7 days/week<br>(W)                                                                   | 0, 58.9  | BW, CS, LE,<br>RX    | Repro               |       |                    | 58.9          | <b>Cobalt (II) Chloride Hexahydrate</b><br>Decreased fertility; decreased sperm concentration and motility                                                                                                                     |
| <b>Pedigo et al. 1988</b>                         |                               |                                                                                                  |          |                      |                     |       |                    |               |                                                                                                                                                                                                                                |
| 85                                                | Mouse<br>(CD-1) 5 M           | 7–13 weeks<br>7 days/week<br>(W)                                                                 | 0, 58.9  | HE, OW, RX,<br>WI    | Hemato<br><br>Repro | 58.9  |                    | 58.9          | <b>Cobalt (II) Chloride Hexahydrate</b><br>Decreased fertility at 13 weeks; decreased epididymal sperm concentration and percent motile sperm at ≥11 weeks; decreased absolute and relative testes weight at ≥9 weeks          |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>        | Species (strain) No./group | Exposure parameters                                   | Doses               | Parameters monitored   | Endpoint                     | NOAEL          | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                                                                 |
|--------------------------------|----------------------------|-------------------------------------------------------|---------------------|------------------------|------------------------------|----------------|--------------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pedigo et al. 1988</b>      |                            |                                                       |                     |                        |                              |                |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                                                                                 |
| 86                             | Mouse (CD-1) 5 M           | 12 weeks<br>7 days/week (W)                           | 0, 23.0, 42.0, 72.1 | BC, BW, HE, OW, RX, WI | Bd wt<br><br>Hemato<br>Repro | 42<br><br>72.1 | 72.1<br><br>23     | 72.1          | 10% decrease in final body weight<br><br>LOAEL: Decreased relative testes weight, decreased epididymal sperm concentration, increased serum testosterone levels<br>SLOAEL: Decreased fertility when mated to unexposed female, decreased sperm motility |
| <b>Petrova et al. 2020</b>     |                            |                                                       |                     |                        |                              |                |                    |               | <b>Cobalt (II) Chloride Hexahydrate</b>                                                                                                                                                                                                                 |
| 87                             | Mouse (ICR) NS F           | 27–28 days (2–3 days prior to parturition–PND 25) (W) | 0, 75               | DX                     | Develop                      |                |                    | 75            | Decrease in body weight on PND 18 (24%) and PND 25 (15%)                                                                                                                                                                                                |
| <b>Shrivastava et al. 1996</b> |                            |                                                       |                     |                        |                              |                |                    |               | <b>Cobalt Chloride</b>                                                                                                                                                                                                                                  |
| 88                             | Mouse (Parkes) 6 F         | 45 days, daily (W)                                    | 0, 45               | HP                     | Endocr                       |                |                    | 45            | Degeneration and necrotic changes in thyroid epithelial cells; lymphocytic infiltration                                                                                                                                                                 |

## 2. HEALTH EFFECTS

**Table 2-2. Levels of Significant Exposure to Cobalt – Oral  
(mg Co/kg/day)**

| Figure key <sup>a</sup>      | Species (strain)<br>No./group | Exposure parameters      | Doses | Parameters monitored       | Endpoint                 | NOAEL | Less serious LOAEL | Serious LOAEL | Effects                                                                                                                                                                                                |
|------------------------------|-------------------------------|--------------------------|-------|----------------------------|--------------------------|-------|--------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mohiuddin et al. 1970</b> |                               |                          |       |                            |                          |       |                    |               | <b>Cobalt Sulfate</b>                                                                                                                                                                                  |
| 89                           | Guinea pig (NS) 20 M          | 5 weeks, 7 days/week (F) | 0, 20 | BW, CS, GN, HP, LE, OF, OW | Death<br>Bd wt<br>Cardio | 20    |                    | 20            | 4/20 died<br><br>Cardiomyopathy (pericardial effusion, pericarditis, vacuolar degeneration of the myocardium, thickened and edematous endocardium, mural thrombi; elevated heart weight), abnormal EKG |

<sup>a</sup>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.

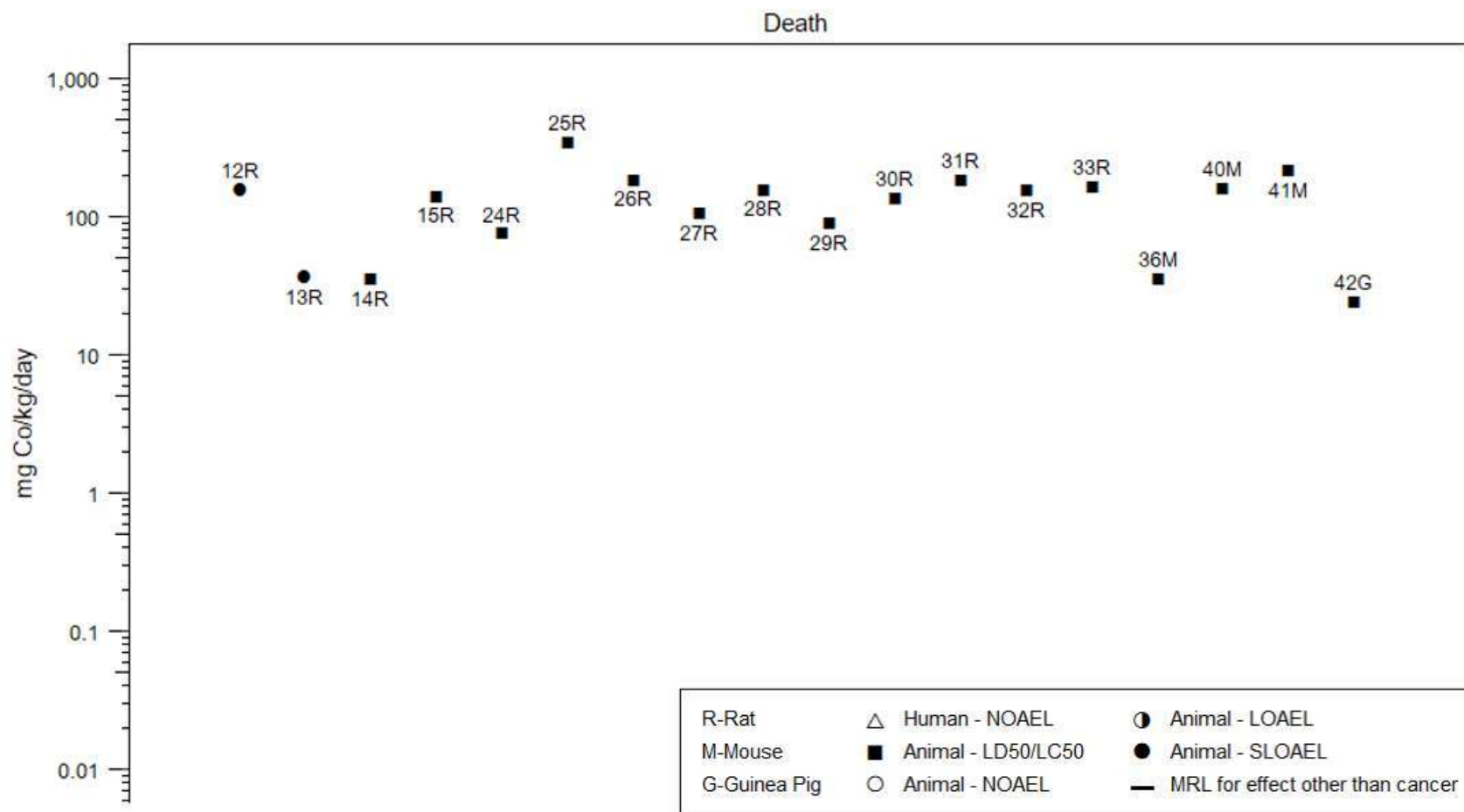
<sup>b</sup>Used to derive an acute-duration oral MRL of 0.03 mg Co/kg/day; dose was divided by an uncertainty factor of 30 (10 for human variability, 3 for use of a minimal LOAEL).

<sup>c</sup>Used to derive an intermediate-duration oral MRL of 0.02 mg Co/kg/day; BMDL<sub>1SD</sub> of 1.95 mg Co/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

AChE = acetylcholinesterase; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both males and females; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMDL = benchmark dose lower confidence limit; BuChE = butyrylcholinesterase; (C) = capsule; Cardio = cardiovascular; CNS = central nervous system; Co = cobalt; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EKG = electrocardiogram; Endocr = endocrine; F = female(s); (F) = feed; FI = food intake; (G) = gavage, not specified; GABA = gamma-aminobutyric acid; Gastro = gastrointestinal; GD = gestational day; GFAP = glial fibrillary acidic protein; GN = gross necropsy; (GW) = gavage in water; HE = hematological; Hemato = hematological; HP = histopathology; IgG = immunoglobulin G; IL-1 $\beta$  = interleukin 1 $\beta$ ; Immuno = immunological; IX = immune function; LD<sub>50</sub> = median lethal dose; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = minimal risk level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; polycythemia = author-reported term associated with increased hemoglobin or erythrocyte count; RX = reproductive function; SD = standard deviation; SLOAEL = serious LOAEL; TNF $\alpha$  = tumor necrosis factor  $\alpha$ ; UR = urinalysis; (W) = water; WI = water intake

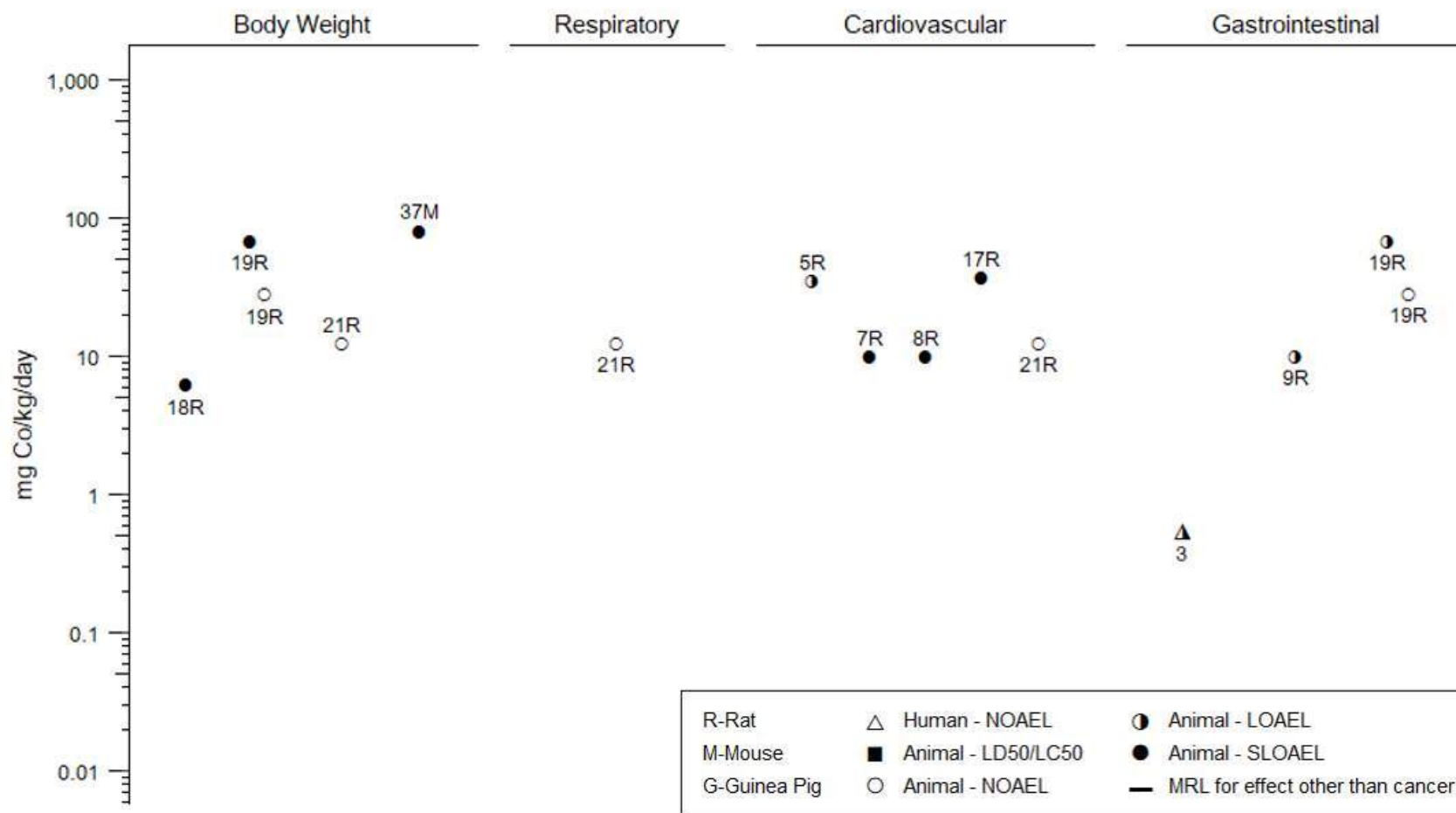
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Acute ( $\leq 14$  days)



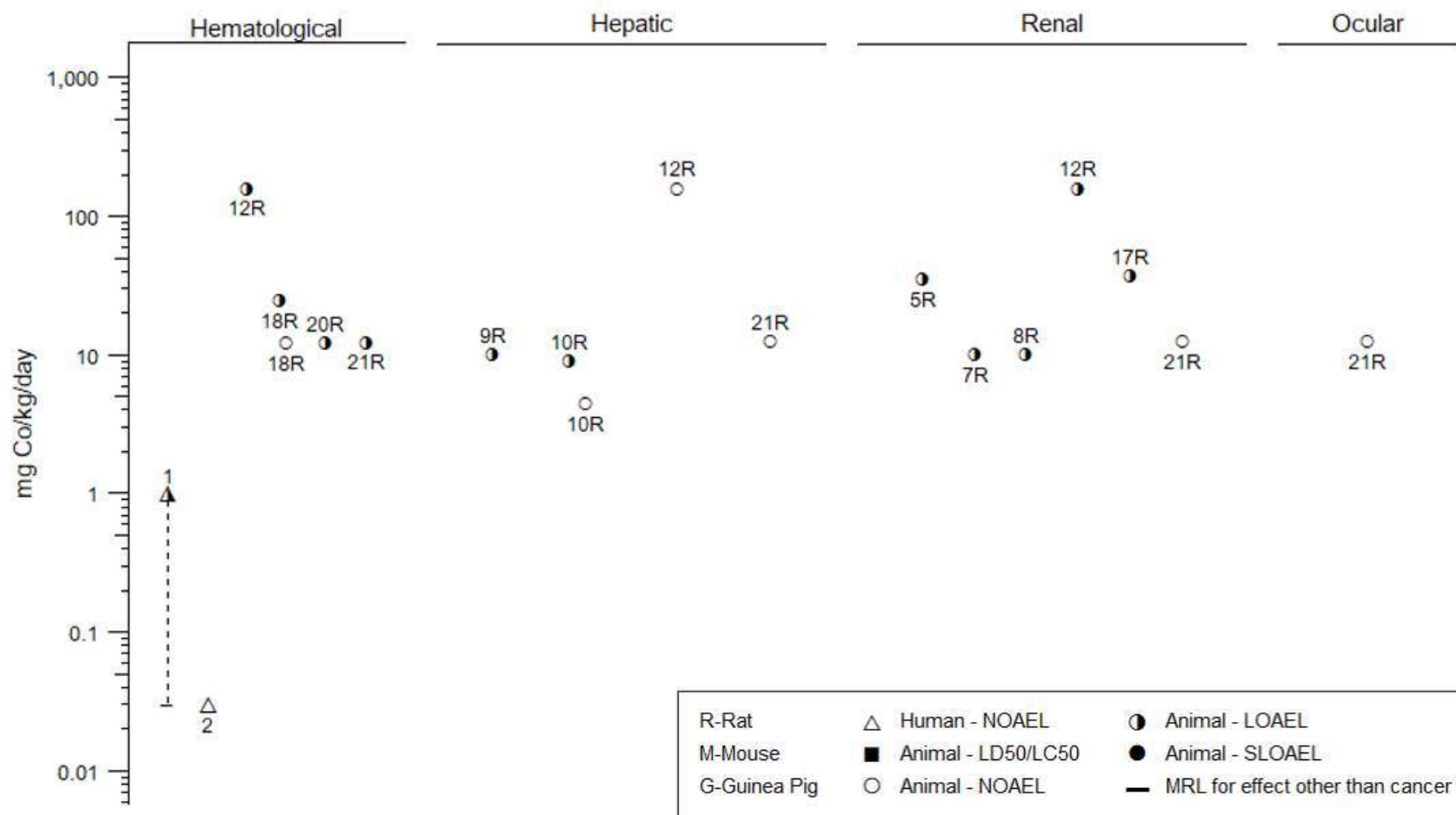
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Acute ( $\leq 14$  days)



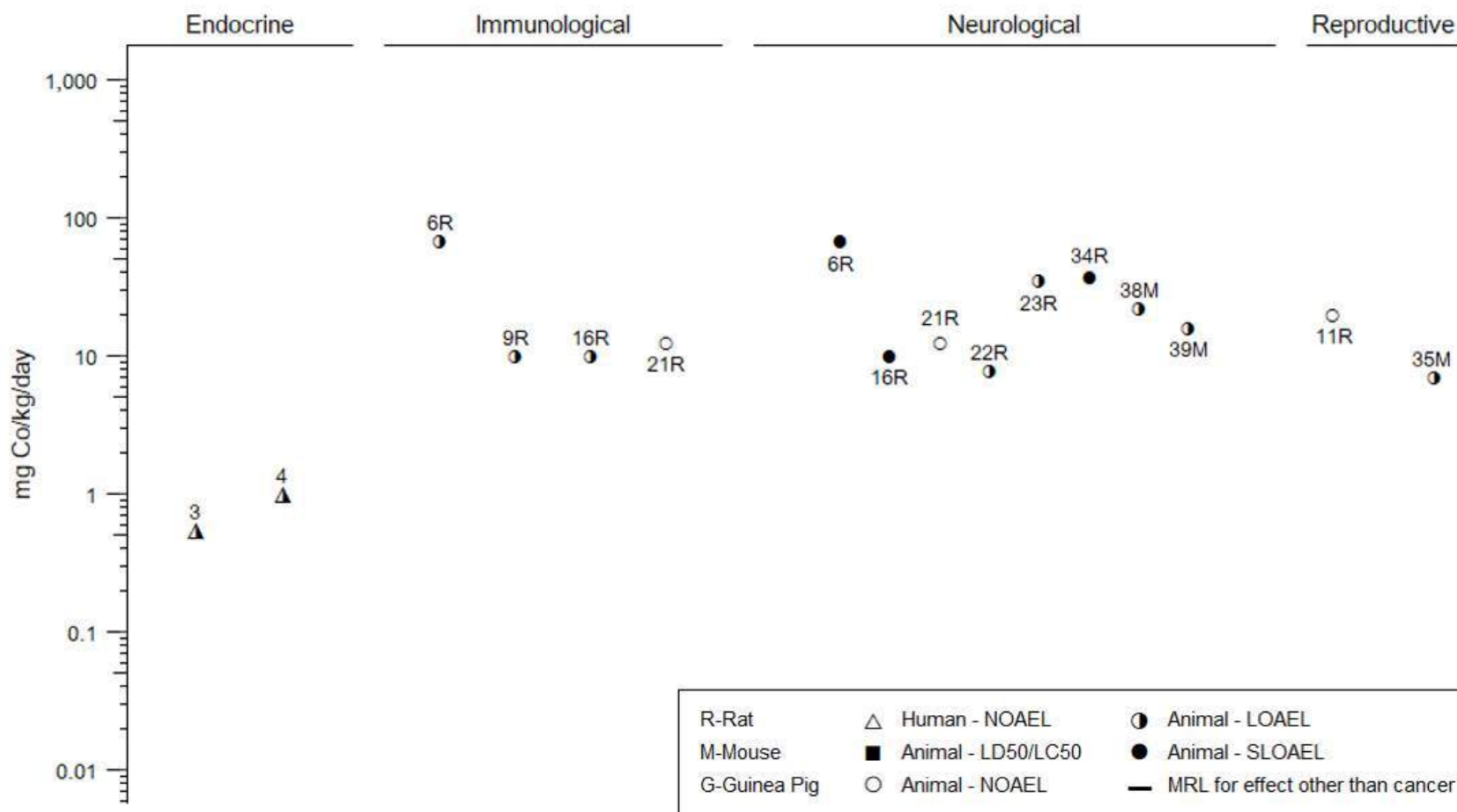
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Acute ( $\leq 14$  days)



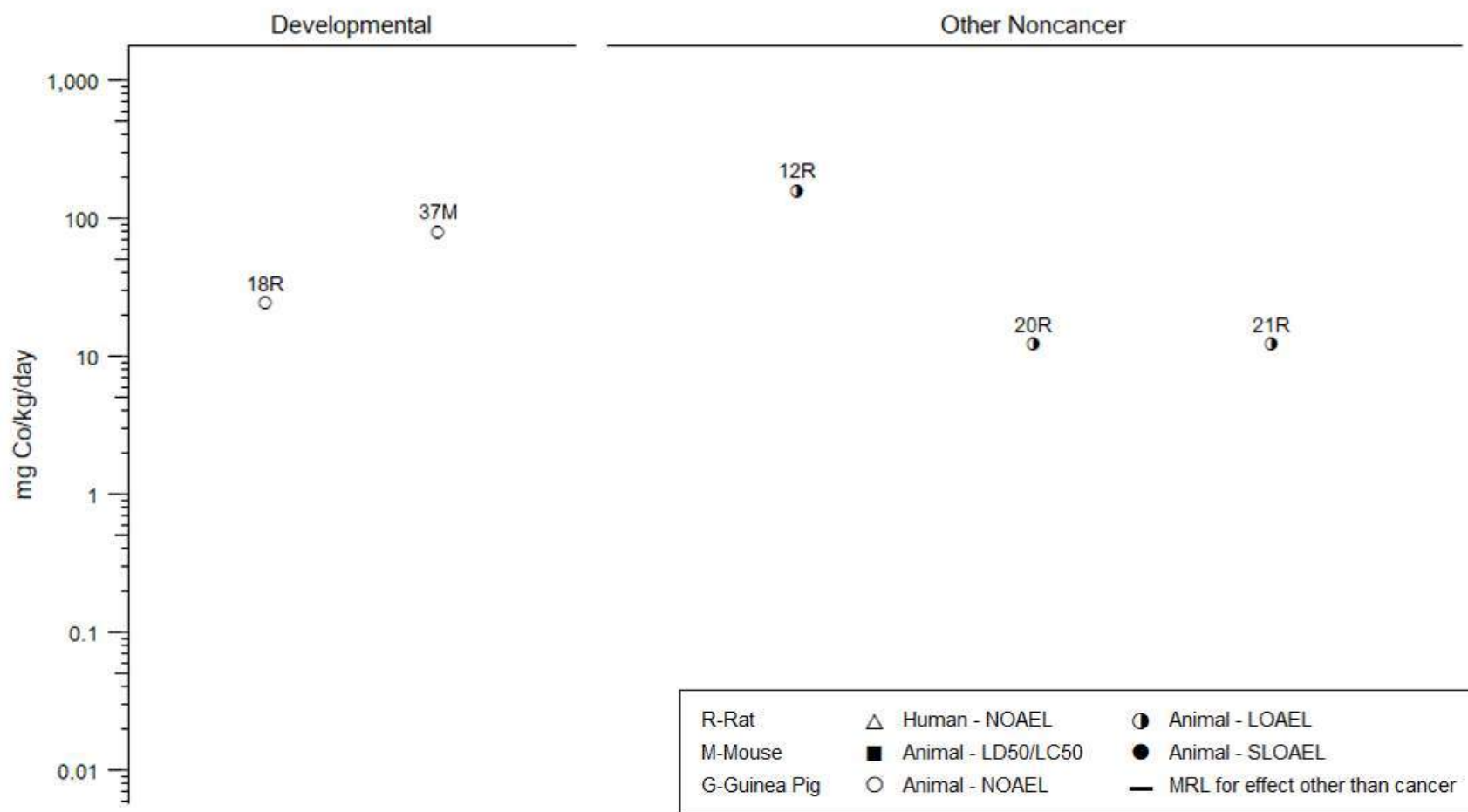
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Acute ( $\leq 14$  days)



## 2. HEALTH EFFECTS

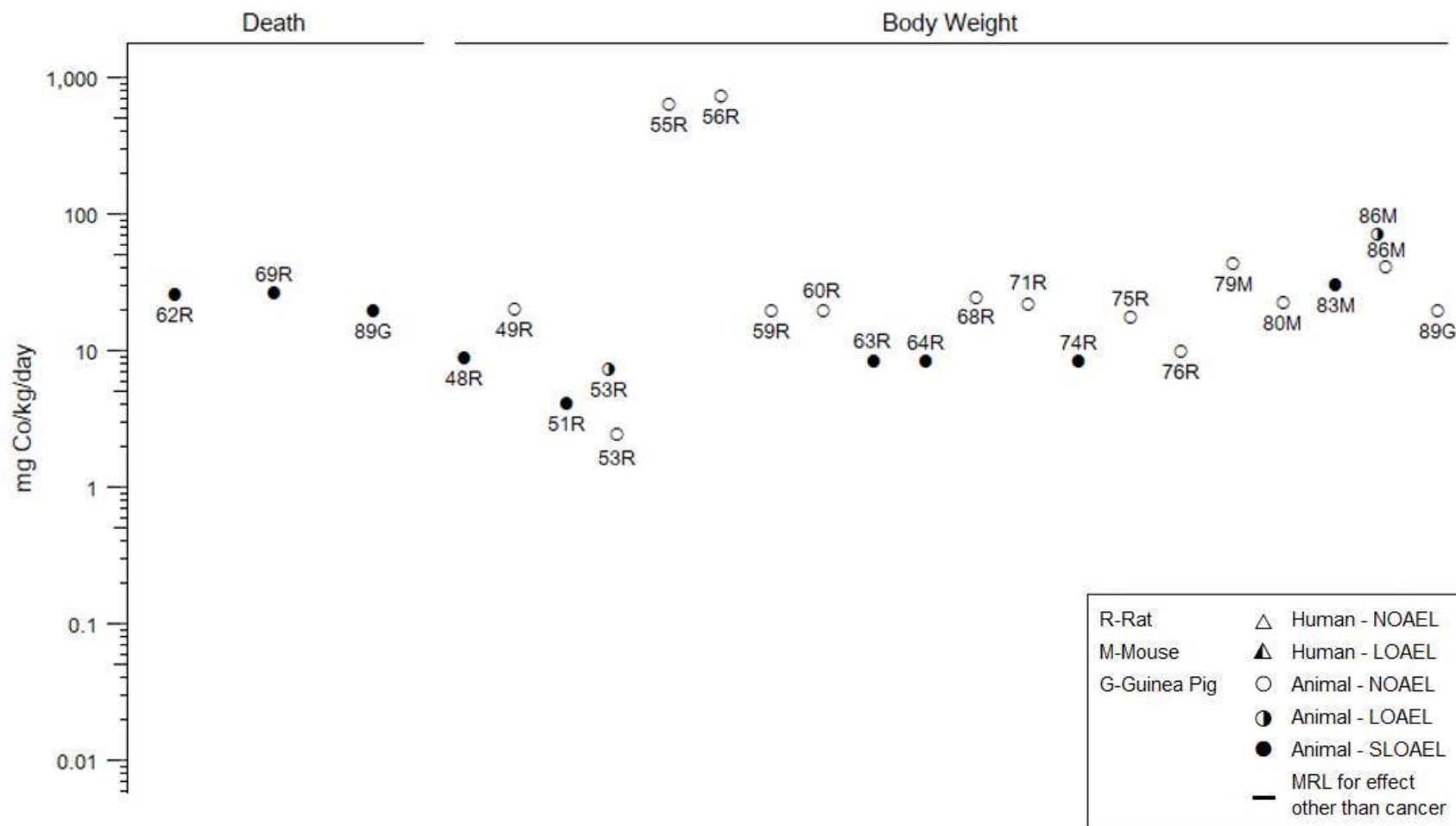
**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Acute ( $\leq 14$  days)





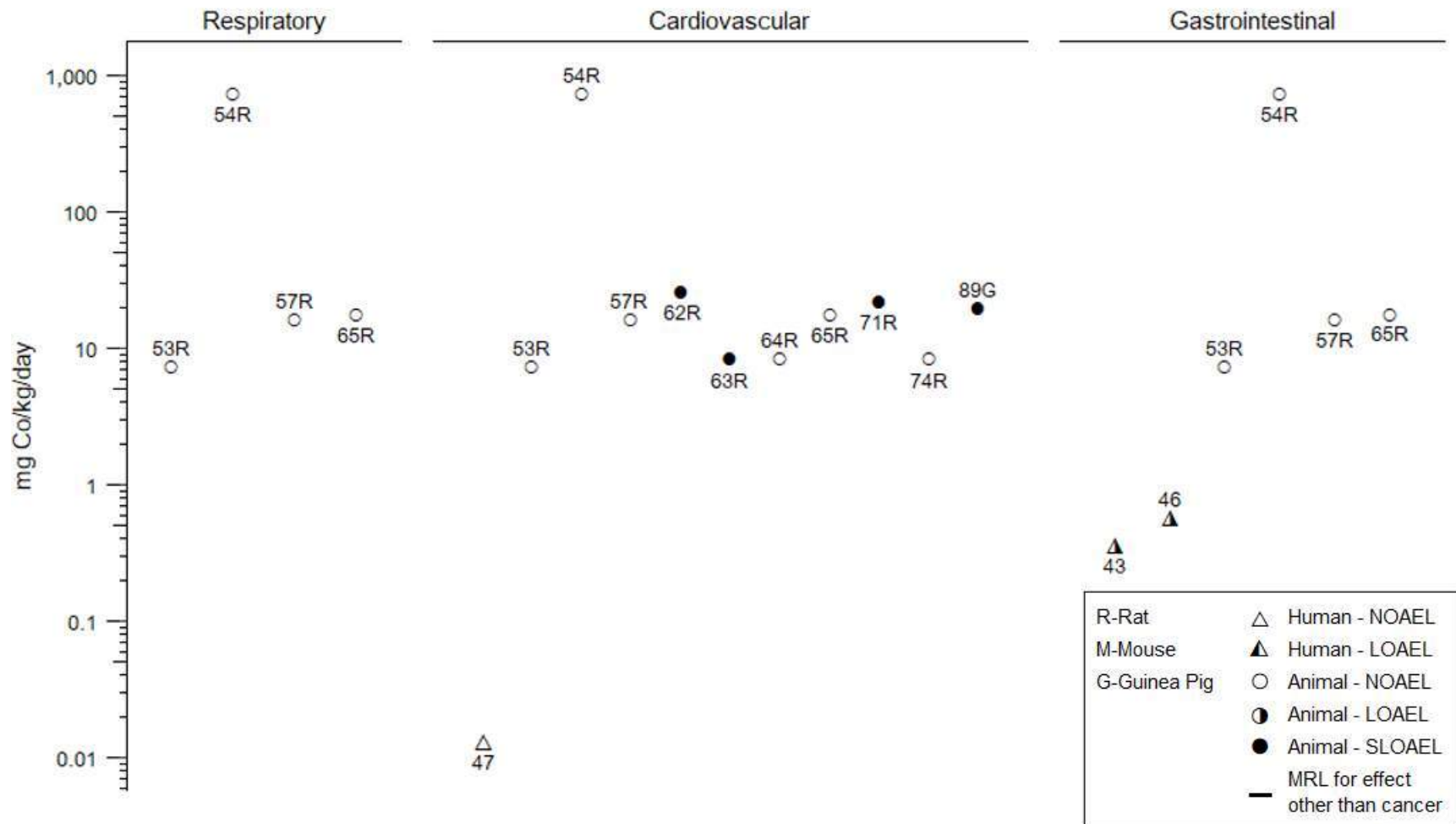
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)



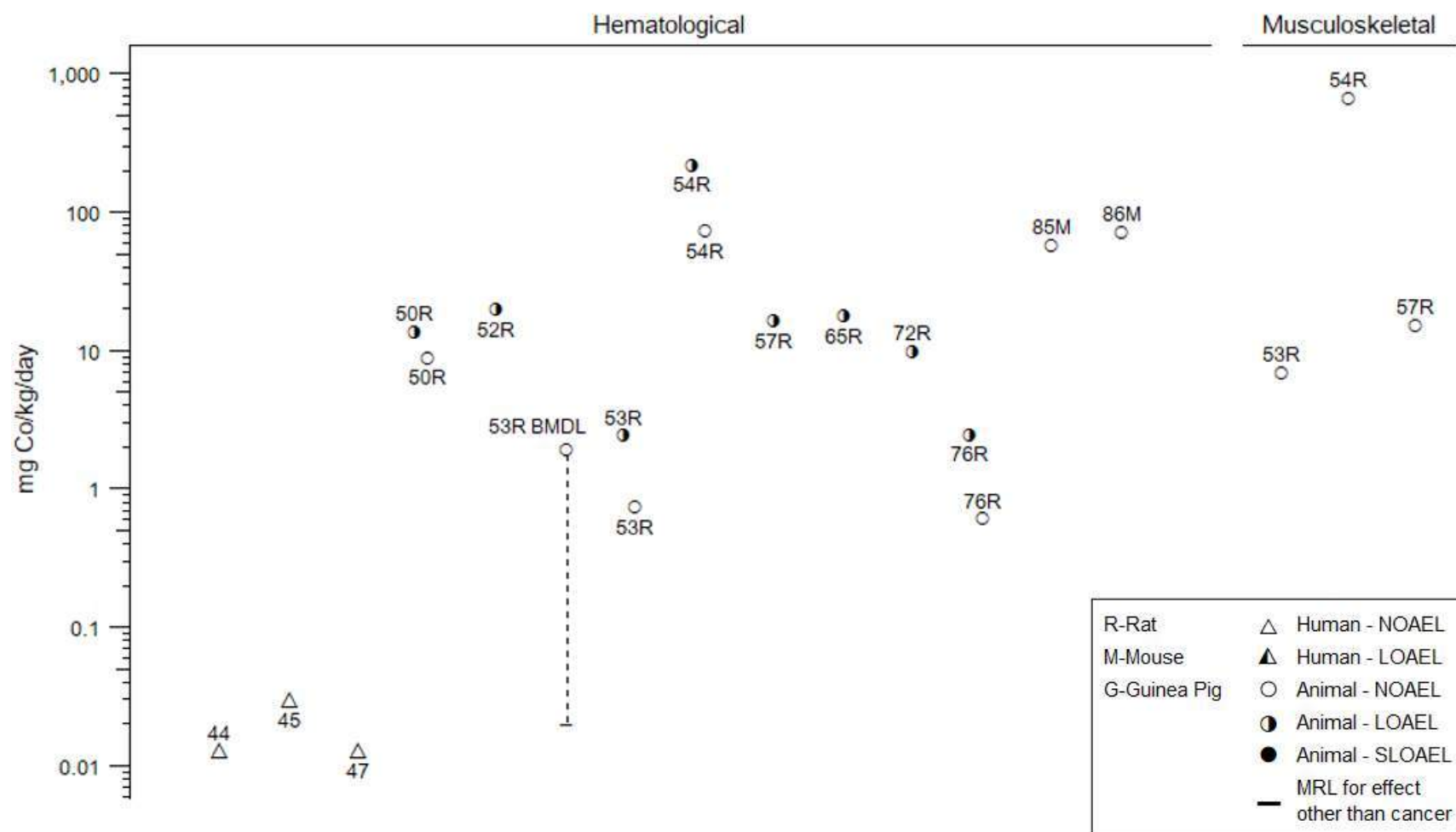
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)



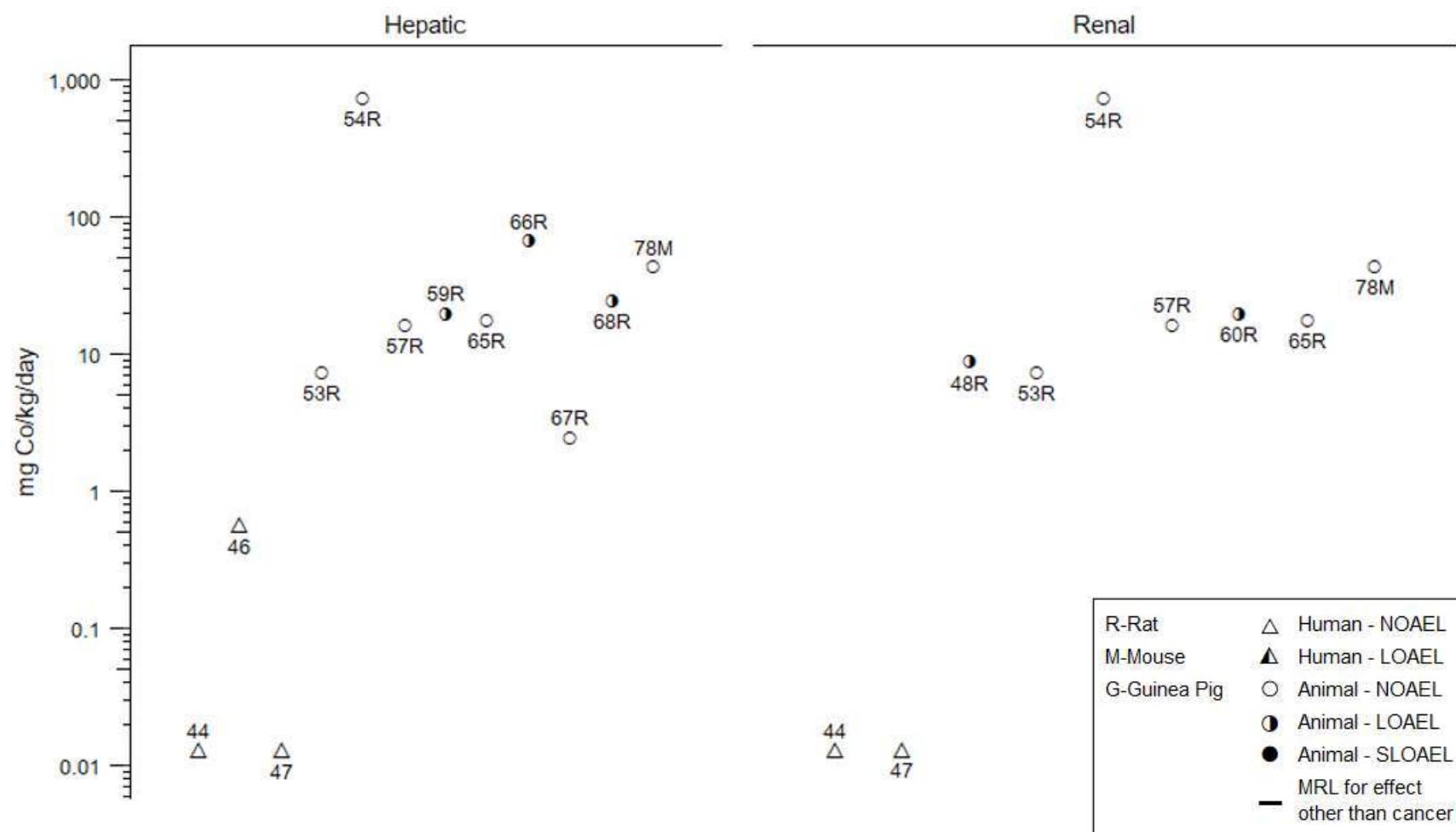
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)



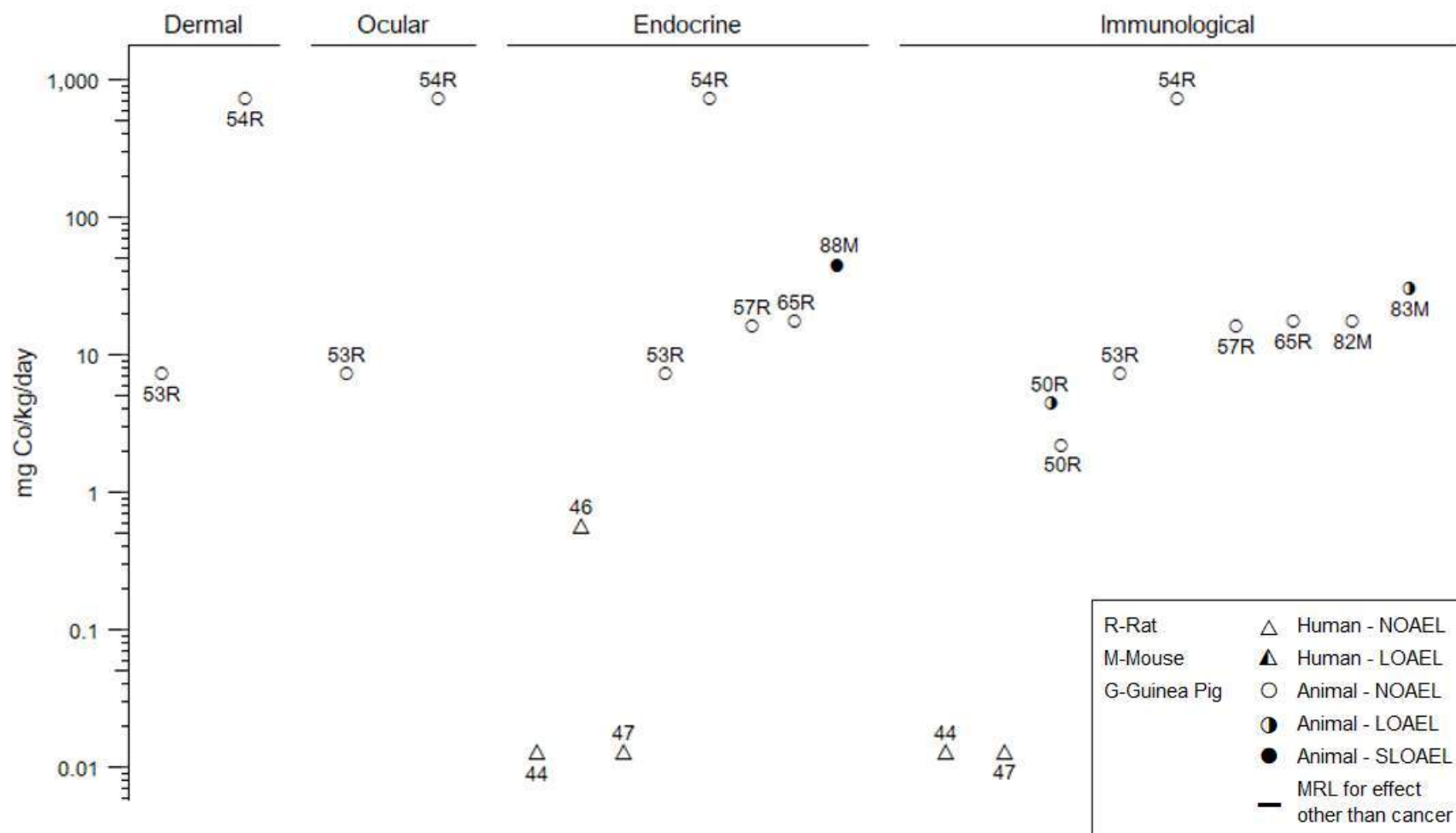
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)



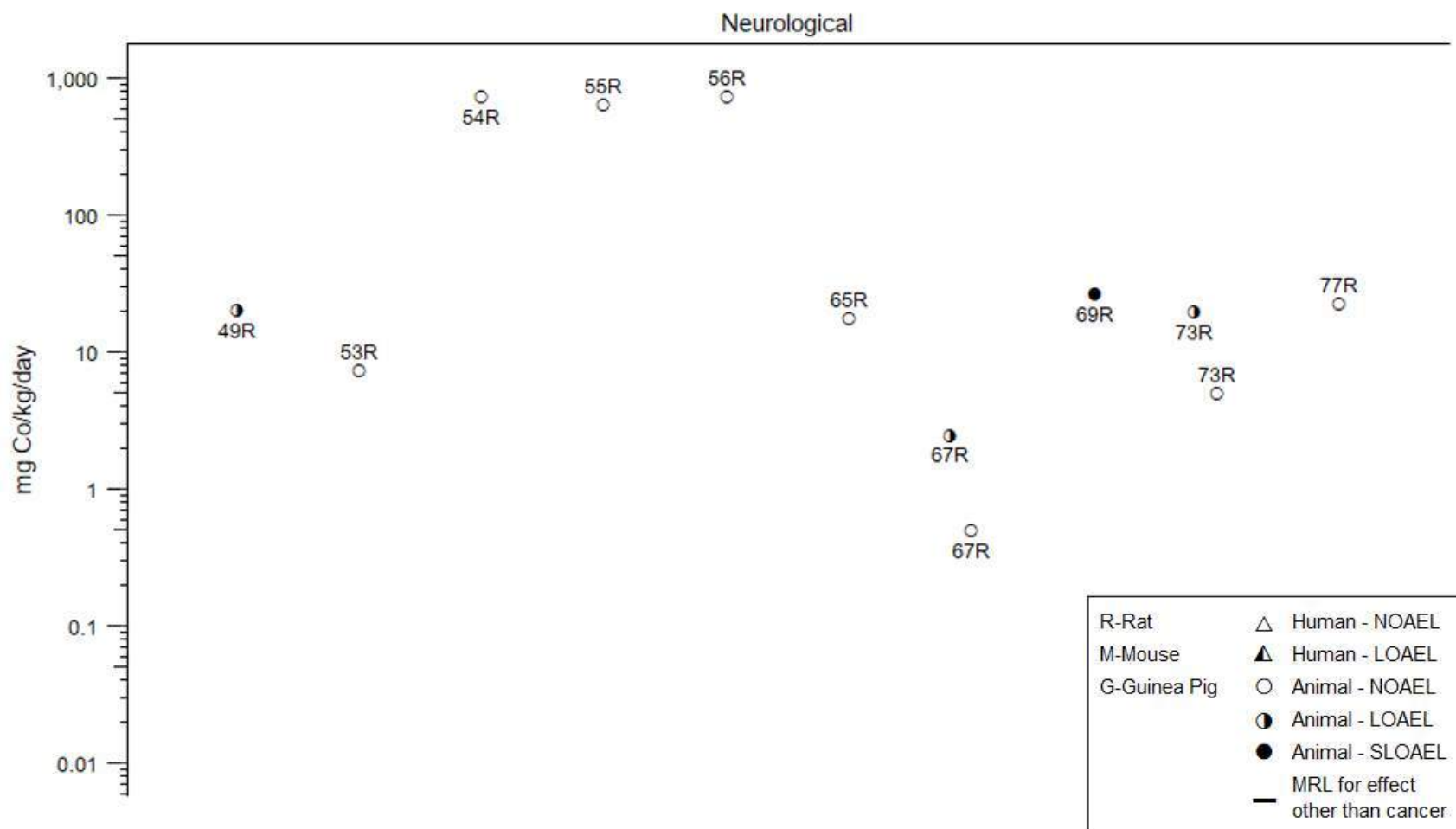
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)



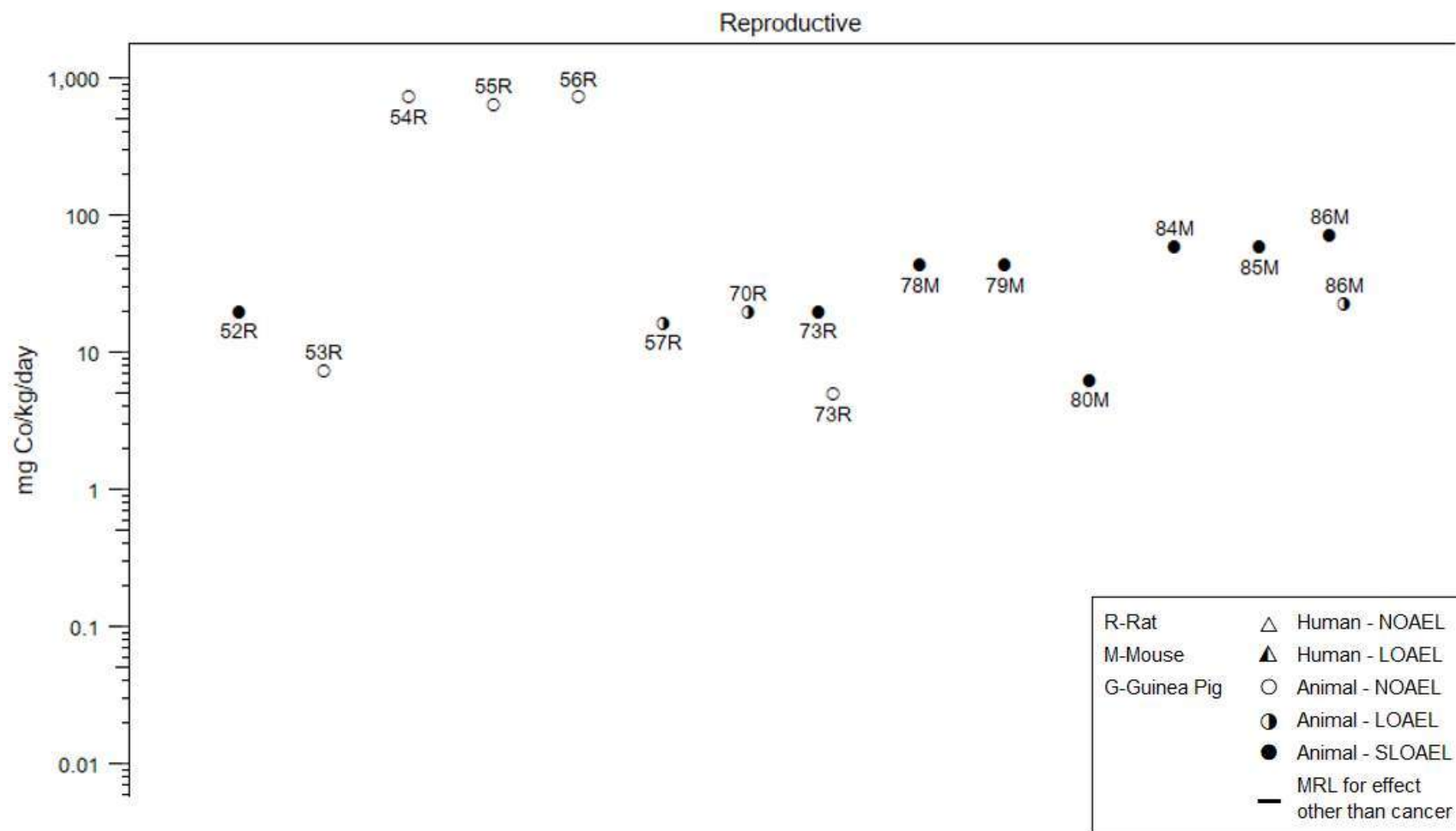
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)



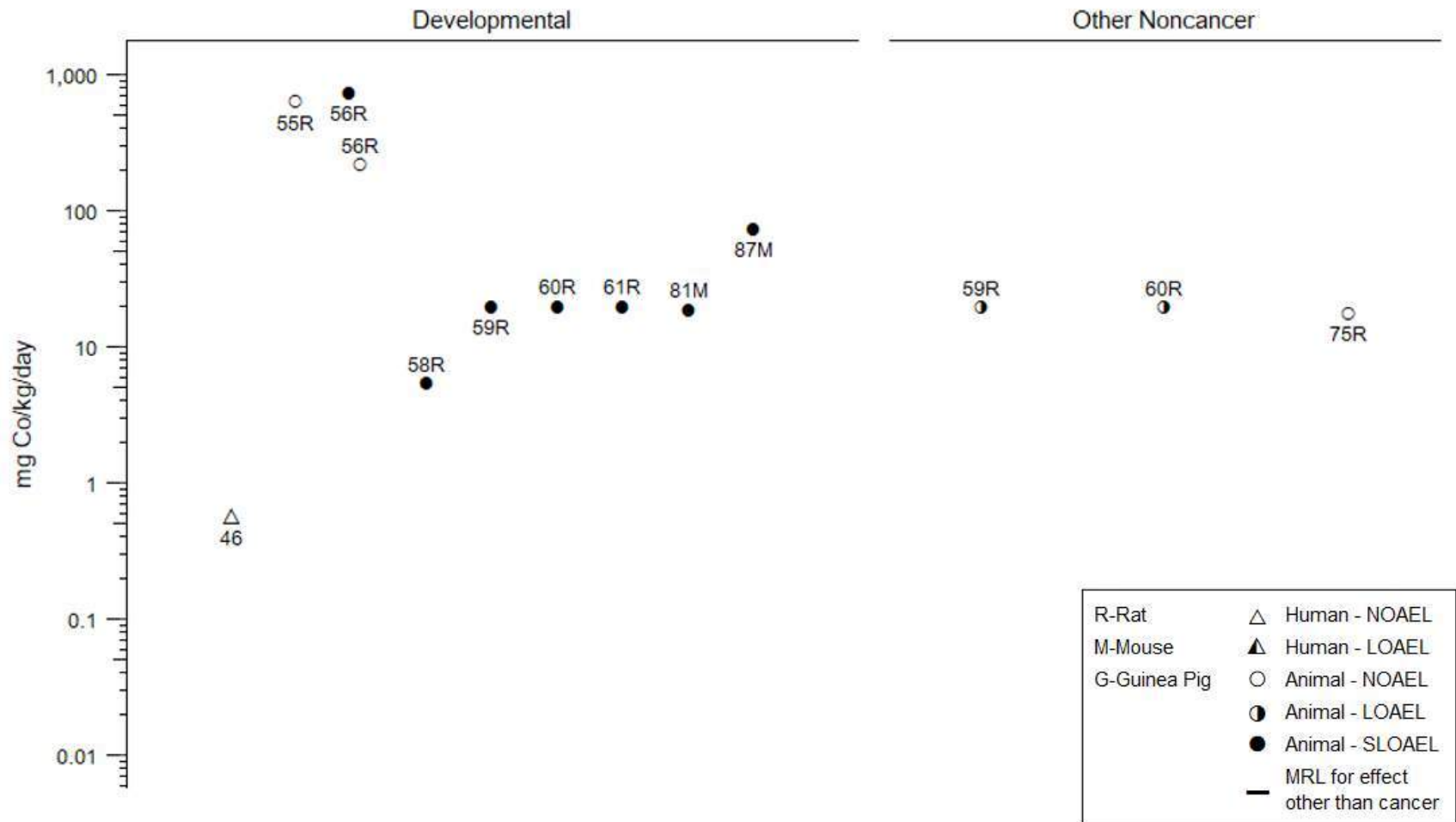
## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)



## 2. HEALTH EFFECTS

**Figure 2-3. Levels of Significant Exposure to Cobalt – Oral (mg Co/kg/day)**  
Intermediate (15–364 days)





## 2. HEALTH EFFECTS

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

| Species (strain)<br>No./group          | Exposure<br>parameters                                          | Doses                                                         | Parameters<br>monitored | Endpoint | NOAEL               | Less<br>serious<br>LOAEL                | Serious<br>LOAEL | Effects                                                                        |
|----------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------|-------------------------|----------|---------------------|-----------------------------------------|------------------|--------------------------------------------------------------------------------|
| <b>ACUTE EXPOSURE</b>                  |                                                                 |                                                               |                         |          |                     |                                         |                  |                                                                                |
| <b>Ikarashi et al. 1992a</b>           |                                                                 |                                                               |                         |          |                     | <b>Cobalt Chloride</b>                  |                  |                                                                                |
| Rat (Fischer-344)<br>3 F               | 3 days<br>1 time/day                                            | 0, 1.8, 3.6,<br>9.1, 18 mg<br>Co/kg/day                       | LE, IX                  | Immuno   | 3.6 mg<br>Co/kg/day | 9.1 mg<br>Co/kg/day                     |                  | Increased proliferation of lymphatic<br>cells (LLNA assay)                     |
| <b>Bonefeld et al. 2015</b>            |                                                                 |                                                               |                         |          |                     | <b>Cobalt Chloride</b>                  |                  |                                                                                |
| Mouse (NS) NS                          | 3 days<br>(sensitization) + 2<br>days (challenge)<br>1 time/day | 0, 4.5%                                                       | CS, IX                  | Immuno   |                     | 4.5%                                    |                  | Skin sensitization (swelling,<br>proliferation of lymphocytes) at<br>challenge |
| <b>Ikarashi et al. 1992a</b>           |                                                                 |                                                               |                         |          |                     | <b>Cobalt Chloride</b>                  |                  |                                                                                |
| Mouse (CBA/N)<br>3 F                   | 3 days<br>1 time/day                                            | 0, 2.3, 4.5,<br>11, 23 mg<br>Co/kg/day                        | LE, IX                  | Immuno   | 2.3 mg<br>Co/kg/day | 4.5 mg<br>Co/kg/day                     |                  | Increased proliferation of lymphatic<br>cells (LLNA assay)                     |
| <b>Ikarashi et al. 1992b</b>           |                                                                 |                                                               |                         |          |                     | <b>Cobalt (II) Chloride Hexahydrate</b> |                  |                                                                                |
| Mouse (BALB/c)<br>3 F                  | 3 days<br>1 time/day                                            | 0, 2.5, 12,<br>25 mg<br>Co/kg/day                             | LE, IX                  | Immuno   | 2.5 mg<br>Co/kg/day | 12 mg<br>Co/kg/day                      |                  | Increased proliferation of lymphatic<br>cells (LLNA assay)                     |
| <b>Mandervelt et al. 1997</b>          |                                                                 |                                                               |                         |          |                     | <b>Cobalt (II) Chloride Hexahydrate</b> |                  |                                                                                |
| Mouse (BALB/c)<br>3 F                  | 3 days<br>1 time/day                                            | 0, 2.5, 6,<br>12 mg<br>Co/kg/day                              | IX                      | Immuno   | 6 mg<br>Co/kg/day   | 12 mg<br>Co/kg/day                      |                  | Increased proliferation of lymphatic<br>cells (LLNA assay)                     |
| <b>Camner et al. 1993</b>              |                                                                 |                                                               |                         |          |                     | <b>Cobalt Chloride</b>                  |                  |                                                                                |
| Guinea pig<br>(Dunkin-Hartley)<br>16 F | 24 hours                                                        | Sensitization:<br>0, 2.3%<br>Challenge:<br>0.05, 0.2,<br>0.5% | IX                      | Immuno   |                     | 2.3%                                    |                  | Skin sensitization                                                             |
| <b>Ikarashi et al. 1992a</b>           |                                                                 |                                                               |                         |          |                     | <b>Cobalt Chloride</b>                  |                  |                                                                                |
| Guinea pig<br>(Hartley)<br>3 F         | 3 days<br>1 time/day                                            | 0, 1.4, 2.8,<br>6.8, 14 mg<br>Co/kg/day                       | LE, IX                  | Immuno   | 6.8 mg<br>Co/kg/day | 14 mg<br>Co/kg/day                      |                  | Increased proliferation of lymphatic<br>cells (LLNA assay)                     |

## 2. HEALTH EFFECTS

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

| Species (strain)<br>No./group                                                                                                               | Exposure<br>parameters                                                  | Doses                                                                 | Parameters<br>monitored | Endpoint            | NOAEL                                 | Less<br>serious<br>LOAEL                | Serious<br>LOAEL | Effects                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------|-------------------------|---------------------|---------------------------------------|-----------------------------------------|------------------|---------------------------------------------------------------|
| <b>INTERMEDIATE EXPOSURE</b>                                                                                                                |                                                                         |                                                                       |                         |                     |                                       |                                         |                  |                                                               |
| <b>NTP 1991, 2023</b>                                                                                                                       |                                                                         |                                                                       |                         |                     | <b>Cobalt Sulfate Heptahydrate</b>    |                                         |                  |                                                               |
| Rat (F344/N)<br>5 M, 5 F                                                                                                                    | 16 days<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per day | 0, 0.035,<br>0.19, 1.80,<br>19.0, 75.7 mg<br>Co/m <sup>3</sup> in air | CS                      | Ocular              | 1.8 mg<br>Co/m <sup>3</sup> in<br>air | 19 mg<br>Co/m <sup>3</sup> in<br>air    |                  | Ocular irritation (chromodacryorrhea)                         |
| Exposure chamber analysis showed that under test conditions, the test substance converted to cobalt sulfate hexahydrate (Behl et al. 2015). |                                                                         |                                                                       |                         |                     |                                       |                                         |                  |                                                               |
| <b>NTP 1991, 2023</b>                                                                                                                       |                                                                         |                                                                       |                         |                     | <b>Cobalt Sulfate Heptahydrate</b>    |                                         |                  |                                                               |
| Mouse (B6C3F1)<br>5 M, 5 F                                                                                                                  | 16 days<br>5 days/week<br>6 hours +<br>12 minutes<br>(T90 time) per day | 0, 0.035,<br>0.19, 1.80,<br>19.0, 75.7 mg<br>Co/m <sup>3</sup> in air | CS                      | Ocular              | 1.8 mg<br>Co/m <sup>3</sup> in<br>air | 19 mg<br>Co/m <sup>3</sup> in<br>air    |                  | Ocular irritation (chromodacryorrhea)                         |
| Exposure chamber analysis showed that under test conditions, the test substance converted to cobalt sulfate hexahydrate (Behl et al. 2015). |                                                                         |                                                                       |                         |                     |                                       |                                         |                  |                                                               |
| <b>Kincaid et al. 1954</b>                                                                                                                  |                                                                         |                                                                       |                         |                     | <b>Dicobalt Octacarbonyl</b>          |                                         |                  |                                                               |
| Guinea pig (NS)<br>3 NS                                                                                                                     | 18 days<br>5 days/week<br>1 time/day                                    | 0, 51.7 mg<br>Co/kg                                                   | CS, LE                  | Bd wt<br><br>Dermal | 51.7 mg<br>Co/kg                      | 51.7 mg<br>Co/kg                        |                  | Skin lesions (scabs and denuded<br>areas) at application site |
| <b>CHRONIC EXPOSURE</b>                                                                                                                     |                                                                         |                                                                       |                         |                     |                                       |                                         |                  |                                                               |
| <b>Swennen et al. 1993</b>                                                                                                                  |                                                                         |                                                                       |                         |                     | <b>Hard Metal</b>                     |                                         |                  |                                                               |
| Human<br>82 M                                                                                                                               | 8 years<br>(occupational)                                               | 0, 0.125 mg<br>Co/m <sup>3</sup> in air                               | CS                      | Dermal              |                                       | 0.125 mg<br>Co/m <sup>3</sup> in<br>air |                  | Eczema and erythema                                           |

Bd wt = body weight; Co = cobalt; CS = clinical signs; F = female(s); Immuno = immunological; IX = immune function; LE = lethality; LLNA = local lymph node assay; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; T90 = the time required for the inhalation chamber concentration to reach 90% of the target concentration

## 2. HEALTH EFFECTS

**2.2 DEATH**

The overall risk of death (from all causes) was not elevated in a cohort of 1,148 workers from an electrochemical plant producing sodium and cobalt in France; specific analysis of only cobalt production workers also showed no increased risk of death (Moulin et al. 1993; Mur et al. 1987). Many studies have evaluated the potential for increased mortality in hard metal workers exposed to cobalt (and other metals such as tungsten and tungsten carbide) from various countries around the world. The majority of them did not find any excess in total (all-cause) mortality in hard metal workers, compared to the general population, as determined by standard mortality ratios (SMRs) (Lasfargues et al. 1994; Marsh et al. 2017a; McElvenny et al. 2017; Morfeld et al. 2017; Moulin et al. 1998, 2000; Wallner et al. 2017; Wild et al. 2000). However, a large multinational cohort combining 32,354 hard metal workers from the United States, Austria, Germany, Sweden, and the United Kingdom exposed to long-term median levels of 0.006 mg Co/m<sup>3</sup> (as well as tungsten and nickel) observed an excess in total (all-cause) mortality compared to both national and regional rates (Marsh et al. 2017b). Specific causes of death that were elevated above national and/or regional rates included malignant neoplasms (buccal cavity and pharyngeal malignant neoplasms; bronchus, trachea, lung), nonmalignant respiratory diseases, emphysema, ischemic heart disease, and accidental deaths. However, due to concurrent exposure to other substances in hard metal, the contribution of cobalt exposure to these deaths is unclear.

A series of studies by Viegas et al. (2022a) demonstrate that acute-duration inhalation lethality in rats is dependent upon the administered compound. Cobalt hydroxide, cobalt metal powder, and cobalt oxide were the most toxic, with 100% mortality following 4-hour, nose-only exposures to 32, 50, and 79 mg Co/m<sup>3</sup>, respectively. Other compounds included cobalt carbonate, with 50% mortality at 3,200 mg Co/m<sup>3</sup>, and cobalt tetraoxide and cobalt sulfide, with 0% mortality at the limit test concentrations of 1,200 and 3,200 mg Co/m<sup>3</sup>, respectively (Viegas et al. 2022a). Differences in toxicity were not attributable to lung disposition; rather, the study authors proposed that increased toxicity of cobalt hydroxide, metal powder, and oxide was attributable to their inflammatory “reactivity” in the lungs. Mortality was associated with inflammatory changes in the lung, including perivascular inflammatory edema, alveolar pulmonary edema, and pneumonia. Less toxic compounds (cobalt carbonate, tetraoxide, and sulfide) were generally associated only with mild perivascular inflammatory edema. Another study reported a 30-minute LC<sub>50</sub> of 165 mg Co/m<sup>3</sup> for cobalt hydrocarbonyl (plus oxide/carbonate decomposition products) in albino rats (Palmer et al. 1959).

## 2. HEALTH EFFECTS

Increased mortality was observed in some intermediate-duration inhalation studies in rodents. Decreased survival was observed in F344/N rats and B6C3F1 mice exposed to cobalt metal at  $\geq 20$  and 40 mg Co/m<sup>3</sup>, respectively, or cobalt sulfate at  $\geq 19$  mg Co/m<sup>3</sup> for 6 hours/day, 5 days/week for 16 or 17 days (NTP 1991, 2014). For cobalt sulfate, female rats were less susceptible, with no mortalities until 75.7 mg Co/m<sup>3</sup> (NTP 1991). Intermediate-duration exposure to 11.4 mg Co/m<sup>3</sup> for 13 weeks caused 20% mortality in male B6C3F1 mice but not female mice or F344/N rats of either sex (Bucher et al. 1990; NTP 1991). In other 13–14-week intermittent exposure inhalation studies, no exposure-related increases in mortality were observed in F344/N rats or B6C3F1 mice exposed to concentrations up to 5 mg Co/m<sup>3</sup> as cobalt metal (NTP 2014) or in albino rats or guinea pigs exposed to 9 mg Co/m<sup>3</sup> as cobalt hydrocarbonyl (plus oxide/carbonate decomposition products) (Palmes et al. 1959).

Increased mortality was observed in some chronic-duration studies in rodents. Chronic-duration exposure to cobalt metal for 105 weeks resulted in a 20–22% reduction in survival in male B6C3F1 mice and female F344/N rats exposed to  $\geq 2.5$  mg Co/m<sup>3</sup>, compared to controls; survival in male rats or female mice was comparable to controls at concentrations up to 5 mg Co/m<sup>3</sup> (Behl et al. 2015; NTP 2014). Chronic-duration exposure for 105 weeks to cobalt sulfate did not have a significant effect on survival in F344/N rats or B6C3F1 mice at concentrations up to 1.11–1.14 mg Co/m<sup>3</sup> (Behl et al. 2015; Bucher et al. 1999; NTP 1998).

A 19-month-old male child who swallowed an unknown amount of a cobalt chloride solution died approximately 6.5 hours after ingestion, despite repeated induced vomiting, gastric lavage, and supportive therapy (Jacobziner and Raybin 1961).

In several studies, lethal cardiomyopathy was reported in people who consumed large quantities of beer containing cobalt sulfate (and ethyl alcohol) (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969). The deaths occurred during the early to mid-1960s, at which time, breweries in Canada, the United States, and Europe were adding cobalt to beer as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Morin et al. 1967, 1971; Sullivan et al. 1969); this practice has been discontinued for decades. Deaths occurred following ingestion of beer containing 0.04–0.14 mg cobalt/kg/day for a period of years (approximately 8–30 pints of beer each day). “Acute mortality” (death within several days of admission) accounted for 18% of the deaths (Alexander 1972). Approximately 43% of the patients admitted to the hospital with cardiomyopathy died within several years of the initial hospital visit. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein poor diets and may have had prior cardiac damage from alcohol abuse.

## 2. HEALTH EFFECTS

Therefore, the role of cobalt in cardiomyopathy, and subsequent death, is unclear. It is noted that treatment of both pregnant and nonpregnant anemic patients with doses of cobalt (0.6–1 mg/kg/day) that were much higher than the doses in the beer did not result in mortality (Davis and Fields 1958; Holly 1955).

Numerous acute-duration oral lethality studies have been conducted in animals. As seen with inhalation, oral LD<sub>50</sub> values vary depending upon administered compound, from as low as 25 mg Co/kg for cobalt chloride to 352 mg Co/kg for cobalt sulfate (Singh and Junnarkar 1991). Reported LD<sub>50</sub> values in rodents were 25–190 mg Co/kg for cobalt chloride, 91 mg Co/kg for cobalt fluoride, 109 mg Co/kg for cobalt bromide, 140 mg Co/kg for cobalt nitrate, 159 mg Co/kg/day for cobalt oxide, 161–352 mg Co/kg for cobalt sulfate, 168 mg Co/kg for cobalt acetate, and 187 mg Co/kg for cobalt phosphate (Krasovskii and Fridlyand 1971; Murdock 1959; Singh and Junnarkar 1991; Speijers et al. 1982). In other acute-duration oral studies, single oral exposures to 149 or 161 mg Co/kg as cobalt chloride caused death in 10/20 or 11/20 Sprague-Dawley rats, respectively (Domingo and Llobet 1984; Domingo et al. 1985a).

Oral intermediate-duration exposure to cobalt compounds in animals resulted in death in some studies. In an intermediate-duration exposure study, 4/10 Wistar rats died following oral exposure to 27 mg Co/kg/day as cobalt chloride for 60 days (Mohamed et al. 2019). Similarly, 5/10 Wistar rats died during an 8-week exposure to 26 mg Co/kg/day as cobalt sulfate (Grice et al. 1969). 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 deaths were observed in Wistar rat dams exposed to at 20 mg Co/kg/day via gavage as cobalt chloride for 2 weeks during gestation and 2 weeks during lactation (Garoui et al. 2011, 2012, 2013). In Sprague-Dawley rats, no exposure-related mortalities were observed at doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a), 16.5 mg Co/kg/day as cobalt chloride in drinking water for 13 weeks (Domingo et al. 1984), or 68 mg Co/kg/day as cobalt chloride in drinking water for 4 weeks (Khalil et al. 2020). In Swiss mice, 1/10 and 2/10 mice died at 11.62 and 23.01 mg Co/kg/day as cobalt chloride in drinking water, respectively, during the 10<sup>th</sup> week of a 12-week exposure; however, the cause of death was not discussed so it is unknown if these deaths were compound-related (Elbetieha et al. 2008). No deaths were observed in male B6C3F1 mice exposed to 58.9 mg Co/kg/day as cobalt chloride in drinking water for 10 weeks (Pedigo and Vernon 1993). 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).

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No studies were identified regarding death in humans after dermal exposure to cobalt. In animals, no mortalities have been reported following dermal exposures to cobalt compounds. Acute-duration dermal exposure to cobalt chloride did not cause death in rats, mice, or guinea pigs at doses up to 18, 25, or 14 mg Co/kg/day, respectively (Ikarashi et al. 1992a, 1992b). Intermediate-duration 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 (Kincaid et al. 1954).

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 at a dose of 12 mg Co/kg/day via 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). Domingo 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.

Studies evaluating body weight in animals following acute-duration inhalation exposure are limited. No body weight effects were noted in Wistar rats exposed to cobalt tetroxide for 6 hours/day at concentrations up to 160.90 mg Co/m<sup>3</sup> for 14 days (Burzlaff et al. 2022a).

Several studies in rats indicate that intermediate-duration inhalation exposure to cobalt results in exposure-related decreases in body weight, compared to control. In rats, no biologically significant decreases in body weight were observed following intermediate-duration inhalation exposure to cobalt metal or cobalt compounds at concentrations up to 9 mg Co/m<sup>3</sup> (Bucher et al. 1990; Burzlaff et al. 2022a, 2022b; NTP 1991, 2014; Palmes et al. 1959). Intermittent exposure to cobalt metal at 10 mg Co/m<sup>3</sup> for 16 days resulted in serious decreases in final body weight in male rats (20%) and less serious decreases in female rats (12%), compared to control (NTP 2014). Serious decreases in female body weight (45%) were observed following exposure to cobalt metal at 20 mg Co/m<sup>3</sup> for 16 days (NTP 2014). Male rats were also more sensitive to cobalt sulfate at a similar concentration of 11.4 mg Co/m<sup>3</sup> for 13 weeks, showing a 14% decrease in final body weight, compared to control; female rats did not show exposure-

## 2. HEALTH EFFECTS

related body weight changes at this concentration (Bucher et al. 1990; NTP 1991). Exposure to  $\geq 19.0$  mg Co/m<sup>3</sup> as cobalt sulfate for 16 days resulted in decreases in body weight  $\geq 20\%$  in female and male rats, compared to control rats (NTP 1991). No body weight effects were observed in Wistar rats exposed to cobalt tetraoxide for 6 hours/day at concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a).

Mice show similar body weight effects as rats following intermediate-duration inhalation exposure, with no exposure-related effects at concentrations up to 5 mg Co/m<sup>3</sup> (Bucher et al. 1990; NTP 1991, 2014). Intermittent exposure to cobalt metal at 10 mg Co/m<sup>3</sup> for 14 weeks resulted in a 13–14% decrease in final body weight in both male and female mice, compared to control (NTP 2014). Similarly, intermittent inhalation exposure to 11.4 mg Co/m<sup>3</sup> as cobalt sulfate for 13 weeks reduced the final body weights in male rats by 14% and in female rats by 22%, compared to control (Bucher et al. 1990; NTP 1991). Final body weight decreases  $>20\%$  were observed in both sexes after exposure to 19 mg Co/m<sup>3</sup> as cobalt sulfate for 16 days, compared to control mice (Bucher et al. 1990; NTP 1991). Similarly, when compared to control, exposure to 20 mg Co/m<sup>3</sup> as cobalt metal for 17 days resulted in a 16% decrease in final body weight in female mice, and exposure to 40 mg Co/m<sup>3</sup> as cobalt metal for 17 days or 14 weeks resulted in  $>20\%$  decrease in final body weight in both sexes (NTP 2014).

In other species, no exposure-related decreases in body weight were observed in guinea pigs exposed to 9 mg Co/m<sup>3</sup> as cobalt hydrocarbonyl (plus oxide/carbonate decomposition products) for 3 months, compared to control (Palmes et al. 1959). A 3-month exposure to cobalt metal for 5 days/week, 6 hours/day at 0.1 mg Co/m<sup>3</sup> resulted in a 16% decrease in final body weight in pigs, compared to control pigs (Kerfoot 1974).

Chronic-duration inhalation exposure to 5 mg Co/m<sup>3</sup> as cobalt metal for 105 weeks (5 days/week, 6 hours/day) caused a  $>20\%$  decrease in final body weight in male and female rats and mice, compared to respective control groups (NTP 2014). In rats, the next lower concentration (2.5 mg Co/m<sup>3</sup>) resulted in final body weight decreases of 11% in males and 16% in females, compared to controls (NTP 2014). No body weight effects were noted at 1.25 mg Co/m<sup>3</sup> in either species. No body weight effects were noted in rats or mice exposed to concentrations up to 1.11 or 1.14 Co/m<sup>3</sup>, respectively, as cobalt sulfate for 105 weeks (Bucher et al. 1999; NTP 1998). Lifetime exposure (5 days/week, 7 hours/day) to 7.9 mg Co/m<sup>3</sup> as cobalt oxide did not result in decreased body weight gain in hamsters (Wehner et al. 1977).

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Decreased body weight or body weight gain were observed in animals orally exposed to cobalt and its compounds. In acute-duration studies, exposure to oral doses up to 28 mg Co/kg/day as cobalt chloride were generally not associated with body weight effects in rats (Salami et al. 2023; Shrivastava et al. 2010). Acute doses  $\geq 68$  mg Co/kg/day as cobalt chloride resulted in body weight loss in exposed rats ( $>13\%$  decrease compared to starting weights, compared to 8% body weight gains in control rats) (Salami et al. 2023). However, pregnant animals may be more susceptible to body weight effects. Maternal body weight gains were decreased by  $>20\%$  in Sprague-Dawley rat dams exposed to doses  $\geq 6.2$  mg Co/kg/day via gavage as cobalt chloride on gestation days (GDs) 6–15 (Paternian and Domingo 1988) and in ICR mouse dams exposed to 81 mg Co/kg/day via gavage as cobalt chloride on GDs 8–12 (Seidenberg et al. 1986).

While several studies reported body weight effects in rats following intermediate-duration oral exposure to cobalt compounds, inconsistencies regarding dose-response across studies have been found for most studied compounds. Male Sprague-Dawley rats showed an 11% decrease in body weight at the end of a 90-day gavage exposure to 7.44 mg Co/kg/day as cobalt chloride, compared to control. At 4 weeks postexposure, body weight decreases were more pronounced in males at 17%, and females showed a 13% decrease, compared to control (Danzeisen et al. 2020a). No body weight effects were noted at  $\leq 2.48$  mg Co/kg/day for 90 days. Sprague-Dawley rats exposed to 8.9 mg Co/kg/day as cobalt chloride in drinking water for 4 weeks lost 7% of their initial body weight, compared to a body weight gain of 8% in controls (Abdel-Daim et al. 2020). One study reported a 45–61% reduction in body weight gain in Sprague-Dawley rats following dietary exposure 0.45–13.8 mg Co/kg/day as cobalt chloride for 30 days; however, there was a lack of a clear dose-response relationship and food intake data were not reported (Chetty et al. 1979). Additional studies in rats evaluating cobalt chloride did not report biologically significant decreases in body weight, including Sprague-Dawley rats exposed to drinking water doses up to 18 mg Co/kg/day for 16 days or 20.3 mg Co/kg/day for 57 days (Bourg et al. 1985; Saker et al. 1998), CFY rats exposed to a gavage dose of 22 mg Co/kg/day for 3 weeks (Morvai et al. 1993), Wistar rats exposed to a gavage dose of 25 mg Co/kg/day for 60 days (Mathur et al. 2011), pregnant Wistar rats exposed to a drinking water dose of 20 mg Co/kg/day for 28 days (2 weeks gestation plus 2 weeks lactation) (Garoui et al. 2011, 2012), or albino rats exposed to 9.9 mg Co/kg/day via gelatin capsule for 8 weeks (Stanley et al. 1947).

Sprague-Dawley rats showed  $>20\%$  decreases in final body weights following dietary exposure to  $\geq 4.2$  mg Co/kg/day as cobalt sulfate for  $\geq 8$  weeks, compared to control (Clyne et al. 1988; Haga et al. 1996; Pehrsson et al. 1991). No body weight effects were noted in pregnant Sprague-Dawley rats



## 2. HEALTH EFFECTS

exposed to gavage doses up to 648 mg Co/kg/day as cobalt sulfide or 734 mg Co/kg/day as cobalt tetraoxide for 2 weeks prenatally through postnatal day (PND) 3 (Danzeisen et al. 2020a). Danzeisen et al. (2020a) also examined the effects of oral exposure to tricobalt tetraoxide at a dose of 734 mg Co/kg/day for 90 days in male and female Sprague-Dawley rats and reported “slight” reductions in male rat body weight and “marginal” effects in female body weight; however, quantitative data were not reported.

Data on body weight effects following intermediate-duration oral exposure in other species are limited. A 33% decrease in body weight was observed in BALB/c mice exposed to 31 mg Co/kg/day as cobalt chloride starting 2–3 days prior to birth and during lactation (via dam) and directly on PNDs 26–60 via drinking water (Legostaeva et al. 2013; Zaksas et al. 2013). In studies with adult mice, drinking water exposure to doses up to 43.4 mg Co/kg/day as cobalt chloride for 12–13 weeks did not result in body weight effects (Anderson et al. 1993; Elbetieha et al. 2008; Pedigo et al. 1988). Drinking water exposure to 72.1 mg Co/kg/day for 12 weeks was associated with a 10% decrease in body weight in male CD-1 mice (Pedigo et al. 1988). No body weight effects were observed in male guinea pigs exposed to dietary cobalt sulfate at 20 mg Co/kg/day for 5 weeks (Mohiuddin et al. 1970).

No body weight changes were observed after intermediate-duration dermal exposure to 51.7 mg Co/kg/day as dicobalt octacarbonyl in methyl ether ketone in guinea pigs (Kincaid et al. 1954).

A 24% weight loss was reported by week 6 of an 8-week study in albino rats exposed to 2.5 mg Co/kg/day as cobalt chloride via subcutaneous injection; no weight changes were observed at 0.6 mg Co/kg/day (Stanley et al. 1947).

### 2.4 RESPIRATORY

The respiratory tract is a sensitive target of toxicity following inhalation exposure to cobalt. Adverse effects observed in humans occupationally exposed to cobalt metal and cobalt compounds included altered spirometry and evidence of pulmonary irritation and dyspnea at higher exposure concentrations. In laboratory animal studies, inflammatory changes throughout the respiratory tract were consistently observed in multiple species following exposure for any duration, with necrosis progressing to hyperplasia and metaplasia with repeated exposure.

## 2. HEALTH EFFECTS

There are limited data regarding respiratory effects in humans following acute-duration exposure to cobalt. An acute 6-hour exposure to cobalt hard metal dust at an average concentration of 0.038 mg Co/m<sup>3</sup> resulted in decreased lung forced vital capacity (FVC) in 15 healthy male volunteers, compared to diurnal FVC changes during a comparable 6-hour period without exposure (Kusaka et al. 1986a). The study authors noted that the FVC changes did not correlate with cobalt concentration, although those data were not presented. No other measures of lung function were altered. The exposed volunteers also had subjective complaints of respiratory irritation. The same investigators did not observe any significant changes in lung function in a group of 42 metal shapers after a 7-hour work shift, compared to pre-shift lung function measures. Mean cobalt levels during the work shift were 0.085 mg Co/m<sup>3</sup> (mean exposure over the previous 3 years was 0.126 mg Co/m<sup>3</sup>) and the mean employment duration for workers was 10 years and 4 months (Kusaka et al. 1986a).

Numerous occupational studies evaluated potential associations between long-term exposure to cobalt and adverse respiratory effects (Table 2-4). In general, factory workers evaluated in the studies discussed below were subjected to co-exposures with other metals, such as nickel and chromium, and irritant gases; therefore, the health effects observed might not be caused by cobalt alone. Additionally, some of the endpoints (such as lung function) may be confounded by the healthy worker effect or exposure to other chemicals outside working hours. More details on the quality and confidence in available epidemiological studies evaluating respiratory effects can be found in Appendix C.

**Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects**

| Reference, study type, and population                                                                                              | Exposure concentration                                                                                  | Outcome evaluated                                                                                 | Result                                  |
|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>Al-Abcha et al. 2021</b><br><br>Cohort; 498 cobalt exposed workers (Michigan, United States)                                    | Current air concentration, mg Co/m <sup>3</sup><br>Low: ≤0.05<br>High: >0.05                            | Respiratory symptoms (daily or weekly chest tightness, shortness of breath, wheezing)             | ↔ (low versus high)                     |
|                                                                                                                                    |                                                                                                         | Onset of asthma since employment                                                                  | ↔ (low versus high)                     |
| <b>Andersson et al. 2020</b><br><br>Cohort with cross-sectional analysis; 72 workers (63 males, 9 females; mean age 42 years; mean | Current air concentration, mg Co/m <sup>3</sup><br>Median: 0.0009<br>Mean: 0.0017<br>8-hour TWA: 0.0034 | Respiratory symptoms (asthmatic symptoms, nasal drip, cough without infection, cough with phlegm) | ↔ (current 8-hour TWA, air; cumulative) |
|                                                                                                                                    |                                                                                                         | Lung function<br>FVC, FEV <sub>1</sub>                                                            | ↔ (current 8-hour TWA, air; cumulative) |

## 2. HEALTH EFFECTS

**Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects**

| Reference, study type, and population                                                                                                                                                                                                                                                           | Exposure concentration                                                                                                                                                          | Outcome evaluated                                                                                       | Result                                                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| employment 11 years) from the hard metal industry (Sweden)                                                                                                                                                                                                                                      | Cumulative exposure, mg Co-year/m <sup>3</sup> :<br>T1: ≤0.01<br>T2: 0.02–0.05<br>T3: ≥0.06                                                                                     | Asthma diagnosis                                                                                        | ↔ (cumulative)                                                                    |
| <b>Deng et al. 1991</b><br><br>Cross-sectional; 362 workers (75% males; mean age 45 years; mean employment 21 years), including 310 active workers and 52 retired workers from the sintered magnet industry, and 1,370 unexposed blue-collar workers (age range 20–59 years) (United States)    | Current air concentration, mean:<br>0.0175 mg Co/m <sup>3</sup>                                                                                                                 | Respiratory symptoms (chronic cough and bronchitis, dyspnea, wheezing with/without shortness of breath) | ↔ (workers versus referents)                                                      |
|                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                 | Lung function<br>FVC, FEV <sub>1</sub>                                                                  | ↑ (workers versus referents)                                                      |
|                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                 | Abnormal findings on chest x-ray                                                                        | ↔ (workers versus referents)                                                      |
| <b>Gennart and Lauwerys 1990</b><br><br>Retrospective cohort; 48 workers (14 females, 34 males; range of mean ages 28.7–33.8 years; mean employment 6 years) from the diamond-cobalt tool manufacturing industry and 23 unexposed workers (12 females, 11 males; mean age 32.5 years) (Belgium) | Current air concentration, geometric mean, mg Co/m <sup>3</sup> :<br>Mixing: 0.1355<br>Oven: 0.0152                                                                             | Lung function<br>FVC, FEV <sub>1</sub> , PEF                                                            | ↓ (nonsmokers: workers versus referents)<br>↓ (smokers: workers versus referents) |
|                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                 | FEV <sub>1</sub> /FVC                                                                                   | ↔ (nonsmokers: workers versus referents)<br>↔ (smokers: workers versus referents) |
|                                                                                                                                                                                                                                                                                                 | Current urine cobalt levels, mean:<br>Exposed nonsmokers: 40.7 µg/g creatinine<br>Exposed smokers: 25.7 µg/g creatinine<br>Unexposed controls, nonsmokers: 0.18 µg/g creatinine | MEF <sub>25</sub> or MEF <sub>50</sub>                                                                  | ↔ (nonsmokers: workers versus referents)<br>↔ (smokers: workers versus referents) |
|                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                 | MEF <sub>75</sub>                                                                                       | ↔ (nonsmokers: workers versus referents)<br>↓ (smokers: workers versus referents) |
|                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                 | Respiratory symptoms (cough, sputum, dyspnea)                                                           | ↑ (workers versus referents)                                                      |

## 2. HEALTH EFFECTS

**Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects**

| Reference, study type, and population                                                                                                                                                                                                             | Exposure concentration                                                                                                                                                                                                | Outcome evaluated                                                                                                                                              | Result                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| <b>Hamzah et al. 2014</b><br><br>Cross-sectional; 402 exposed male workers (mean age 36.8 years; mean employment 12.2 years) from the steel industry (Malaysia)                                                                                   | Current air concentration, range of 8-hour TWA means in different job categories:<br>0.01–0.19 mg Co/m <sup>3</sup>                                                                                                   | Respiratory symptoms (chronic cough and phlegm, chest tightness, shortness of breath)<br><br>Lung function<br>FEV <sub>1</sub><br>FVC<br>FEV <sub>1</sub> /FVC | ↑<br><br><br>↓<br>↓<br>↔                                                                 |
| <b>Kusaka et al. 1986a</b><br><br>Retrospective cohort; 42 workers (8 females, 34 males; mean age 42 years; employed for 3 years) from the hard metal shaping industry and 84 unexposed workers (16 females, 68 males; mean age 42 years) (Japan) | Current exposure, mean 7-hour exposure concentration (range):<br>0.085 (0.017–0.610) mg Co/m <sup>3</sup><br><br>Historical exposure, mean (range) over the past 3 years:<br>0.126 (0.006–0.610) mg Co/m <sup>3</sup> | Lung function<br>FVC, FEV <sub>1</sub> , PEF, MMEF, Vmax<br><br>FEV <sub>1</sub> /FVC <sup>a</sup>                                                             | ↔ (historical: workers versus referents)<br><br>↓ (historical: workers versus referents) |
| <b>Kusaka et al. 1986b</b><br><br>Retrospective cohort; 319 workers (sex and employment duration not reported; range of mean ages 31–61 years, employed 5–17 years) from the hard metal industry (Japan)                                          | Measured air concentration during 3-year period, range of mean values:<br>0.003–1.292 mg Co/m <sup>3</sup>                                                                                                            | Occupational asthma<br><br>Abnormal chest radiograph (diffuse shadows of category 1 or greater)<br><br>Interstitial pneumonitis                                | ↑<br><br>↑<br><br>↔                                                                      |

## 2. HEALTH EFFECTS

**Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects**

| Reference, study type, and population                                                                                                                                                                                                         | Exposure concentration                                                | Outcome evaluated                                                                                     | Result                                                                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| <b>Linna et al. 2003</b><br><br>Retrospective cohort; 110 exposed male workers (mean age 50.3 years; mean employment 22.1 years) from the cobalt industry and 140 unexposed males (mean age 48.8 years; mean employment 24.7 years) (Finland) | Historical exposure levels, range: 0.01–0.1 mg Co/m <sup>3</sup>      | Suspected asthma (general or work-related)                                                            | ↑ (workers versus referents)                                                       |
|                                                                                                                                                                                                                                               | Cumulative exposure, median: 0.6 mg Co-year/m <sup>3</sup>            | Respiratory symptoms (phlegm, cough with wheezing, dyspnea with wheezing, breathlessness on exertion) | ↑ (workers versus referents)                                                       |
|                                                                                                                                                                                                                                               |                                                                       | Chest x-rays                                                                                          | ↔ (workers versus referents)                                                       |
|                                                                                                                                                                                                                                               |                                                                       | Lung function                                                                                         |                                                                                    |
|                                                                                                                                                                                                                                               |                                                                       | FVC                                                                                                   | ↔ (workers versus referents)                                                       |
|                                                                                                                                                                                                                                               |                                                                       | FEV <sub>1</sub>                                                                                      | ↓ (smokers: workers versus referents)<br>↔ (nonsmokers: workers versus referents)  |
|                                                                                                                                                                                                                                               |                                                                       | MEF <sub>50</sub> or MEF <sub>25</sub>                                                                | ↓ (smokers: workers versus referents)<br>↔ (nonsmokers: workers versus referents)  |
|                                                                                                                                                                                                                                               |                                                                       | DLCO or DLCO/VA                                                                                       | ↔ (workers versus referents)                                                       |
| <b>Meyer-Bisch et al. 1989</b><br><br>Cross-sectional; 425 workers (351 men, 74 women) exposed to hard metal dusts and 88 unexposed workers (69 men, 19 women) from three hard metal plants (France)                                          | Current air concentration, mean, mg Co/m <sup>3</sup> :               | Lung function                                                                                         |                                                                                    |
|                                                                                                                                                                                                                                               | Finishing work area ("hard" carbide): 0.030–0.210                     | Restrictive syndrome <sup>b</sup>                                                                     | ↔ (exposed versus unexposed)                                                       |
|                                                                                                                                                                                                                                               | Powder, presses, and forming work areas ("soft" carbide): 0.030–0.272 | Obstructive syndrome <sup>c</sup>                                                                     | ↔ (exposed versus unexposed)                                                       |
|                                                                                                                                                                                                                                               |                                                                       | Bronchial hyperreactivity <sup>d</sup>                                                                | ↔ (men)<br>↑ (women; hard versus unexposed)                                        |
|                                                                                                                                                                                                                                               | Maintenance workers (men only): not reported                          | Abnormal diffusing capacity (altered TCO <sub>ss</sub> )                                              | ↑ (men; soft versus unexposed)<br>↑ (women; hard versus unexposed)                 |
|                                                                                                                                                                                                                                               |                                                                       | FuaCO                                                                                                 | ↓ (men; soft or hard versus unexposed)<br>↓ (women; soft or hard versus unexposed) |

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**Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects**

| Reference, study type, and population                                                                                                                                                                                                                                                         | Exposure concentration                                                                                                                                                     | Outcome evaluated                                                                                                                                                              | Result                                                                                                                                                                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                               |                                                                                                                                                                            |                                                                                                                                                                                | ↓ (nonsmokers; soft or hard versus unexposed)                                                                                                                                                                |
|                                                                                                                                                                                                                                                                                               |                                                                                                                                                                            | FVC, FEV <sub>1</sub> , FEV <sub>1</sub> /FVC<br>FEF                                                                                                                           | ↔ (exposed versus unexposed; all or stratified by smoking status)                                                                                                                                            |
|                                                                                                                                                                                                                                                                                               |                                                                                                                                                                            | Respiratory symptoms<br>Cough, sputum                                                                                                                                          | ↑ (men; soft versus unexposed)<br>↑ (women; hard versus unexposed)                                                                                                                                           |
|                                                                                                                                                                                                                                                                                               |                                                                                                                                                                            | Dyspnea, bronchitis, rhinopharyngeal symptoms, asthma                                                                                                                          | ↔ (exposed versus unexposed)                                                                                                                                                                                 |
|                                                                                                                                                                                                                                                                                               |                                                                                                                                                                            | Abnormal pulmonary radiograph                                                                                                                                                  | ↑ (men; soft versus unexposed)<br>↔ (women)                                                                                                                                                                  |
| <b>Nemery et al. 1992</b><br><br>Cross-sectional; 194 workers (28 females, 166 males, range of mean ages 25.4–32.8 years; employment duration not reported) from the diamond polishing industry and 59 unexposed workers (13 females, 46 males, range of mean ages 21.1–28.2 years) (Belgium) | Current air concentration, mean, mg Co/m <sup>3</sup> :<br>Low: 0.0053<br>High: 0.0151<br><br>Current urine cobalt level, mean, µg/g creatinine:<br>Low: 7.0<br>High: 20.5 | Respiratory symptoms<br>Upper airway irritation, cough, phlegm<br><br>Dyspnea, wheezing<br><br>Lung function<br>FVC, FEV <sub>1</sub> , MMEF, PEF<br><br>FEV <sub>1</sub> /FVC | ↑ (high exposure versus referents)<br>↔ (low versus referents)<br><br>↔ (workers versus referents)<br><br>↓ (high exposure versus referents)<br>↔ (low versus referents)<br><br>↔ (workers versus referents) |
| <b>Rehfishch et al. 2012</b><br><br>Cohort; 582 workers (362 men, 220 women) from a hard metal plant; employed at least 1 year with at least two sets of spirometry data (Sweden)                                                                                                             | Exposure categories (job-exposure matrix), mg Co/m <sup>3</sup> :<br>0: Unexposed<br>1: <0.00099<br>2: >0.001–<0.049<br>3: >0.05                                           | Change in lung function over time<br>FVC, FEV <sub>1</sub> , FEV <sub>1</sub> /FVC                                                                                             | ↔ (smokers)<br>↔ (nonsmokers)                                                                                                                                                                                |

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**Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects**

| Reference, study type, and population                                                                                                                                                                                                                         | Exposure concentration                                                                           | Outcome evaluated                                                                   | Result                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Roto 1980</b>                                                                                                                                                                                                                                              | Historical concentrations, mg Co/m <sup>3</sup> :                                                | Risk of asthma (case-control analysis)                                              | ↑ (exposed versus unexposed)                                                      |
| Cross-sectional with nested case-control; 147 workers from a cobalt plant and 60 unexposed workers (duration of employment not reported); subjects included 21 clinically diagnosed cases of asthma and 55 randomly selected workers without asthma (Finland) | Cobalt roasting building: Cobalt dust: 8–19<br>Soluble cobalt: 0.05–0.1                          | Bronchial hyperreactivity <sup>e</sup> (cross-sectional analysis)                   | ↔ (exposed versus unexposed)                                                      |
|                                                                                                                                                                                                                                                               | Cobalt packing area in leaching building: Cobalt dust: 0.01–0.1                                  |                                                                                     |                                                                                   |
| <b>Roto 1980</b>                                                                                                                                                                                                                                              | Historical concentrations, mg Co/m <sup>3</sup> :                                                | Symptoms of chronic bronchitis (chronic cough, phlegm, wheezing)                    | ↔ (workers versus referents, adjusted for smoking)                                |
| Cross-sectional; 224 male cobalt workers (mean age 33.6 years; mean of 7.3 years of employment) and 151 unexposed male referents (mean age 33.7 years) (Finland)                                                                                              | Cobalt roasting building: Cobalt dust: 8–19<br>Soluble cobalt: 0.05–0.1                          | Lung function<br>FVC, FEV <sub>1</sub> , FEV (%), Vmax                              | ↔ (workers versus referents)                                                      |
|                                                                                                                                                                                                                                                               | Cobalt packing area in leaching building: Cobalt dust: 0.01–0.1                                  |                                                                                     |                                                                                   |
| <b>Swennen et al. 1993</b>                                                                                                                                                                                                                                    | Current air concentration, mean: 0.125 mg Co/m <sup>3</sup>                                      | Respiratory symptoms<br>Dyspnea, wheezing (self-reported)                           | ↑ (workers versus referents; smokers)<br>↔ (workers versus referents; nonsmokers) |
| Cross-sectional; 82 male workers (mean age 33 years; mean employment duration 8 years) from a cobalt refinery and 82 referents (mean age 38 years) (Belgium)                                                                                                  | Current pre-shift urine cobalt level, median (µg/g creatinine):<br>Monday: 22.9<br>Friday: 44.9  | Cough or sputum in cold season, rhinitis, hay fever                                 | ↔ (workers versus referents)                                                      |
|                                                                                                                                                                                                                                                               | Current post-shift urine cobalt level, median (µg/g creatinine):<br>Monday: 44.1<br>Friday: 72.4 | Lung function<br>FVC, FEV <sub>1</sub> , PEF, MEF <sub>50</sub> , MEF <sub>75</sub> | ↔ (workers versus referents)                                                      |

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**Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Respiratory Effects**

| Reference, study type, and population                                                                                                                                            | Exposure concentration                                                                                                                                                                       | Outcome evaluated                                              | Result                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------|
| <b>Verougstraete et al. 2004</b>                                                                                                                                                 | Historical post-shift urine cobalt concentrations in workers from different job areas; $\mu\text{g/g}$ creatinine <sup>f</sup>                                                               | Change in lung function (1988–2001)<br>FVC<br>FEV <sub>1</sub> | $\leftrightarrow$<br>$\downarrow$ (smokers only)                  |
| Prospective cohort; 122 workers (mean age 43.7 years; mean employment duration 205.8 months) from a cobalt plant (Belgium)                                                       | <div>Job area</div> <div>Dry Wet Mixed</div> <div>1992 275 20 35</div> <div>1997 150 25 20</div> <div>2001 65 15 10</div>                                                                    |                                                                |                                                                   |
| <b>Walters et al. 2012</b>                                                                                                                                                       | Current urine cobalt concentration, mean: 0.6 $\mu\text{g/g}$ creatinine (0.6 $\mu\text{g/L}$ )                                                                                              | Occupational rhinitis<br>Occupational asthma                   | $\leftrightarrow$ (urinary cobalt)<br>$\uparrow$ (urinary cobalt) |
| Cross-sectional; 62 metal workers (toolmakers/grinders; 54 males, 8 females) involved in the manufacturing of precision engineering parts (mean age 39.5 years) (United Kingdom) | By diagnosis:<br>Occupational asthma: 1.6 $\mu\text{g/L}$<br>Non-occupational asthma: 0.4 $\mu\text{g/L}$<br>Occupational rhinitis: 1.2 $\mu\text{g/L}$<br>Asymptomatic: 0.4 $\mu\text{g/L}$ |                                                                |                                                                   |

<sup>a</sup>FEV<sub>1</sub>/FVC reported as FEV<sub>1%</sub> by the study authors.

<sup>b</sup>Restrictive syndrome is defined as a normal FEV<sub>1</sub>/VC ratio with VC and TLC <80% of predicted values.

<sup>c</sup>Obstructive syndrome is defined as normal VC with FEV<sub>1</sub> or MMEF <80% of predicted values.

<sup>d</sup>Bronchial reactivity defined as a change of  $\geq 10\%$  in FEV<sub>1</sub> and/or  $\geq 15\%$  in FEF<sub>75–75</sub> after a challenge (exposure to acetylcholine at 100 mg/L via nebulizer for 3 minutes).

<sup>e</sup>Bronchial reactivity defined as decrease of  $\geq 15\%$  in FEV<sub>1</sub> after a challenge (exposure to 1% methacholine vapor via nebulizer; 1, 5, and 15 inhalations at intervals of 2 minutes).

<sup>f</sup>Estimated from Figure 1 in Verougstraete et al. (2004) using WebPlotDigitizer.

$\uparrow$  = association;  $\downarrow$  = inverse association;  $\leftrightarrow$  = no association; FEF<sub>75/50/25</sub> = forced expiratory flow at 75, 50, and 25% of the vital capacity, respectively; FEV<sub>1</sub> = forced expiratory volume in 1 second; FEV % = (FEV<sub>1</sub>/FVC)  $\times$  100; FuaCO = alveolar capillary fractional uptake; FVC = forced vital capacity; DLCO = diffusing capacity of the lungs for carbon monoxide; DLCO/VA = specific diffusion capacity; MEF<sub>75/50/25</sub> = flow rate at 75, 50, and 25% of the vital capacity, respectively; MMEF = maximal mid expiratory flow; PEF = mean peak expiratory flow rate; T = tertile; TCO<sub>ss</sub> = total steady-state carbon monoxide uptake; TLC = total lung capacity; TWA = time-weighted average; VA = alveolar volume; VC = vital capacity; Vmax = reduction in flow

Impaired lung function and increased complaints of respiratory symptoms were frequent findings in occupational cohorts of workers chronically exposed to cobalt. Decreased lung function, specifically a 2.7% decrease in forced expiratory volume in 1 second (FEV<sub>1</sub>), was observed in 42 cobalt metal workers exposed to mean cobalt metal exposure levels of 0.126 mg Co/m<sup>3</sup> over the past 3 years, compared to unexposed referents (Kusaka et al. 1986a). Similarly, Belgian diamond-cobalt tool manufacturers



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exposed to cobalt concentrations ranging from 0.0152 to 0.1355 mg Co/m<sup>3</sup> showed decreased FVC, FEV<sub>1</sub>, and peak expiratory flow (PEF), compared to unexposed referents (Gennart and Lauwerys 1990). In workers who smoked only, decreased expiratory flow at 75% vital capacity was also observed compared to unexposed referents (nonsmokers). While cumulative exposure estimates were not determined, analysis showed that lung function parameters were negatively correlated with duration of employment. Findings were not correlated with current urinary cobalt levels. Verougstraete et al. (2004) also reported an association between cobalt exposure and a mild, but measurable, excess decline in FEV<sub>1</sub> over a 13-year follow-up period (1988–2001) in a cohort of workers from a Belgian cobalt production plant; however, this association was only observed in workers who smoked. No associations between cobalt exposure and decrements in FVC were observed. The highest airborne cobalt levels were measured in the early 1990s (1 mg Co/m<sup>3</sup>) and declined thereafter (to an unspecified level). Mean urinary cobalt levels for different job areas ranged from approximately 35–275 µg/g creatinine in 1992, falling to approximately 10–65 µg/g creatinine in 2001 (Verougstraete et al. 2004). Impaired respiratory function was also reported in workers exposed to cobalt concentrations ranging from 0.01 to 0.1 mg Co/m<sup>3</sup>, including decreased FVC, FEV<sub>1</sub>, and maximal expiratory flow at 25 and 50% vital capacity (Linna et al. 2003). Reported respiratory symptoms in workers included phlegm, cough with wheezing, dyspnea with wheezing, and breathlessness on exertion. Calculated median cumulative cobalt exposure levels were 0.6 mg-year Co /m<sup>3</sup>. No associations between cobalt exposure and changes in lung function over time, as measured by FVC, FEV<sub>1</sub>, or FEV<sub>1</sub>/FVC, were observed in workers employed in a Swedish hard metal plant for at least 1 year with at least two sets of spirometry data (Rehfisch et al. 2012). Mean exposure estimates were not reported; however, low-, medium-, and high-exposure groups (based on a job-exposure matrix) were defined as <0.00099, >0.001–<0.049, and >0.05 mg Co/m<sup>3</sup>, respectively. However, a major limitation of this study was lack of a consistent latency between spirometry measurements and a limited number of measurements per study subject.

In a cross-sectional study from the diamond polishing industry, workers exposed to cobalt at a concentration of 0.0151 mg Co/m<sup>3</sup> showed decreases in several lung function parameters by approximately 5%, including FEV<sub>1</sub>, FVC, maximal mid expiratory flow (MMEF), and PEF, compared to unexposed referents; workers exposed to a mean lower concentration of 0.0053 mg Co/m<sup>3</sup> did not show impaired lung function (Nemery et al. 1992). The exposed workers also exhibited increased incidence of cough (11/91), wheezing (4/91), and upper airway irritation (40/91). Among the workers subjected to work-related exposure, upper airway effects were seen in 30% of controls, 26% of low-exposure individuals, and 43% of high-exposure individuals. Work-related cough was not observed in the control subjects but was observed in 4% of low-exposure individuals and 12% of high-exposure individuals.

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While the respiratory effects appeared at a greater rate in individuals who were exposed to higher concentrations of cobalt, 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, and 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, and control).

Additional cross-sectional studies reported associations between current estimates of cobalt exposure and lung function and/or respiratory symptoms. In Malaysian factory workers exposed to 8-hour cobalt concentrations ranging from 0.01 to 0.19 mg Co/m<sup>3</sup>, exposure to cobalt was associated with significant increases in chronic phlegm and decreases in FVC and FEV<sub>1</sub> (Hamzah et al. 2014). In Belgian cobalt refinery workers exposed to mean concentrations of 0.125 mg Co/m<sup>3</sup>, self-reported dyspnea and wheezing were increased in workers who smoked compared to unexposed referents who smoked; this effect was not observed in nonsmokers (Swennen et al. 1993). Lung function parameters in all workers were comparable to referents in this cohort. No changes in FVC, FEV<sub>1</sub>, or end respiratory flow (FEF) were observed in French hard metal workers exposed to cobalt dust concentrations of 0.030–0.272 mg Co/m<sup>3</sup> (Meyer-Bisch et al. 1989). However, decreased alveolar capillary fractional uptake of carbon monoxide and altered diffusing capacity (i.e., decreased steady-state carbon monoxide uptake) were observed along with increased incidence of self-reported cough and sputum in exposed workers, compared to unexposed workers. Women workers from the finishing work area (exposed to “hard” carbides) also showed increased bronchial reactivity, while male workers from the powder, presses, and forming work areas (exposed to “soft” carbides) showed increased incidence of abnormal pulmonary radiographs (Meyer-Bisch et al. 1989). In other cross-sectional studies, no associations between occupational exposure to cobalt and prevalence of respiratory symptoms, abnormal chest x-ray, or impaired lung function were reported at mean air concentrations ranging from 0.0017 to 19 mg Co/m<sup>3</sup> (Andersson et al. 2020; Deng et al. 1991; Roto 1980) or urinary concentrations of 0.6 µg/g creatinine (Walters et al. 2012). In some cases, measurements of lung function were improved in cobalt-exposed workers, compared to unexposed referents from blue-collar industries (Deng et al. 1991).

Findings of adverse lung effects from cohort and cross-sectional studies of cobalt-exposed workers are supported from case reports of lung disease and damage in cobalt-exposed workers. Demedts et al. (1984) reported five cases of “cobalt lung” in diamond polishers. Unlike hard metal workers, mineralogic

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analysis of lung tissue in these patients found that cobalt was not alloyed to carbides of hard metals, therefore concluding that cobalt was the only toxic agent. Cases of “cobalt lung” presented with various respiratory complaints (rhinitis, cough, chest tightness, dyspnea), impaired lung function (restrictive deficits), fibrosing alveolitis, mononuclear cell infiltrate, interalveolar desquamation, multinucleated giant cells, and/or centrilobular fibrosis. Cessation of exposure relieved subjective complaints and partially improved lung function. Cobalt exposure levels were not measured; however, the study authors noted that in some cases, workshops did not have adequate ventilation.

Evidence for an association between occupational cobalt exposure and increased risk of asthma is mixed. In retrospective cohorts, increased prevalence of asthma in workers was observed at exposure levels of cobalt ranging from 0.003 to 1.292 mg Co/m<sup>3</sup>; findings were associated with abnormal chest radiographs in some cases (Kusaka et al. 1986b; Linna et al. 2003). Walters et al. (2012) found that current urinary cobalt concentrations were significantly higher in a cross-sectional study of workers with probable or definite occupational asthma, compared to asymptomatic workers. However, no association was observed between estimated cumulative exposure and the prevalence of asthma diagnosis in a cohort of 72 hard metal workers employed for an average of 11 years (Andersson et al. 2020).

Sauni et al. (2010) conducted a review of cases of occupational asthma in cobalt plant workers in Finland from 1967 to 2003, where the mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m<sup>3</sup>. Until 1987, cobalt was being produced from pyrite ore concentrate, which led to co-exposures with irritant gases like sulfur dioxide and ammonia (known respiratory irritants) (Andersson et al. 2006; ATSDR 1998; Huber and Loving 1991). Starting in 1987, and in subsequent years, cobalt was instead predominantly produced using byproducts of the metallurgic industry as raw material, which eliminated the co-exposure to the irritant gases. After this switch in production method, the incidence of asthma decreased to only 1 case between 1987 and 2003 compared to 21 cases between 1967 and 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. In a small case-control study of 21 cases of asthma and 55 controls, the risk of asthma was increased in subjects with a work history of intermittent or regular employment in a cobalt plant with exposure to cobalt dust ranging from 0.01 to 19 mg Co/m<sup>3</sup> (depending on work area), compared to unexposed subjects (Roto 1980). Similar to Sauni et al. (2010), findings in this study are also confounded by co-exposure to irritant gases (ammonia, hydrogen sulfide, sulfur dioxide).

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Al-Abcha et al. (2021) reported a case-series of 35 work-related cases of asthma between 1988 and 2017 in the state of Michigan that were attributed to cobalt exposure, prompting industrial hygiene surveys of 21 workplaces and interviews of 498 exposed coworkers of asthma cases. Most workers were involved in the hard metal industry. Of these workplaces, six had exposure levels above the Michigan permissible exposure limit (PEL) of 0.05 mg Co/m<sup>3</sup> and five had cobalt air levels above the federal PEL of 0.1 mg Co/m<sup>3</sup>. Respiratory symptoms, including daily or weekly chest tightness, shortness of breath, wheezing or new onset of asthma since employment began, were reported in 11% of coworkers; however, reported symptoms were not associated with cobalt exposure levels (Al-Abcha et al. 2021). Other potential occupational exposures in these cases were not addressed. More convincing evidence for cobalt-induced asthma comes from review of 14 cases of occupational asthma in workers involved in grinding and polishing automotive engine valves containing cobalt between 1996 and 2005 (Walters et al. 2014). Nine of the cases had confirmed sensitization to cobalt chloride. A limited number of cases of occupational asthma associated with cobalt exposure have also been reported in diamond polishers, in which co-exposure to other substances in hard metal does not occur (Gheysens et al. 1985).

Animal studies have consistently observed respiratory effects following inhalation exposure in multiple species, consistent with findings in human studies. Findings show both dose- and duration-dependency, and toxicity differed between administered compounds.

As discussed in Section 2.2 (Death), acute lethality following exposure to high concentrations of cobalt or cobalt concentrations is often due to, and/or associated with, severe pulmonary effects (Palmes et al. 1959; Viegas et al. 2022a). Compounds showing increased “inflammatory” reactivity in the lungs, such as cobalt hydroxide, metal powder, and oxide, were more acutely toxic; however, concentrations associated with inflammatory changes for these compounds were not reported (Viegas et al. 2022a). Following a 30-minute exposure to cobalt hydrocarbonyl (plus oxide/carbonate decomposition products), severe pulmonary irritation was listed as the cause of death for rats that died at concentrations  $\geq 78$  mg Co/m<sup>3</sup> (Palmes et al. 1959). Rats that survived exhibited labored breathing and disturbed respiration. Concentration-dependent increases in the incidence of pulmonary edema and gross lung damage (hemorrhage, edema, consolidation, congestion, pleuritis, bronchiectasis, emphysema, or atelectasis) were observed at  $\geq 83$  mg Co/m<sup>3</sup> (Palmes et al. 1959).

At sublethal concentrations, evidence of inflammatory reactivity in the lungs following acute-duration exposure was detected as increased neutrophil numbers in bronchoalveolar lavage fluid (BALF) collected from rats 1 day after being exposed to concentrations  $\geq 2.2$  mg Co/m<sup>3</sup> as cobalt sulfate for 4 hours (Viegas

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et al. 2022a, 2022b). BALF cell viability was also decreased at 4–16 hours after exposure to  $\geq 2.1$  mg Co/m<sup>3</sup>. No histopathological lesions were noted immediately postexposure, but squamous cell metaplasia of the epiglottis in the larynx was observed in almost all rats exposed to 6.7 mg Co/m<sup>3</sup> and evaluated 16 days postexposure (Viegas et al. 2022a). Increased BALF neutrophils, as well as lactate dehydrogenase (LDH) levels, were also observed in rats intermittently exposed to cobalt tetroxide at concentrations  $\geq 33.87$  mg Co/m<sup>3</sup> for 14 days (Burzlaff et al. 2022a). Observed inflammatory changes in the lungs of rats exposed to poorly soluble cobalt tetroxide resembled those associated with exposure to inert dust. No histopathological changes were noted at concentrations up to 160.90 mg Co/m<sup>3</sup>.

Widespread respiratory damage was consistently observed in rats and mice following intermittent intermediate- or chronic-duration inhalation exposure to cobalt sulfate; the larynx was the most sensitive location in the respiratory tract. Focal squamous metaplasia with inflammatory changes in the larynx, along with elevated BALF neutrophils and LDH levels, were observed in Wistar rats exposed to 0.46 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a, 2022b). Various histopathological lesions were observed throughout the respiratory tract epithelium (nasal turbinates, larynx, trachea, and bronchioles) in F344/N rats exposed to 19 mg Co/m<sup>3</sup> and B6C3F1 mice exposed to concentrations  $\geq 1.9$  mg Co/m<sup>3</sup> for 16 days, including inflammation, necrosis, hyperplasia, metaplasia, acanthosis, fibrosis, histiocytic infiltration, and/or degeneration (NTP 1991). Increased lung weight was observed in the mice at 19 mg Co/m<sup>3</sup>. With longer exposure, respiratory tract lesions were observed at all tested concentrations ( $\geq 0.1$  mg Co/m<sup>3</sup>), including squamous metaplasia of the larynx in rats exposed for 13 or 104 weeks, histiocytic infiltrates in the lung in male mice exposed for 13 weeks, and hyperplasia and metaplasia of various upper and lower respiratory tract tissues, pulmonary fibrosis, and inflammatory changes in lungs in mice exposed for 104 weeks (Behl et al. 2015; Bucher et al. 1990, 1999; NTP 1991, 1998). In rats and mice exposed for 13 weeks and rats exposed for 104 weeks, findings became widespread throughout the respiratory system at higher concentrations, consistent with the 16-day studies and the findings at the low concentration in the chronic-duration mouse study (e.g., elevated lung weights, histiocytic infiltrates of the lung, chronic inflammation of the larynx and lung, alveolar epithelium hyperplasia, bronchiolar epithelium regeneration, pulmonary fibrosis, olfactory epithelium degeneration, and respiratory epithelium squamous hyperplasia/metaplasia in the nose).

As seen in studies with cobalt sulfate, intermediate- and chronic-duration exposure to cobalt metal consistently produced adverse respiratory effects in multiple species. In rats and mice, mild lesions in the respiratory tract were observed after exposure for 16–17 days at all tested concentrations ( $\geq 2.5$  mg Co/m<sup>3</sup>) in both rats and mice (NTP 2014). Findings included minimal cytoplasmic vacuolization of bronchiolar

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epithelium and minimal-to-mild nasal lesions (necrosis and/or atrophy of olfactory epithelium; vacuolization of respiratory epithelium) in both species with histiocytic infiltrates in the lungs of male mice. Elevated absolute and/or relative lung weights were observed in female rats exposed to  $\geq 10$  mg Co/m<sup>3</sup> for 16 days and male and female mice exposed to  $\geq 5$  mg Co/m<sup>3</sup> for 16 days (NTP 2014). At  $\geq 20$  mg Co/m<sup>3</sup>, rats showed abnormal breathing with lung hemorrhage in males and nasal respiratory epithelium necrosis in females. Mice exposed to  $\geq 20$  mg Co/m<sup>3</sup> showed pulmonary fibrosis, olfactory epithelial necrosis, respiratory epithelial metaplasia, and alveolar/bronchiolar karyomegaly. Lesions were observed in both rats and mice following exposure for 14 weeks at all tested concentrations ( $\geq 0.625$  mg Co/m<sup>3</sup>), including chronic active inflammation in lung, pulmonary alveolar proteinosis, and increased relative lung weight in rats and squamous metaplasia of the larynx, cytoplasmic vacuolization of bronchiole epithelium, and alveolar histiocytic cellular infiltration in mice (NTP 2014). Pulmonary hemorrhage was observed in mice exposed to  $\geq 5$  mg Co/m<sup>3</sup> for 14 weeks (NTP 2014). Similarly, lesions were observed in both rats and mice following exposure for 105 weeks to  $\geq 1.25$  mg Co/m<sup>3</sup> (Behl et al. 2015; NTP 2014). Rats showed lesions in the lungs (hyperplasia and cytoplasmic vacuolization of alveolar/bronchiolar epithelium), nasal turbinate (atrophy), nasal olfactory epithelium (atrophy, hyperplasia, and metaplasia), and nasal respiratory epithelium (cytoplasmic vacuolization and squamous metaplasia). Mice similarly showed lesions of the lungs (alveolar epithelium hyperplasia and proteinosis, bronchiole epithelium hyperplasia) and nose (hyperplasia, metaplasia, necrosis, and atrophy of the olfactory epithelium and nasal turbinate). In mice, elevated lung weights were only observed at higher concentrations,  $\geq 2.5$  mg Co/m<sup>3</sup> in males and  $\geq 5$  mg Co/m<sup>3</sup> in females (NTP 2014). In other species, a 3-month exposure to 0.1 mg Co/m<sup>3</sup> in pigs decreased respiratory compliance, a metric of mechanical ventilation (Kerfoot 1974). A 17-week intermittent exposure in male rabbits to 0.4 mg Co/m<sup>3</sup> caused inflammation in lungs and accumulation of macrophages; at 2 mg Co/m<sup>3</sup>, severe inflammation and edema of the lower lobes of the lung were noted (Johansson et al. 1987).

Findings following repeated inhalation exposure to other forms of cobalt are limited. Inflammatory lesions in the lung and increased cellularity BALF, with decreased percent macrophages and increased percent monocytes, were observed in male rabbits after intermittent exposure to 0.6 mg Co/m<sup>3</sup> as cobalt chloride for 4 months (Johansson et al. 1992). No adverse lung effects were observed in male rabbits similarly exposed to 0.5 mg Co/m<sup>3</sup> as cobalt chloride for 4 months (Johansson et al. 1991). Increased LDH and neutrophil count in BALF and alveolar lipoproteinosis were observed in Wistar rats intermittently exposed to cobalt tetroxide at concentrations  $\geq 15.05$  mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a). Moderate interstitial fibrosis and interstitial inflammatory cell infiltration were also observed at 59.31 mg Co/m<sup>3</sup> (Burzlaff et al. 2022a). Lifetime intermittent exposure to cobalt oxide at 7.9 mg Co/m<sup>3</sup>

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caused lung inflammation and emphysema in male ENG:ELA hamsters (Wehner et al. 1977). The “most prominent” finding in the lungs in male albino rats and guinea pigs (unspecified strain) exposed to 9 mg Co/m<sup>3</sup> as cobalt hydrocarbonyl (plus oxide/carbonate decomposition products) intermittently for 3 months was a transient increase in particle-laden macrophages (Palmes et al. 1959), indicative of active clearance of inhaled particles. Palmes et al. (1959) also reported transient evidence of moderate interstitial and peribronchial fibrosis, mild emphysema, and moderate peribronchial lymphoid hyperplasia in exposed animals; however, it is unclear if these findings were observed in both species and at what incidence; therefore, a NOAEL/LOAEL determination could not be made for lung effects from this study.

No studies examined respiratory toxicity in humans following oral exposure to cobalt. In oral studies in rats, no changes in lung weight or histology were observed following exposure to cobalt chloride at a dose of 12.5 mg Co/kg/day for 7 day (Shrivastava et al. 2010), cobalt chloride at doses up to 7.44 mg Co/kg/day for 90 days (Danzeisen et al. 2020a), cobalt chloride at doses up to 18 mg Co/kg/day for 4 months (Holly 1955) or 16.5 mg/kg/day for 13 weeks (Domingo et al. 1984), or cobalt tetroxide at doses up to 734 mg Co/kg/day for 90 days (Danzeisen et al. 2020a).

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

### 2.5 CARDIOVASCULAR

A few studies examined cardiovascular effects in humans after occupational inhalation exposure to cobalt (Table 2-5). These studies provided limited and contradictory evidence of cardiovascular toxicity following inhalation exposure to cobalt. Using Doppler analysis, echocardiogram, and electrocardiogram (ECG), Lantin et al. (2013) found no association between urinary cobalt levels or estimated cumulative cobalt exposures and dilated cardiomyopathy (i.e., increased left ventricular volume) in a study of 256 male cobalt refinery workers in Belgium exposed to 0.001–0.108 mg Co/m<sup>3</sup>. In fact, the echocardiogram showed an association between increased urinary cobalt and decreased left ventricle volume. The only other observed association was a positive association between urinary cobalt and heart rate (Lantin et al. 2013). In a study of Finnish factory workers and a 6-year follow-up, no differences in ECG findings, heart rate, or blood pressure were associated with historical exposure to concentrations ranging from 0.01 to 1.0 mg Co/m<sup>3</sup> (Linna et al. 2004, 2020). At the initial evaluation, exposed workers did show significant changes in left ventricular relaxation and filling on the echocardiogram, indicating altered diastole (Linna et al. 2004). However, no abnormalities were observed in the echocardiogram in

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workers at the 6-year follow-up (Linna et al. 2020). Additionally, at follow-up, prevalences of heart disease, hypertension, and stroke were similar in exposed and unexposed workers (Linna et al. 2020).

**Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cardiovascular Effects**

| Reference, study type, and population                                                                                                                                                                                                | Exposure concentration                                                                          | Outcome evaluated          | Result                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------|------------------------------|
| <b>Lantin et al. 2013</b><br><br>Cohort with cross-sectional analysis; 256 male workers (median age 46 years; median employment 12.42 years), including 237 active workers and 19 retired workers from the cobalt industry (Belgium) | Measured air concentration (2007), range: 0.001–0.108 mg Co/m <sup>3</sup>                      | Doppler                    | ↔ (current, cumulative)      |
|                                                                                                                                                                                                                                      |                                                                                                 | ECG                        |                              |
|                                                                                                                                                                                                                                      | Current urine cobalt levels, median (µg/g creatinine):<br>Day of ECG: 3.90<br>Day of ECHO: 3.95 | Heart rate                 | ↑ (current urine)            |
|                                                                                                                                                                                                                                      |                                                                                                 | ECHO                       |                              |
|                                                                                                                                                                                                                                      | Cumulative exposure (IEI), median (µg/g creatinine x years):<br>ECG: 106.72<br>ECHO: 107.25     | LVIDd                      | ↓ (current urine)            |
|                                                                                                                                                                                                                                      |                                                                                                 | LVIDs                      | ↓ (current urine)            |
| <b>Linna et al. 2004</b><br><br>Cohort; 203 exposed male workers (median age 45 years; median employment 20 years) from the cobalt industry and 94 unexposed males (median age 44 years; median employment 25 years) (Finland)       | Historical exposure levels, range: 0.01–1.0 mg Co/m <sup>3</sup>                                | LV mass                    | ↓ (current urine)            |
|                                                                                                                                                                                                                                      |                                                                                                 |                            |                              |
|                                                                                                                                                                                                                                      | Cumulative exposure, median: 0.18 mg Co-year/m <sup>3</sup>                                     | Abnormal ECHO <sup>a</sup> | ↑ (workers versus referents) |
|                                                                                                                                                                                                                                      |                                                                                                 | ECG                        | ↔ (workers versus referents) |
|                                                                                                                                                                                                                                      |                                                                                                 | Blood pressure             | ↔ (workers versus referents) |
|                                                                                                                                                                                                                                      |                                                                                                 | Heart rate                 | ↔ (workers versus referents) |



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**Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cardiovascular Effects**

| Reference, study type, and population                                                                                                                                                         | Exposure concentration                                           | Outcome evaluated                                     | Result                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------|------------------------------|
| <b>Linna et al. 2020</b>                                                                                                                                                                      | Historical exposure levels, range: 0.01–1.0 mg Co/m <sup>3</sup> | ECHO                                                  | ↔ (workers versus referents) |
| Cohort; 93 exposed male workers (median age 56 years; median employment 31 years) from the cobalt industry and 49 unexposed males (median age 56 years; median employment 32 years) (Finland) | Cumulative exposure, median: 0.55 mg Co-years                    | ECG                                                   | ↔ (workers versus referents) |
|                                                                                                                                                                                               |                                                                  | Blood pressure                                        | ↔ (workers versus referents) |
|                                                                                                                                                                                               |                                                                  | Heart rate                                            | ↔ (workers versus referents) |
|                                                                                                                                                                                               |                                                                  | Prevalence of heart disease, hypertension, and stroke | ↔ (workers versus referents) |
|                                                                                                                                                                                               |                                                                  |                                                       |                              |
| <i>Follow-up to Linna et al. (2004)</i>                                                                                                                                                       |                                                                  |                                                       |                              |

<sup>a</sup>Increased left ventricular isovolumetric relaxation time and deceleration time of the velocity of the early rapid filling wave.

↑ = association; ↓ = inverse association; ↔ = no association; ECG = electrocardiogram; ECHO = echocardiogram; IEI = integrated exposure index; LV = left ventricle; LVIDd = left ventricular diameter at diastole; LVIDs = left ventricular diameter at systole

There is very limited evidence from animal studies suggesting altered cardiac function following inhalation exposure to cobalt. Intermittent exposure to cobalt metal at 0.1 mg Co/m<sup>3</sup> for 3 months in pigs caused a 14% increase in heart rate, a 38% decrease in QRS amplitude, and ECG abnormalities that may reflect ventricular impairment (Kerfoot 1974). In rodents, no exposure-related changes in heart weight or histology were observed in F344/N rats or B6C3F1 mice following exposure to cobalt sulfate at concentrations up to 75.7 mg Co/m<sup>3</sup> for 16 days, 11.4 mg Co/m<sup>3</sup> for 13 weeks, or 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et al. 1990, 1999; NTP 1991, 1998) or in F344/N rats or B6C3F1 mice following exposure to cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively, or 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; NTP 2014). No exposure-related histopathological changes in the heart were observed in Wistar rats intermittently exposed to cobalt tetraoxide at concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a).

As discussed in Section 2.2 (Death), an increase in lethal cardiomyopathy was observed in the mid-1960s in people who heavily and routinely consumed beer containing ethyl alcohol with cobalt sulfate added as a foam stabilizer (Alexander 1969, 1972; Bonenfant et al. 1969; Kesteloot et al. 1968; Morin et al. 1967, 1971; Sullivan et al. 1969). So-called “beer-cobalt cardiomyopathy” was observed in drinkers who

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consumed large volumes of beer daily (approximately 8–30 pints of beer each day), resulting in an average daily cobalt intake of 0.04–0.14 mg Co/kg/day (Alexander 1969, 1972; Morin et al. 1971, n=28). The cardiomyopathy was characterized by sinus tachycardia, left ventricular failure, cardiogenic shock, diminished myocardial compliance, absence of a myocardial response to exercise or catecholamine, enlarged heart, pericardial effusion, and extensive intracellular changes (changes in the myofibers, mitochondria, glycogen, and lipids). The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy, but the onset of beer-cobalt cardiomyopathy was very abrupt, suggesting that cobalt may have an etiological contribution. However, due to confounding by potential cardiac damage from alcohol abuse combined with concurrent protein-poor diets, the role of cobalt in cardiomyopathy is unclear. No exposure-related changes were found in echocardiograms of 10 volunteers given low-dose cobalt supplements (mean dose of 0.013 mg Co/kg/day) for 3 months (Tvermoes et al. 2014).

Animal studies indicate that acute-duration oral exposure to cobalt can alter cardiovascular function and cause structural heart damage in rats; however, observed effects were sometimes inconsistent between studies. Elevated systolic (45%), diastolic (60%), and mean arterial (50%) blood pressure were observed in Wistar rats exposed to 35 mg Co/kg/day as cobalt chloride in drinking water for 2 weeks (Ajibade et al. 2017). In contrast, decreased systolic (17%), diastolic (24%), and mean arterial (21%) blood pressure were observed in Wistar rats exposed to 10 mg Co/kg/day as cobalt chloride in drinking water for 7 days (Akinrinde et al. 2016b). Wistar rats similarly exposed to 10 mg Co/kg/day for 2 weeks showed a 12% decrease in systolic blood pressure; no changes were observed in diastolic or mean arterial blood pressure or ECG measurements (Akinrinde et al. 2016a). All three studies qualitatively reported histopathological changes in cardiac tissue, including inflammatory changes (cellular infiltration, cardiac cell swelling) and/or areas of myocardial infarction with damage to coronary blood vessels. However, no changes in heart weight or histology were observed in Sprague-Dawley rats exposed to 12.5 mg Co/kg/day for 7 days as cobalt chloride via gavage (Shrivastava et al. 2010). At higher doses (37 mg Co/kg/day as cobalt chloride), histopathological changes to cardiac muscle (atrophy and patchy degeneration of myofibers, loss of striation) as well as distension of interstitium were observed in Wistar rats exposed via gavage for 8 days (Oyagbemi et al. 2020). While there were no control groups included, Wistar rats exposed to a single gavage dose  $\geq 176.6$  mg Co/kg as cobalt fluoride or  $\geq 795$  mg Co/kg as cobalt oxide in an acute lethality study showed a proliferation of interstitial tissue, swollen muscle fibers, and focal degeneration in the cardiac tissues (Speijers et al. 1982).

Some intermediate-duration studies in rodents also reported altered cardiovascular function and/or structural heart damage; however, findings varied across administered compounds and, in some cases,

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were inconsistent across studies evaluating the same compound. Most adverse effects were observed in rodents exposed to cobalt sulfate. Exposure of Sprague-Dawley rats to 8.4 mg Co/kg/day as cobalt sulfate for 24 weeks via the diet resulted in impaired left ventricular systolic and diastolic functions (Haga et al. 1996). Dietary exposure to 8.4 mg Co/kg/day as cobalt sulfate for shorter durations (8 or 16 weeks) did not impair ventricular function or cardiac hemodynamics (Haga et al. 1996; Pehrsson et al. 1991). Daily exposures for 2 months to 26 mg Co/kg/day as cobalt sulfate via gavage resulted in degenerative heart lesions in Wistar rats, including degeneration and swelling in myocardial cells, decreased myofibrils, and ultrastructural mitochondrial damage (Grice et al. 1969). An oral exposure to 20 mg Co/kg/day for 5 weeks as cobalt sulfate in guinea pigs 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 microscopically. Lesions observed included pericarditis, vacuolar degeneration of the myocardium, thickened and edematous endocardium, and mural thrombi. Exposure also caused an increase in relative bradycardia, decrease in QRS voltage, and a significant increase in abnormal ECG findings (Mohiuddin et al. 1970).

A 3-week exposure to 22 mg Co/kg/day as cobalt chloride in male CFY rats resulted in cardiac damage, presenting as multifocal myocytolysis with myofibril degeneration, as well as decreased cardiac output and arterial blood pressure (Morvai et al. 1993). However, no histopathological changes in the heart were observed in Wistar rats exposed to 18 mg Co/kg/day as cobalt chloride via gavage for 4 months (Holly 1955). In Sprague-Dawley rats, no pathological changes were observed in the heart following drinking water exposure to 16.5 mg Co/kg/day as cobalt chloride for 3 months (Domingo et al. 1984) or gavage exposure to doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetroxide for 90 days (Danzeisen et al. 2020a).

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

### 2.6 GASTROINTESTINAL

No studies were identified that examined gastrointestinal effects in humans after inhalation exposure to cobalt. In laboratory animals, no exposure-related histopathological changes were observed in the esophagus, stomach, duodenum, ileum, jejunum, cecum, colon, or rectum of F344/N rats or B6C3F1 mice following intermittent inhalation exposure to cobalt sulfate at concentrations up to 75.7 mg Co/m<sup>3</sup> for 16 days, 11.4 mg Co/m<sup>3</sup> for 13 weeks, or 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et

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al. 1990, 1999; NTP 1991, 1998). Similarly, no exposure-related histopathological changes in the gastrointestinal tract were observed in F344/N rats or B6C3F1 mice following exposure to cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively, or 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; NTP 2014). No exposure-related histopathological changes in the esophagus or stomach were observed in Wistar rats intermittently exposed to cobalt tetroxide at concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a).

In studies evaluating cobalt chloride supplements in humans as a potential treatment for anemia or hyperthyroidism, doses of 0.36–0.57 mg Co/kg/day resulted in gastric intolerance in some patients, including nausea, vomiting, and constipation (Duckham and Lee 1976; Holly 1955; Paley et al. 1958). Some patients stopped treatment due to severity of effects.

There is limited evidence that acute-duration oral exposure to cobalt may result in altered gastrointestinal function and/or damage in animals. Decreased relative small intestine weight as well as qualitatively reported histopathological damage to the intestine, including significant depletion of absorptive epithelial cells, were observed in Wistar rats exposed to 10 mg Co/kg/day as cobalt chloride via drinking water for 7 days (Akinrinde et al. 2016c). Salami et al. (2023) found that exposure to ≥68 mg Co/kg/day as cobalt chloride via drinking water for 8 days increased cryptal depth in the small intestine and altered gut motility in Wistar rats, resulting in increased gastric emptying time. Acute-duration oral exposure to cobalt chloride at 37 mg Co/kg/day also altered the overall composition of the gut microbiota in Sprague-Dawley rats; changes were predominantly a relative increase in bacteria from the Verrucomicrobia phylum (Richardson et al. 2018). However, no specific genus within the phylum differed significantly from control. Of the 42 tested genera, only *Allobaculum* from the phylum *Erysipelotrichaceae* was increased significantly. However, the biological adversity of altered composition of the gut microbiota is unknown.

In intermediate-duration oral studies, no histopathological changes in the gastrointestinal system were observed in Sprague-Dawley rats exposed to 16.5 mg Co/kg/day as cobalt chloride in drinking water for 3 months (Domingo et al. 1984), in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetroxide for 90 days (Danzeisen et al. 2020a), or in Wistar rats exposed to 18 mg Co/kg/day via gavage for 4 months (Holly 1955).

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

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## 2.7 HEMATOLOGICAL

Occupational studies evaluating hematological effects in humans from inhalation exposure to cobalt have reported mixed findings (Table 2-6). In a cross-sectional study, mild decreases in red blood cells, hemoglobin, and hematocrit levels and increased total white blood cell counts were observed in 82 refinery workers exposed to 0.125 mg Co/m<sup>3</sup>, compared to unexposed referents (Swennen et al. 1993). Other cross-sectional studies in cobalt production or hard metal industries did not find consistent associations between measures of cobalt exposure and red or white blood cell parameters (Hedbrant et al. 2022; Lantin et al. 2011). Andersson et al. (2021) reported some associations between cobalt exposure and alterations in coagulation parameters in a cross-sectional study of 72 workers from the hard metal industry in Sweden. The study authors proposed that observed alterations may be a risk for cardiovascular disease. Positive associations were observed between respirable cobalt dust levels and two of five measures of coagulation (coagulation factor VIII and von Willebrand factor); these factors were not associated with cobalt levels in the blood or urine. A slight inverse association was observed between urinary cobalt levels and serum fibrinogen levels; no associations were observed between fibrinogen levels and cobalt dust levels or cobalt blood levels. No associations were observed between measures of cobalt exposure and other biomarkers of coagulation (plasminogen activator inhibitor-1, D-dimer).

**Table 2-6. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Hematological Effects**

| Reference, study type, and population                                                                                                                                    | Exposure concentration                                                                                                                         | Outcome evaluated                 | Result                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------|
| <b>Andersson et al. 2021</b><br><br>Cross-sectional; 72 workers (9 females, 63 males; mean age 42 years; mean employment 11 years) from the hard metal industry (Sweden) | Current 8-hour TWA, median: 0.0023 mg Co/m <sup>3</sup>                                                                                        | Coagulation factor VIII           | ↑ (high versus low stationary: inhalable, total, respirable)<br>↔ (blood, urine) |
|                                                                                                                                                                          | Stationary cobalt measurements:<br>Inhalable cobalt, mg Co/m <sup>3</sup> :<br>Low: ≤0.0001500<br>Mid: 0.0001501–0.0004700<br>High: ≥0.0004701 | von Willebrand factor             | ↑ (high versus low stationary: respirable)<br>↔ (blood, urine)                   |
|                                                                                                                                                                          | Total dust cobalt, mg Co/m <sup>3</sup> :<br>Low: ≤0.0001200<br>Mid: 0.0001201–0.0004100<br>High: ≥0.0004101                                   | Fibrinogen                        | ↓ (high versus low, urine)<br>↔ (air, blood)                                     |
|                                                                                                                                                                          | Respirable dust cobalt, mg Co/m <sup>3</sup> :<br>Low: ≤0.0000594                                                                              | Plasminogen activator inhibitor-1 | ↔ (air, blood, urine)                                                            |

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**Table 2-6. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Hematological Effects**

| Reference, study type, and population                                                                                                                                                                                                               | Exposure concentration                                                                                                                                                                       | Outcome evaluated | Result                                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------------------|
|                                                                                                                                                                                                                                                     | Mid: 0.0000595–0.0000665<br>High: $\geq 0.0000666$                                                                                                                                           | D-dimer           | $\leftrightarrow$ (air, blood, urine)                             |
|                                                                                                                                                                                                                                                     | Current cobalt concentrations,<br>Blood, nmol/L:<br>Low: $\leq 5.20$<br>Mid: 5.21–8.00<br>High: $\geq 8.21$<br>Urine, nmol/L:<br>Low: $\leq 25.56$<br>Mid: 25.57–53.67<br>High: $\geq 53.68$ |                   |                                                                   |
|                                                                                                                                                                                                                                                     | Cumulative exposure, range:<br>0.21– $\leq 0.0870$ mg Co-year/m <sup>3</sup>                                                                                                                 |                   |                                                                   |
| <b>Hedbrant et al. 2022</b><br><br>Cross-sectional; 72 workers (9 females, 63 males; mean age 42.3 years; mean employment 10.4 years) from the hard metal industry (Sweden)                                                                         | Current 8-hour TWA, mean:<br>0.0034 mg Co/m <sup>3</sup> ; respirator adjusted: 0.0017 mg Co/m <sup>3</sup>                                                                                  | Total WBC         | $\leftrightarrow$ (air, blood, urine)                             |
|                                                                                                                                                                                                                                                     |                                                                                                                                                                                              | Neutrophils       | $\leftrightarrow$ (air, blood, urine)                             |
|                                                                                                                                                                                                                                                     | Current cobalt concentrations, mean:<br>AM blood: 6.5 nmol/L<br>PM blood: 7.1 nmol/L<br>AM urine: 34 nmol/L<br>PM urine: 44 nmol/L                                                           | Lymphocytes       | $\uparrow$ (AM urine)<br>$\leftrightarrow$ (PM urine, air, blood) |
|                                                                                                                                                                                                                                                     |                                                                                                                                                                                              | Monocytes         | $\leftrightarrow$ (air, blood, urine)                             |
|                                                                                                                                                                                                                                                     |                                                                                                                                                                                              | Eosinophils       | $\leftrightarrow$ (air, blood, urine)                             |
| <b>Lantin et al. 2011</b><br><br>Cross-sectional; 249 male workers (median age 46 years; median employment 12.27 years), including 230 active workers and 19 retired workers (~5 years of retirement) from a cobalt production department (Belgium) | Measured air concentration (2007), range:<br>0.001–0.108 mg Co/m <sup>3</sup>                                                                                                                | Hemoglobin        | $\leftrightarrow$ (current air, blood, urine; cumulative)         |
|                                                                                                                                                                                                                                                     | Current cobalt concentrations, median:<br>Blood: 0.10 $\mu\text{g}/100$ mL<br>Urine: 3.90 $\mu\text{g}/\text{g}$ creatinine                                                                  | Hematocrit        | $\leftrightarrow$ (current air, blood, urine; cumulative)         |
|                                                                                                                                                                                                                                                     | Cumulative exposure, median:<br>106.09 $\mu\text{g}/\text{g}$ creatinine x years                                                                                                             | WBC count         | $\leftrightarrow$ (current blood, urine; cumulative)              |

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**Table 2-6. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Hematological Effects**

| Reference, study type, and population                                                                                                                                                          | Exposure concentration                                                                           | Outcome evaluated | Result                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------|------------------------------|
| <b>Swennen et al. 1993</b><br><br>Cross-sectional; 82 male workers (mean age 33 years; mean employment duration 8 years) from a cobalt refinery and 82 referents (mean age 38 years) (Belgium) | Current air concentration, mean:<br>0.125 mg Co/m <sup>3</sup>                                   | RBC count         | ↓ (workers versus referents) |
|                                                                                                                                                                                                |                                                                                                  | Hemoglobin        | ↓ (workers versus referents) |
|                                                                                                                                                                                                | Current pre-shift urine cobalt level, median (µg/g creatinine):<br>Monday: 22.9<br>Friday: 44.9  | Hematocrit        | ↓ (workers versus referents) |
|                                                                                                                                                                                                |                                                                                                  | WBC count         | ↑ (workers versus referents) |
|                                                                                                                                                                                                | Current post-shift urine cobalt level, median (µg/g creatinine):<br>Monday: 44.1<br>Friday: 72.4 | Platelets         | ↔ (workers versus referents) |

↑ = association; ↓ = inverse association; ↔ = no association; RBC = red blood cell; TWA = time weighted average; WBC = white blood cell

In rodents, most inhalation studies reported increases in erythrocyte (red blood cell) count, hemoglobin, and/or hematocrit following intermediate-duration exposure. Mild increases in hemoglobin levels were observed in albino rats (10%) and guinea pigs of an unspecified strain (5%) following intermittent exposure to 9 mg Co/m<sup>3</sup> as cobalt hydrocarbonyl (plus oxide/carbonate decomposition products) for 3 months; no other red cell parameters were measured (Palmes et al. 1959). Polycythemia (as defined by the study authors) was reported in male and female F344/N rats exposed to  $\geq 1.11$  and  $\geq 3.78$  mg Co/m<sup>3</sup>, respectively, as cobalt sulfate for 13 weeks; hematological changes included 4–32% increases in erythrocyte count, hemoglobin, and hematocrit levels (Bucher et al. 1990; NTP 1991). Female rats also showed increased reticulocytes at 11.4 mg Co/m<sup>3</sup>. In B6C3F1 mice similarly exposed to cobalt sulfate, no consistent, exposure-related changes in red blood cell parameters were observed at concentrations up to 11.4 mg Co/m<sup>3</sup> (Bucher et al. 1990; NTP 1991). Increased erythrocyte parameters (hematocrit, hemoglobin, and/or erythrocyte count) were also observed following a 14-week exposure to cobalt metal at concentrations  $\geq 0.625$  mg Co/m<sup>3</sup> in male F344/N rats,  $\geq 1.25$  mg Co/m<sup>3</sup> in female F344/N rats, and 10 mg Co/m<sup>3</sup> in male and female B6C3F1 mice (NTP 2014). Reticulocytes were also elevated in male and female rats at 5 and  $\geq 2.5$  mg Co/m<sup>3</sup>, respectively. In a study with cobalt tetraoxide, no exposure-related hematological effects were observed in Wistar rats following intermittent exposure to concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a). No hematological effects were seen in pigs after a 3-month exposure to cobalt metal (Kerfoot 1974).

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Additional hematological effects were occasionally noted in rodents following intermediate-duration inhalation. In white cell differentials, the percent of monocytes was decreased and the percent of basophils was increased in albino rats exposed to 9 mg Co/m<sup>3</sup> as cobalt hydrocarbonyl (plus oxide/carbonate decomposition products) for 3 months (Palmes et al. 1959). In similarly exposed guinea pigs, the percent of lymphocytes was decreased and the percent of basophils was increased at 9 mg Co/m<sup>3</sup> (Palmes et al. 1959). Following intermittent exposure to cobalt sulfate for 13 weeks, decreased platelets were observed in male and female F344/N rats at  $\geq 3.78$  mg Co/m<sup>3</sup> and in female B6C3F1 mice at 11.4 mg Co/m<sup>3</sup> (NTP 1991). Similarly, following intermittent exposure to cobalt metal for 14 weeks, platelets were decreased in male and female F344/N rats at  $\geq 1.25$  mg Co/m<sup>3</sup> and in male B6C3F1 mice at 10 mg Co/m<sup>3</sup> (NTP 2014).

Due to observed effects on the hematological system, cobalt chloride has been evaluated as a potential treatment for anemia. To evaluate the effects, several studies have been conducted in small groups of both healthy and anemic individuals. Acute-duration oral exposure to 1 mg Co/kg/day for 7–14 days induced an average 14% increase in red blood cells in five healthy male volunteers, compared to pre-exposure levels (Davis and Fields 1958). In all five volunteers, red blood cells were outside the clinically normal range at the end of exposure, indicating polycythemia. Red blood cell counts returned to baseline levels (within medical norms) for all individuals 4–9 days after cessation of cobalt administration. This study also evaluated the effect of exposure to 0.8 mg Co/kg/day for 15 days in a single volunteer; no biologically relevant changes in red blood cell counts were observed, while another volunteer (one from the acute-duration study) exposed to 1 mg Co/kg/day for 15 days showed an 18% increase over pre-exposure values (Davis and Fields 1958). When the dose for the single volunteer at 0.8 mg Co/kg/day was increased to 1 mg Co/kg/day for the next 7 days, red blood cell counts increased by 5%. These data suggest that the no-adverse-effect level may be around 0.8 mg Co/kg/day for intermediate-duration oral studies; however, with only a single subject per dose group, this study is of insufficient study design to make that determination. Other volunteer studies did not find clinically adverse hematological effects following exposure to low-dose cobalt chloride supplements for 7–21 days at mean intakes of 0.03 mg Co/kg/day (Hoffmeister et al. 2018) or 31–91 days at mean intakes of 0.013 mg Co/kg/day (Finley et al. 2013; Tvermoes et al. 2014).

Additional studies conducted in anemic patients have evaluated potential therapeutic effects of cobalt. In a controlled human study designed to evaluate the potential for cobalt chloride supplementation to reverse pregnancy-related anemia, no changes in hematological parameters were observed in 20 pregnant women exposed to 0.57 mg Co/kg/day for at least 90 days prior to delivery, compared to 55 unexposed controls



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(Holly 1955). However, in anephric patients (with non-functioning kidneys) with anemia, cobalt chloride supplementation for  $\geq 12$  weeks to  $\geq 0.16$  mg Co/kg/day has been shown to increase hemoglobin levels, eliminating the need for transfusions in some patients (Duckham and Lee 1976; Taylor et al. 1977). Hematological endpoints from these studies are not included in the LSE table since NOAEL/LOAEL determinations could not be made (i.e., elevation of red blood cell parameters in anemic patients would be therapeutic); however, these studies were useful for evaluating potential adverse side effects in other systems (e.g., gastrointestinal, hepatic, etc.).

Acute-duration oral exposure to cobalt has also led to hematological effects in rats. An 8% increase in hematocrit levels was observed in Sprague-Dawley rats following a single gavage exposure to 161 mg Co/kg as cobalt chloride (Domingo and Llobet 1984). Elevated red blood cells (44%), hematocrit (7–25%), and hemoglobin (11–20%) were also increased in Sprague-Dawley rats exposed to cobalt chloride for 7 days at 12.5 mg Co/kg/day via gavage (Shrivastava et al. 2008, 2010). Differential lymphocyte counts also showed increased percentages of granulocytes and monocytes (Shrivastava et al. 2010). In pregnant rats, increased hematocrit (11%), hemoglobin (14%), and reticulocytes (100%) were observed following exposure to 24.8 mg CO/kg/day as cobalt chloride via gavage on GDs 6–15 (Paternain and Domingo 1988).

Intermediate-duration oral exposure to cobalt also consistently induced hematological effects in rats, predominantly related to polycythemia. The most sensitive studies were by Stanley et al. (1947) and Danzeisen et al. (2020a), which reported dose-related increases in red cell parameters in Sprague-Dawley rats following exposure to cobalt chloride at doses of  $\geq 2.5$  mg Co/kg/day via capsule for 8 weeks or  $\geq 2.48$  mg Co/kg/day via gavage for 90 days, respectively. Stanley et al. (1947) reported increases in erythrocyte numbers and hemoglobin levels starting in week 4 of exposure. By 8 weeks of exposure, respective increases in erythrocytes and hemoglobin levels, compared to control, were 15 and 23% at 2.5 mg Co/kg/day and 26 and 34% at 9.9 mg Co/kg/day; values at 0.6 mg Co/kg/day were comparable to control (Stanley et al. 1947). In the study by Danzeisen et al. (2020a), 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 were 11, 9, and 10% increases in hemoglobin, erythrocytes, and hematocrit, respectively. Parameters were further altered at 7.44 mg Co/kg/day, showing respective increases of 26, 20, and 24%. While the male rats were more sensitive and showed changes in hematological parameters at lower doses, female rats showed increases of 13 and 10% in hemoglobin and erythrocytes, respectively, at 7.44 mg Co/kg/day (Danzeisen et al. 2020a). In both sexes, erythroid hyperplasia in the bone marrow was observed at  $\geq 2.48$  mg Co/kg/day. A satellite group of animals exposed to 7.44 mg Co/kg/day for 90 days followed by a 28-day

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recovery period demonstrated reversibility of hematological and bone marrow effects in both male and female rats (Danzeisen et al. 2020a).

Danzeisen et al. (2020a) also examined effects of cobalt tetroxide on hematological parameters and found that a daily oral dose of 220 mg Co/kg/day increased hemoglobin, erythrocytes, and hematocrit by 10, 10, and 9%, respectively, in male rats; a mild 6% increase in hemoglobin level was observed in female rats. At the highest dose of 734 mg Co/kg/day, males and female rats showed an increase in hemoglobin (25% males and 16% females), erythrocytes (23% males and 13% females), and hematocrit (24% males and 14% females) (Danzeisen et al. 2020a). Bone marrow hyperplasia was not observed in rats following exposure to cobalt tetroxide.

In other intermediate-duration studies in rats, similar findings were observed. Increase in red blood cells and hemoglobin were observed in Wistar rats exposed to cobalt chloride at 18 Co/kg/day via gavage for 4 months (Holly 1955). Sprague-Dawley rats exposed to 16.5–20 mg Co/kg/day as cobalt chloride for 13–14 weeks in food or drinking water showed increases in red blood cells (41%), hemoglobin (28–31%), hematocrit (29%), and/or packed cell volume (56%) (Corrier et al. 1985; Domingo et al. 1984). Increased red blood cell count, hemoglobin, and hematocrit were also observed in rats (strain not specified) exposed to 10 mg Co/kg/day as cobalt chloride 5 days/week via gavage for 150 days (Murdock 1959). In contrast, a 30-day exposure to 13.8 mg Co/kg/day as cobalt chloride caused a 20% decrease in hemoglobin in male Sprague-Dawley rats (Chetty et al. 1979).

Another study briefly noted “mild and transient polycythemia” in rats exposed to 0.5 mg Co/kg/day as cobalt chloride via gavage for 7 months, with increased hemoglobin and red blood cell levels at 2.5 mg Co/kg/day (Krasovskii and Fridlyand 1971). However, due to the qualitative nature of the reporting, the magnitude (and therefore the biological significance) of the findings cannot be determined. Therefore, a NOAEL/LOAEL determination cannot be made for this study.

In mice, no exposure-related changes in hematocrit were observed in male CD-1 mice exposed to cobalt chloride in drinking water at doses of 58.9 mg Co/kg/day for 7–13 weeks or doses up to 72.1 mg Co/kg/day for 12 weeks (Pedigo et al. 1988). 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 140 mg Co/kg as cobalt chloride in the drinking water; however, findings are difficult to interpret due to concurrent decreases in water intake resulting in dehydration (Bryan and Bright 1973). When mice were similarly exposed for 3 or 13 weeks, these mild changes in serum protein

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levels were no longer observed (Bryan and Bright 1973). Due to minimal effects of unclear adversity, along with limited endpoints evaluated, this study was not included in the LSE table.

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

Acute-duration exposure to cobalt chloride by 10 subcutaneous injections in a controlled exposure human study (9-day gap between two blocks of five consecutive injections) of 18 mg Co/kg/day 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 ( $r=0.4$ ,  $p=0.01$ ). Domingo 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 subcutaneous injection study in Sprague-Dawley rats showed a 29% increase in erythrocyte number and a 38–39% increase in hemoglobin concentration following administration of cobalt chloride at doses of 0.6 or 2.5 mg Co/kg/day for 8 weeks (Stanley et al. 1947). Elevated levels were first observed after 4 weeks of exposure. At the highest dose, 9.9 mg Co/kg/day, slight increases of 8–11% were observed in erythrocyte number and hemoglobin by 2 weeks of exposure; however, all animals died prior to the 4-week analysis (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.

No exposure-related histopathological changes were observed in the skeletal bone of F344/N rats or B6C3F1 mice following intermittent inhalation exposure to cobalt sulfate at concentrations up to 75.7 mg Co/m<sup>3</sup> for 16 days, 11.4 mg Co/m<sup>3</sup> for 13 weeks, or 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et al. 1990, 1999; NTP 1991, 1998). Similarly, no exposure-related histopathological changes in the musculoskeletal system were observed in F344/N rats or B6C3F1 mice following exposure to cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively, or 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; NTP 2014). No exposure-related histopathological changes in the femur were observed

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in Wistar rats intermittently exposed to cobalt tetroxide at concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a).

No morphological changes were found in the skeletal muscle of Sprague-Dawley rats exposed to drinking water doses of 16.5 mg Co/kg/day as cobalt chloride for 3 months (Domingo et al. 1984) or gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetroxide for 90 days (Danzeisen et al. 2020a).

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

### 2.9 HEPATIC

No studies were identified regarding hepatic effects in humans after inhalation exposure to cobalt.

The liver is not a consistent or sensitive target of cobalt toxicity following inhalation exposure. Decreased absolute and/or relative liver weights were observed following intermittent exposure to cobalt metal at concentrations  $\geq 2.5$  mg Co/m<sup>3</sup> in male F344/N rats and male and female B6C3F1 mice and  $\geq 5$  mg Co/m<sup>3</sup> in female F344/N rats for 16–17 days (NTP 2014). However, no exposure-related changes in liver weight were observed in rats or mice of either sex exposed to concentrations up to 5 mg Co/m<sup>3</sup> for 14 or 105 weeks (Behl et al. 2015; NTP 2014). Decreased absolute and relative liver weights were observed in mice exposed to 10 mg Co/m<sup>3</sup> for 14 weeks; rats were not evaluated at this exposure concentration for this duration (NTP 2014). No histopathological lesions were observed at concentrations up to 40 mg Co/m<sup>3</sup> for 16–17 days or 5 mg Co/m<sup>3</sup> (rats) or 10 mg Co/m<sup>3</sup> (mice) for 14 weeks (NTP 2014). After 105 weeks, basophilic foci were observed in male and female rats exposed to 1.25 and 5 mg Co/m<sup>3</sup>, respectively; no histopathological liver lesions were observed in similarly exposed mice at concentrations up to 5 mg Co/m<sup>3</sup> (Behl et al. 2015; NTP 2014). No exposure-related changes in serum alkaline phosphatase (ALP), alanine aminotransferase (ALT) or sorbitol dehydrogenase (SDH) were observed in rats or mice at concentrations up to 5 or 10 mg Co/m<sup>3</sup>, respectively, for 14 weeks; hepatic clinical chemistry was not evaluated at additional timepoints (NTP 2014). In a similar set of experiments with cobalt sulfate, liver effects were only observed in F344/N rats and B6C3F1 mice that died following exposure to 75 and  $\geq 19$  mg Co/m<sup>3</sup>, respectively, for up to 16 days; findings at autopsy included congestion and necrosis of the liver (NTP 1991). No changes in liver weight or histology were observed in rats or mice exposed to cobalt sulfate at concentrations up to 11.4 mg Co/m<sup>3</sup> for 13 weeks or 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et al. 1990, 1999; NTP 1991, 1998). No

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exposure-related changes in hepatic clinical chemistry parameters or liver weight or histology were observed in Wistar rats intermittently exposed to concentrations up to 59.31 mg Co/m<sup>3</sup> as cobalt tetroxide for 28 days (Burzlaff et al. 2022a). No histological effects on the liver were found in pigs (strain not specified) exposed  $\leq 1.0$  mg Co/m<sup>3</sup> as cobalt metal dust intermittently for 3 months (Kerfoot 1974).

In a controlled human study designed to evaluate the potential for cobalt chloride supplementation to reverse pregnancy-related anemia, no adverse changes in serum or urinary markers of liver function were noted in 20 pregnant women exposed to 0.57 mg Co/kg/day for at least 90 days prior to delivery, compared to 55 unexposed controls (Holly 1955). No exposure-related changes were found in hepatic serum clinical chemistry parameters of 10 volunteers given low-dose cobalt chloride supplements (mean dose of 0.013 mg Co/kg/day) for up to 91 days (Finley et al. 2013; Tvermoes et al. 2014).

In acute-duration oral exposure studies in rats, decreased relative liver weight and histopathological alterations were observed at doses  $\geq 8.9$  mg Co/kg/day as cobalt chloride in drinking water for 7 days (Akinrinde et al. 2016c; Awoyemi et al. 2017). Observed lesions included evidence of hepatocellular damage, focal necrosis, vascular congestion, and mild infiltration of inflammatory cells; lesions were not observed at 8.2 mg Co/kg/day. 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 exposed once to doses  $\geq 68$  mg Co/kg as cobalt fluoride or  $\geq 157$  mg Co/kg as cobalt oxide (Speijers et al. 1982). However, no changes in liver weight or histology were observed in Sprague-Dawley rats exposed to 12.5 mg Co/kg/day for 7 days as cobalt chloride via gavage (Shrivastava et al. 2010). No biologically relevant changes in hepatic clinical chemistry were observed in rats following a single oral exposure to 161 mg Co/kg as cobalt chloride (Domingo and Llobet 1984) or a 7-day oral exposure up to 18 mg Co/kg as cobalt chloride (Akinrinde et al. 2016c; Awoyemi et al. 2017; Shrivastava et al. 2010).

Hepatic effects were noted in some intermediate-duration oral exposure studies following exposure to cobalt. A 13-week exposure to 16.5 mg Co/kg/day as cobalt chloride in the drinking water did not result in adverse changes in serum ALT, ALP, or aspartate aminotransferase (AST) in rats (Domingo et al. 1984). Garoui et al. (2011) demonstrated that daily exposure to 20 mg Co/kg/day as cobalt chloride via drinking water for 2 weeks during gestation and 2 weeks during lactation resulted in a 10% decrease in absolute liver weight with evidence of liver injury (infiltration of mononuclear cells and vascular congestion) in maternal Wistar rats. Wistar rats exposed to 25 mg Co/kg/day as cobalt chloride for

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60 days showed an increase in relative liver weight by 13%, along with degradation and alteration in the morphology and atrophy of liver cells; alterations in liver biochemistry 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 drinking water as cobalt chloride increased LDH by 3.6-fold; increased ALP, AST, and ALT by 1.7-, 4.5-, and 1.7-fold, respectively; and increased total bilirubin levels by 1.9-fold in Sprague-Dawley rats (Khalil et al. 2020).

In other intermediate-duration oral studies, no hepatic effects were observed. No changes in hepatic function, as measured by bromsulphthalein challenge, were observed in rats exposed to oral doses up to 2.5 mg Co/kg/day for 7 months (Krasovskii and Fridlyand 1971). No histopathological changes in the liver were observed in Sprague-Dawley rats exposed to 16.5 mg Co/kg/day as cobalt chloride in drinking water for 3 months (Domingo et al. 1984), in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetroxide for 90 days (Danzeisen et al. 2020a), or in Wistar rats exposed to 18 mg Co/kg/day via gavage for 4 months (Holly 1955).

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

### 2.10 RENAL

In a prospective cohort that followed 100 male welders over the course of 2 years, urinary cobalt levels were associated with elevated serum creatinine levels (Wu et al. 2023a). No additional renal endpoints were evaluated in this cohort, and no additional studies evaluating renal endpoints in humans following inhalation exposure to cobalt were identified.

The kidney is not a consistent or sensitive target of cobalt toxicity following inhalation exposure. No exposure-related renal lesions were observed in F344/N rats or B6C3F1 mice following exposure to cobalt metal at concentrations up to 5 and 10 mg Co/m<sup>3</sup> for 14 weeks, respectively, or 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; NTP 2014). However, elevated urinary creatinine levels and decreased urine volume were observed in male and female rats following exposure to concentrations  $\geq 10$  and 20 mg Co/m<sup>3</sup> for 16 days, respectively (NTP 2014). After exposure to 5 mg Co/m<sup>3</sup> for 14 weeks, findings included increased serum creatinine in male rats, increased relative kidney weight in female rats, and decreased absolute and relative kidney weights in male and female mice (NTP 2014). Kidney weight, urinalysis, and serum clinical chemistry were not evaluated at 105 weeks. No exposure-related changes in kidney weight or histology were observed in F344/N rats or B6C3F1 mice following intermittent

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inhalation exposure to cobalt sulfate at concentrations up to 75.7 mg Co/m<sup>3</sup> for 16 days, 11.4 mg Co/m<sup>3</sup> for 13 weeks, or 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et al. 1990, 1999; NTP 1991, 1998). No exposure-related changes were observed in serum creatinine levels in the 13-week studies (not evaluated at other timepoints) (NTP 1991). No exposure-related changes in renal clinical chemistry parameters or kidney weight or histology were observed in Wistar rats intermittently exposed to concentrations up to 59.31 mg Co/m<sup>3</sup> as cobalt tetraoxide for 28 days (Burzlaff et al. 2022a). No histological effects on the kidneys were found in pigs exposed  $\leq 1.0$  mg Co/m<sup>3</sup> as cobalt metal for 3 months (Kerfoot 1974).

Changes in renal clinical chemistry and histology have been reported following exposure to high acute oral doses of cobalt compounds. Domingo and Llobet (1984) showed that a single gavage exposure to 161 mg Co/kg as cobalt chloride caused a 68% increase in serum urea in Sprague-Dawley rats, which suggests alterations in renal function; however, no additional renal endpoints were evaluated in this study (Domingo and Llobet 1984). Wistar rats exposed to  $\geq 10$  mg Co/kg/day as cobalt chloride via drinking water for 2 weeks showed an increase in serum creatinine and/or serum urea levels (Ajibade et al. 2017; Akinrinde et al. 2016a). Both studies qualitatively reported histopathological changes in renal tissue including inflammatory changes (cellular infiltration) and renal tubular degeneration. Inflammation in the peritubular and perivascular areas, along with focal tubular necrosis, were also observed in Wistar rats exposed to 10 mg Co/kg/day as cobalt chloride in drinking water for 7 days (Akinrinde et al. 2016b). Mild tubular atrophy, necrotizing nephritis, and inflammatory cell infiltrate were observed in Wistar rats exposed to 37 mg Co/kg/day via gavage as cobalt chloride for 8 days (Oyagbemi et al. 2020). While there were no control animals in this study, renal injury, evidenced by swelling and degeneration of the proximal tubules, was observed in Wistar rats exposed once to doses  $\geq 42$  mg Co/kg as cobalt fluoride (Speijers et al. 1982). However, no changes in serum clinical chemistry or kidney weight or histology were observed in Sprague-Dawley rats exposed to 12.5 mg Co/kg/day for 7 days as cobalt chloride via gavage (Shrivastava et al. 2010).

No exposure-related changes were found in renal serum clinical chemistry parameters of 10 volunteers given low-dose cobalt chloride supplements (mean dose of 0.013 mg Co/kg/day) for up to 91 days (Finley et al. 2013; Tvermoes et al. 2014). No additional studies evaluating renal endpoints in humans following oral exposure to cobalt were identified.

There is limited evidence for renal effects in rats following intermediate-duration oral exposure to cobalt compounds. Abdel-Daim et al. (2020) showed increased serum urea (105%) and creatinine (137%) in

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Sprague-Dawley rats exposed to 8.9 mg Co/kg/day in drinking water as cobalt chloride for 4 weeks; no change in relative kidney weight was observed. Garoui et al. (2012) observed that daily exposure to 20 mg Co/kg/day in drinking water as cobalt chloride for 2 weeks during gestation and 2 weeks during lactation caused vascular congestion, reduction of glomerular space, and infiltration of leukocyte cells between tubules in the kidneys of Wistar rat dams. Additional renal findings included a 35% increase in plasma urea, a 34% decrease in urinary creatinine, 38% decrease in urinary urea, and a slight 8% reduction in relative kidney weight, compared to controls (Garoui et al. 2012).

No exposure-related renal changes were observed in other intermediate-duration oral studies in rodents. After a 13-week exposure to 16.5 mg Co/kg/day as cobalt chloride in the drinking water, no adverse changes in renal clinical chemistry or morphological changes in the kidney were observed in Sprague-Dawley rats; the observed decrease in urine volume was attributable to decreased water intake (Domingo et al. 1984). No changes in kidney weight or histology were observed in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetroxide for 90 days (Danzeisen et al. 2020a) or in Wistar rats exposed to 18 mg Co/kg/day via gavage for 4 months (Holly 1955). No histopathological changes in the kidney were observed in CD-1 mice exposed to 43.4 mg Co/kg/day in drinking water as cobalt chloride for 7–13 weeks (Anderson et al. 1992).

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

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 transient increase in excretion of methemoglobin within 3 hours from the renal tissues in Wistar rats (Horiguchi et al. 2004). 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). An intermediate-duration exposure to 1.6 mg Co/kg/day as subcutaneous injections of cobalt nitrate for 4 weeks caused glomerular-tubular nephrosis with degenerative changes and was toxic to the renal tubule cells in albino rats (Hanafy and Soltan 2004).



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**2.11 DERMAL**

Studies in humans evaluating the potential association between exposure to cobalt and dermal effects are limited to two occupational cohort studies and several case reports of dermal exposure. In a cohort of metal factory workers (n=71) exposed to air cobalt concentrations ranging from 0.0001 to 0.019 mg/m<sup>3</sup>, there was a high prevalence of self-reported dry skin (42%) and eczema (6–7%) (Wahlqvist et al. 2020). Similarly, increased numbers of skin lesions (eczema, erythema) were identified in a cross-sectional study of 82 workers from a cobalt refinery with mean airborne cobalt concentrations of 0.125 mg/m<sup>3</sup> (range 0.001–7.7 mg/m<sup>3</sup>) (Swennen et al. 1993). In both occupational studies, it is likely that any association between cobalt exposure and dermal conditions is due to direct contact with cobalt particles in the air. Dermal exposure to cobalt has also been associated with eczema and contact dermatitis in several case reports (Alinaghi et al. 2020; 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 >10% cobalt by weight (Alinaghi et al. 2020). 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).

No exposure-related histopathological changes to the skin were observed in F344/N rats or B6C3F1 mice following intermittent inhalation exposure to cobalt sulfate at concentrations up to 75.7 mg Co/m<sup>3</sup> for 16 days, 11.4 mg Co/m<sup>3</sup> for 13 weeks, or 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et al. 1990, 1999; NTP 1991, 1998). Similarly, no exposure-related histopathological changes in the gastrointestinal tract were observed in F344/N rats or B6C3F1 mice following exposure to cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively, or 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; NTP 2014).

No histopathological changes to the skin were observed in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a).

In an intermediate-duration 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).

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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.

Ocular irritation (chromodacryorrhea) was observed in F344/N rats and B6C3F1 mice during and after 6-hour exposures to cobalt sulfate at concentrations of  $\geq 19$  mg Co/m<sup>3</sup>/day; clinical signs worsened over the 16-day exposure period (NTP 1991). This finding is likely due to direct ocular exposure to cobalt particles in the air, rather than a systemic effect of inhalation exposure.

No histological lesions were reported in the eyes of F344/N rats intermittently exposed to cobalt metal at concentrations up to 5 mg Co/m<sup>3</sup> for 14 or 105 weeks (Behl et al. 2015; NTP 2014). Similarly, no histological lesions were reported in the eyes of B6C3F1 mice intermittently exposed to cobalt metal at concentrations up to 10 mg Co/m<sup>3</sup> for 14 weeks or 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; NTP 2014).

No ophthalmological changes were observed in Sprague-Dawley rats exposed to cobalt chloride via gavage at 12.5 mg Co/kg/day for 7 days (Shrivastava et al. 2010). No ophthalmological or histopathological changes were observed in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a).

**2.13 ENDOCRINE**

**Thyroid.** Limited data from occupational studies do not provide consistent evidence of alterations in serum thyroid hormone levels following inhalation exposure to cobalt or cobalt compounds (Table 2-7). In a cohort of 249 cobalt refinery workers in Belgium, Lantin et al. (2011) found no association between current blood or urine levels or estimated cumulative cobalt exposures and serum thyroxine (free or total T4), triiodothyronine (free or total T3), or thyroid stimulating hormone (TSH). Measured air concentrations ranged from 0.001 to 0.108 mg/m<sup>3</sup>. In contrast, Swennen et al. (1993) reported a significant reduction in serum T3 in a cohort of 82 workers from Belgium occupationally exposed to cobalt oxides, cobalt salts, and cobalt metal at a mean air concentration of 0.125 mg/m<sup>3</sup>, compared to

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unexposed referents. No changes were observed in serum T4 or TSH levels. A study of Danish porcelain workers found alterations in serum thyroid hormone levels in workers utilizing semi-soluble cobalt dye (cobalt-zinc silicate), but not in workers utilizing insoluble cobalt dye (cobalt aluminate), despite measured air cobalt levels of 0.05 mg Co/m<sup>3</sup> (Prescott et al. 1992). Compared to unexposed referents, workers exposed to cobalt-zinc silicate showed elevated levels of serum total and free T4 but no change in serum T3 or TSH levels. It is unclear if findings in workers exposed to cobalt-zinc silicate are attributable to increased solubility of this form of cobalt, as these workers showed elevated urinary levels of cobalt and workers exposed to cobalt aluminate did not, or due to co-exposure with zinc.

**Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Thyroid Effects**

| Reference, study type, and population                                                                                                                                                                                                                                                                                                                                     | Exposure concentration                                                                                                       | Outcome evaluated | Result                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------------------------------------------------|
| <b>Lantin et al. 2011</b><br><br>Cohort; 249 male workers (median age 46 years; median employment 12.27 years), including 230 active workers and 19 retired workers (~5 years of retirement) from a cobalt production department (Belgium)                                                                                                                                | Measured air concentration (2007), range:<br>0.001–0.108 mg Co/m <sup>3</sup>                                                | TSH               | ↔ (current blood, urine; cumulative)                             |
|                                                                                                                                                                                                                                                                                                                                                                           | Current cobalt concentrations, median:<br>Blood: 0.10 µg/100 mL<br>Urine: 3.90 µg/g creatinine                               | FT4               | ↔ (current blood, urine; cumulative)                             |
|                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                              | T4                | ↔ (current blood, urine; cumulative)                             |
|                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                              | FT3               | ↔ (current blood, urine; cumulative)                             |
|                                                                                                                                                                                                                                                                                                                                                                           | Cumulative cobalt exposure (IEI), median:<br>106.09 µg/g creatinine x years                                                  | T3                | ↔ (current blood, urine; cumulative)                             |
| <b>Prescott et al. 1992</b><br><br>Cross-sectional; 35 female plate painters from Factory 1 exposed to cobalt aluminate (mean age 41.4 years, mean length of employment 14.6 years), 25 female plate painters from Factory 2 exposed to cobalt-zinc silicate (mean age 42.9 years, mean length of employment 16.2 years) and 48 referents (mean age 41.3 years) (Denmark) | Measured air concentrations (1987–1988) in both factories:<br>0.05 mg Co/m <sup>3</sup>                                      | TSH               | ↔ (Factory 1 or 2 versus referents)                              |
|                                                                                                                                                                                                                                                                                                                                                                           | Current urinary cobalt concentrations, mean:<br>Factory 1: 0.20 µg/mmol<br>Factory 2: 1.17 µg/mmol<br>Referent: 0.13 µg/mmol | FT4               | ↔ (Factory 1 versus referents)<br>↑ (Factory 2 versus referents) |
|                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                              | T4                | ↔ (Factory 1 versus referents)<br>↑ (Factory 2 versus referents) |
|                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                              | FT3               | ↔ (Factory 1 or 2 versus referents)                              |
|                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                              | T3                | ↔ (Factory 1 or 2 versus referents)                              |

## 2. HEALTH EFFECTS

**Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Thyroid Effects**

| Reference, study type, and population                                                                                                                                                          | Exposure concentration                                                                           | Outcome evaluated | Result                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------|------------------------------|
| <b>Swennen et al. 1993</b><br><br>Cross-sectional; 82 male workers (mean age 33 years; mean employment duration 8 years) from a cobalt refinery and 82 referents (mean age 38 years) (Belgium) | Current air concentration, mean: 0.125 mg Co/m <sup>3</sup>                                      | TSH               | ↔ (workers versus referents) |
|                                                                                                                                                                                                | Current pre-shift urine cobalt level, median (µg/g creatinine):                                  | T4                | ↔ (workers versus referents) |
|                                                                                                                                                                                                | Monday: 22.9<br>Friday: 44.9                                                                     | T3                | ↓ (workers versus referents) |
|                                                                                                                                                                                                | Current post-shift urine cobalt level, median (µg/g creatinine):<br>Monday: 44.1<br>Friday: 72.4 |                   |                              |

↑ = association; ↓ = inverse association; ↔ = no association; FT3 = free triiodothyronine; FT4 = free thyroxine; IEI = integrated exposure index; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone

Data pertaining to thyroid function in animals following inhalation exposure to cobalt are limited.

Exposure-related changes in serum thyroid hormone levels observed in F344/N rats following intermittent exposure to cobalt sulfate for 13 weeks included decreased serum T3 in females at  $\geq 3.78$  mg Co/m<sup>3</sup> and decreased TSH in males at 11.4 mg Co/m<sup>3</sup>; no exposure-related changes in serum total or free T4 were observed in either sex (Bucher et al. 1990; NTP 1991). No other inhalation studies identified measured serum thyroid hormone levels following cobalt exposure.

No exposure-related changes in thyroid gland weight and/or histology were observed in F344/N rats or B6C3F1 mice following exposure to cobalt sulfate at concentrations up to 75.7 mg Co/m<sup>3</sup> for 16 days, 11.4 mg Co/m<sup>3</sup> for 13 weeks, or 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et al. 1990, 1999; NTP 1991, 1998) or in F344/N rats or B6C3F1 mice following exposure to cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively, or 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; NTP 2014). No exposure-related histopathological changes in the thyroid were observed in Wistar rats intermittently exposed to cobalt tetraoxide at concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a).

Several patients, including children, have developed goiter (enlargement of the thyroid gland) and/or hypothyroidism following cobalt therapy for anemia associated with sickle-cell anemia, pregnancy, or chronic renal disease (Chamberlain 1961; Duckham and Lee 1976; Gross et al. 1955; Kriss et al. 1955;

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Little and Sunico 1958; Washburn and Kaplan 1964). Due to case reports of altered thyroid function, a study by Roche and Layrisse (1956) examined iodine-131 uptake in 12 euthyroid (normal thyroid) patients who were orally administered approximately 1 mg Co/kg/day (assuming a body weight of 70 kg) as cobalt chloride for 2 weeks. After 1 week, reduced uptake of 48-hour radioactive iodine-131 by the thyroid was observed. By 2 weeks, uptake of iodine-131 was almost zero (Roche and Layrisse 1956). Iodine uptake returned to baseline following cessation of treatment. Similar findings were observed in three euthyroid males exposed to 0.54 mg Co/kg/day for 10–14 days (Paley et al. 1958). Decreased iodine-131 uptake was more pronounced in a hyperthyroid patient similarly exposed to 0.54 mg Co/kg/day for 21 days (Paley et al. 1958). No other clinical details, such as thyroid hormone levels, were provided for the human subjects in these studies. Paley et al. (1958) proposed that the decreased uptake was likely a result of cobalt blocking the organic binding of iodine-131.

In another controlled trial, no exposure-related changes in serum thyroid hormone levels were observed in 9/10 volunteers given low doses of a cobalt chloride dietary supplement (0.013 mg Co/kg/day) for up to 91 days (Tvermoes et al. 2014). One volunteer showed TSH levels elevated above clinically normal ranges at the end of exposure, coupled with serum T4 levels at the lower end of clinically normal ranges (Tvermoes et al. 2014). No changes were observed in serum thyroid hormone levels in 10 volunteers similarly exposed to a cobalt chloride supplement at 0.013 mg Co/kg/day for 31 days (Finley et al. 2013). In a controlled human study designed to evaluate the potential for cobalt chloride supplementation to reverse pregnancy-related anemia, no evidence of thyroid enlargement was observed in 20 pregnant women exposed to 0.57 mg Co/kg/day for at least 90 days prior to delivery, compared to 55 unexposed controls (Holly 1955). No additional measures of thyroid function (e.g., serum hormone levels) were monitored in this study.

In a 90-day repeat-dose gavage study, no histopathological changes were observed in the thyroid glands of Sprague-Dawley rats exposed to doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetroxide (Danzeisen et al. 2020a). While not explicitly stated, this study was conducted according to Organisation for Economic Co-operation and Development (OECD) 408 guidelines (OECD 2018), which require evaluation of serum T4, T3, and TSH; the study authors indicated that “only those endpoints that were affected by the treatment are reported,” suggesting that these parameters were not altered by treatment. However, it is not entirely clear based upon study reporting. No other identified animal studies evaluated serum thyroid hormone levels following oral exposure to cobalt. However, female Parkes mice exposed to 45 mg Co/kg-day as cobalt chloride in the drinking water for 15–45 days showed histopathological changes to the thyroid gland, including

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degeneration and necrotic changes in thyroid epithelial cells and lymphocytic infiltration; findings increased in severity in a duration-dependent manner (Shrivastava et al. 1996). No morphological changes were seen in the thyroid gland of Wistar rats treated with 18 mg Co/kg/day for 4 months (Holly 1955).

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

**Other Endocrine Endpoints.** Data for non-thyroid endocrine endpoints are limited. In a year-long prospective cohort from Taiwan of 69 shipyard workers exposed to particulate matter and metal fumes, urinary cobalt levels were not associated with urinary cortisol levels (Lai et al. 2021).

In intermediate-duration inhalation studies in animals, no exposure-related histopathological changes were observed in the adrenal gland, pancreas, parathyroid gland, or pituitary gland in F344/N rats or B6C3F1 mice following exposure to cobalt sulfate at concentrations up to 75.7 mg Co/m<sup>3</sup> for 16 days or 11.4 mg Co/m<sup>3</sup> for 13 weeks (Bucher et al. 1990, 1999; NTP 1991) or cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively (NTP 2014). Similarly, no histopathological changes were observed in the adrenal gland in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tertraoxide for 90 days (Danzeisen et al. 2020a).

There is limited evidence for non-neoplastic effects in the adrenal gland following chronic-duration inhalation exposure to cobalt. An increased incidence of medullary hyperplasia in the adrenal gland was seen in female F344/N rats after exposure to cobalt metal at 1.25 mg Co/m<sup>3</sup> for 105 weeks; this was not observed in similarly exposed male F344/N rats or B6C3F1 mice at concentrations up to 5 mg Co/m<sup>3</sup> (Behl et al. 2015; NTP 2014). No exposure-related, non-neoplastic lesions were observed in other endocrine organs (pancreas, parathyroid gland, pituitary gland) in rats or mice at concentrations up to 5 mg Co/m<sup>3</sup> as cobalt metal (Behl et al. 2015; NTP 2014). In studies with cobalt sulfate, no histopathological lesions were observed in the adrenal gland, pancreas, parathyroid gland, or pituitary gland in F344/N rats or B6C3F1 mice exposed to concentrations up to 1.11–1.14 mg Co/m<sup>3</sup> for 105 weeks (Bucher et al. 1999; NTP 1998).

No histopathological changes to the adrenal gland or pancreas were observed in Sprague-Dawley rats exposed to 16.5 mg Co/kg/day as cobalt chloride via drinking water for 30 days (Domingo et al. 1984). No histopathological changes were observed in the adrenal gland, pancreas, parathyroid gland, or

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pituitary gland in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a). No morphological changes were seen in the adrenal gland, pancreas, or pituitary gland of Wistar rats treated with 18 mg Co/kg/day for 4 months (Holly 1955).

Fifteen-day intermediate-duration 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 a 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-duration exposure to cobalt nitrate salts subcutaneously was detrimental to the alpha cells in the pancreas in guinea pigs (strain not specified) (Van Campenhout 1955).

### 2.14 IMMUNOLOGICAL

As discussed in Section 2.4 (Respiratory), occupational exposure to cobalt has been associated with increased risk of asthma in some cohorts (Kusaka et al. 1986b; Linna et al. 2003; Roto 1980; Walters et al. 2012). Shirakawa et al. (1988, 1989) showed an increase in immunoglobulin E (IgE) antibodies specific to cobalt in several cases of occupational asthma associated with hard metal exposure. Similarly, a case-study in a diamond polisher diagnosed with occupational asthma suggests that cobalt-mediated asthma may be IgE-mediated, and that sensitization of lymphocytes could play a crucial role in disease development (Krakowiak et al. 2005). Several studies have examined potential associations between occupational exposure to cobalt and markers of inflammation (e.g., inflammatory cytokines, C-reactive protein, exhaled nitric oxide), but none have observed adverse associations (Table 2-8). In studies of workers in cobalt production or hard metal industries, no positive associations were observed between estimates of current or cumulative exposure to cobalt and markers of inflammation (Andersson et al. 2020, 2021; Hedbrant et al. 2022; Lantin et al. 2011). In a year-long prospective cohort of 69 shipyard workers exposed to particulate matter and metal fumes, urinary cobalt levels were not associated with urinary levels of inflammatory cytokines or exhaled nitric oxide levels (Lai et al. 2021).

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**Table 2-8. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Immunological Effects**

| Reference, study type, and population                                                                                                                                                                                                                 | Exposure concentration                                                                                                                                                                                                                                                                                                                                                                               | Outcome evaluated                             | Result                                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>Andersson et al. 2020</b><br><br>Cohort; 72 workers (9 females, 63 males; mean age 42 years; mean employment 11 years) from the hard metal industry (Sweden)                                                                                       | Current air concentration, mg Co/m <sup>3</sup><br>Median: 0.0009<br>Mean: 0.0017<br>8-hour TWA: 0.0034<br><br>Cumulative exposure, range: ≤0.02–>0.07 mg-year/m <sup>3</sup>                                                                                                                                                                                                                        | FENO                                          | ↔ (cumulative)                                                                             |
| <b>Andersson et al. 2021</b><br><br>Cohort; 72 workers (9 females, 63 males; mean age 42 years; mean employment 11 years) from the hard metal industry (Sweden)                                                                                       | Current 8-hour TWA, median: 0.0023 mg Co/m <sup>3</sup><br><br>Stationary cobalt measurements, median, mg Co/m <sup>3</sup> :<br>Inhalable cobalt: 0.00042<br>Total cobalt: 0.00078<br>Respirable cobalt: 0.000062<br><br>Current cobalt concentrations, range of medians:<br>Blood: 5.9–6.5 nmol/L<br>Urine: 33–35 nmol/L<br><br>Cumulative exposure, range: 0.21–≤0.0870 mg Co-year/m <sup>3</sup> | Cytokines (TNF, IL-6, IL-8, IL-10)<br><br>CRP | ↔ (current air, blood, urine; cumulative)<br><br>↔ (current air, blood, urine; cumulative) |
| <b>Hedbrant et al. 2022</b><br><br>Cross-sectional; 72 workers (9 females, 63 males; mean age 42.3 years; mean employment 10.4 years) from the hard metal industry (Sweden)                                                                           | Current 8-hour TWA, mean: 0.0034 mg Co/m <sup>3</sup> ; respirator adjusted: 0.0017 mg Co/m <sup>3</sup><br>Current cobalt concentrations, mean:<br>AM blood: 6.5 nmol/L<br>PM blood: 7.1 nmol/L<br>AM urine: 34 nmol/L<br>PM urine: 44 nmol/L                                                                                                                                                       | IL-18<br>IL-1β<br>IL-1Ra                      | ↓ (AM, PM blood)<br>↔ (current, blood, urine)<br>↔ (current, blood, urine)                 |
| <b>Lai et al. 2021</b><br><br>Prospective cohort; shipyard workers comprised of: 49 welders (92% male, mean age 44 years; employment duration not reported) and 20 male office workers (mean age 51 years; employment duration not reported) (Taiwan) | Urinary cobalt concentration (post-shift), mean (μg/g creatinine):<br>Initial: 0.00007<br>1 year later: 0.00009                                                                                                                                                                                                                                                                                      | FENO<br>IL-6                                  | ↔ (urinary cobalt)<br>↔ (urinary cobalt)                                                   |



## 2. HEALTH EFFECTS

**Table 2-8. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Immunological Effects**

| Reference, study type, and population                                                                                                                                                                     | Exposure concentration                                                                         | Outcome evaluated                  | Result                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------|
| <b>Lantin et al. 2011</b>                                                                                                                                                                                 | Measured air concentration (2007), range: 0.001—0.108 mg Co/m <sup>3</sup>                     | Cytokines (TNF, IL-6, IL-8, IL-10) | ↔ (current air, blood, urine; cumulative) |
| Cohort; 249 male workers (median age 46 years; median employment 12.27 years), including 230 active workers and 19 retired workers (~5 years of retirement) from a cobalt production department (Belgium) | Current cobalt concentrations, median:<br>Blood: 0.10 µg/100 ml<br>Urine: 3.90 µg/g creatinine | CRP                                | ↔ (current air, blood, urine; cumulative) |
|                                                                                                                                                                                                           | Cumulative exposure (IEI), median:<br>106.09 µg/g creatinine x years                           |                                    |                                           |

↑ = association; ↓ = inverse association; ↔ = no association; CRP = C-reactive protein; FENO = fraction of nitric oxide in exhaled air; IEI = integrated exposure index; IL = interleukin; TNF = tumor necrosis factor; TWA = time weighted average

No studies evaluating immunological function in animals following inhalation exposure to cobalt were identified; however, several studies evaluated organ weight and/or histology of immune organs.

There is limited evidence that exposure to high concentrations can damage the thymus and/or lymph nodes after intermediate-duration exposure; however, findings differed between studies and administered compound. In 16-day studies, lymphoid depletion and/or necrosis of the thymus accompanied by decreased absolute and relative thymus weights were observed in F344/N rats and B6C3F1 mice intermittently exposed to concentrations  $\geq 19$  mg Co/m<sup>3</sup> as cobalt sulfate (NTP 1991). In contrast, exposure to  $\geq 20$  mg Co/m<sup>3</sup> as cobalt metal for 16 days only resulted in decreased thymus weight in female, but not male, F344/N rats (NTP 2014). No exposure-related changes in thymus weight were observed in male or female B6C3F1 mice exposed to cobalt metal at concentrations up to 40 mg Co/m<sup>3</sup> for 17 days (NTP 2014). No changes in other immune organs (spleen, lymph nodes, or bone marrow) were observed in either species at cobalt sulfate concentrations up to 75.7 mg Co/m<sup>3</sup> or cobalt metal concentrations up to 40 mg Co/m<sup>3</sup> (NTP 1991, 2014). In 13-week studies, hyperplasia in the mediastinal lymph nodes was observed in B6C3F1 mice exposed to 11.4 mg Co/m<sup>3</sup> as cobalt sulfate (Bucher et al. 1990; NTP 1991). However, no histopathological changes in the spleen, thymus, lymph nodes, or bone marrow were seen in F344/N rats exposed to cobalt sulfate at concentrations up to 11.4 mg Co/m<sup>3</sup> for 13 weeks (Bucher et al. 1990; NTP 1991) or in F344/N rats or B6C3F1 mice exposed to cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively (Behl et al. 2015; NTP 2014). No

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exposure-related histopathological changes in the thymus, spleen, or bone marrow were observed in Wistar rats intermittently exposed to cobalt tetroxide at concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a). No pathological changes in immune organs were seen in pigs after a 3-month intermittent exposure to cobalt metal at 0.1 mg Co/m<sup>3</sup> (Kerfoot 1974).

In chronic-duration inhalation studies, no non-neoplastic histopathological changes were observed in immune system organs in F344/N rats or B6C3F1 mice exposed at concentrations up to 1.11–1.14 mg Co/m<sup>3</sup> as cobalt sulfate or 5 mg Co/m<sup>3</sup> as cobalt metal (Behl et al. 2015; Bucher et al. 1999; NTP 1998, 2014).

No evidence of cobalt sensitization was observed in 10 volunteers after exposure to low-dose cobalt chloride supplements (mean dose of 0.013 mg Co/kg/day) for 31 or 91 days, as assessed by an *in vitro* lymphocyte transformation test (Finley et al. 2013; Tvermoes et al. 2014). No additional studies evaluating immunological endpoints in humans following oral exposure to cobalt were identified.

The function of the immune system was evaluated in a few oral studies in animals. Decreased immune responses were observed in male Sprague-Dawley rats exposed to dietary cobalt chloride for 30 days, including decreased plaque formation in response to sheep red blood cells at  $\geq 4.53$  mg Co/kg/day and decreased hemagglutinin antibody response at 8.99 mg Co/kg/day (Chetty et al. 1979). Decreased relative thymus weights were also reported at  $\geq 4.53$  mg Co/kg/day; however, findings are difficult to interpret due to concomitant decreases in body weight gain (absolute organ weight data not reported). A 1.5-fold decrease of total immunoglobulin G (IgG) was observed in BALB/c mice exposed to 31 mg Co/kg/day as cobalt chloride starting 2–3 days prior to birth and during lactation (via dam) and directly on PNDs 26–60 via drinking water (Legostaeva et al. 2013). Together, these studies suggest that cobalt may suppress the immune system's ability to fight infection. In contrast, the ability to fight infection was not suppressed in mice following exposure to  $\geq 9$  mg Co/kg/day for 17 days via gavage as cobalt chloride (Huy et al. 2022). In fact, Huy et al. (2022) reported an enhanced immune response to *Brucella abortus* infection in mice following exposure to  $\geq 9$  mg Co/kg/day for 17 days via gavage as cobalt chloride.

Increased levels of proinflammatory cytokines have been reported following acute- and intermediate-duration oral exposure to cobalt in some studies. A 1-week oral exposure to cobalt chloride via gavage caused an approximate 4-fold increase in interleukin 1 $\beta$  (1L-1 $\beta$ ) and an approximate 80% increase in tumor necrosis factor-alpha (TNF- $\alpha$ ) at 67.5 mg Co/kg/day in Wistar rats (Akinrinde and Adebisi 2019). At a lower dose, serum 1L-1 $\beta$  and TNF- $\alpha$  were increased by approximately 3- and 2-fold, respectively, in

## 2. HEALTH EFFECTS

Wistar rats exposed to cobalt chloride at 9.9 mg Co/kg/day for 14 days via gavage (Oria et al. 2022). However, in a 7-day oral exposure study by Akinrinde et al. (2016c), Wistar rats exposed to 19 mg Co/kg/day as cobalt chloride showed an increase IL-1 $\beta$  by about 50% but a decrease in TNF- $\alpha$  by about 33%. In an intermediate-duration exposure, TNF- $\alpha$  was elevated >10-fold in Sprague-Dawley rats exposed to 16.24 mg Co/kg/day as cobalt chloride (Abdel-Daim et al. 2020). Other inflammatory markers (C-reactive protein, nitric oxide, myeloperoxidase) were also elevated.

No additional oral studies in animals were identified that evaluated immune function (or markers of immune function); findings in studies evaluating only the weight and/or histology of immune organs were unremarkable. No changes in spleen weight or histology were observed in Sprague-Dawley rats exposed to 12.5 mg Co/kg/day for 7 days as cobalt chloride via gavage (Shrivastava et al. 2010). No changes in spleen histology were observed in Sprague-Dawley rats after a 13-week exposure to 16.5 mg Co/kg/day as cobalt chloride in the drinking water (Domingo et al. 1984) or Wistar rats after a 4-month exposure to 18 mg Co/kg/day as cobalt chloride via gavage (Holly 1955). No histopathological changes in the spleen, thymus, or lymph nodes were observed in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a). Findings in bone marrow were restricted to erythroid hyperplasia in rats exposed to  $\geq 2.48$  mg Co/kg/day as cobalt chloride, as discussed in Section 2.7 (Hematological).

Cobalt is a skin sensitizer. A meta-analysis of contact allergy in the general population found that cobalt was the third most prevalent hapten (2.7%) in individuals with positive patch tests, behind nickel (11.4%) and fragrance mix (3.5%); however, in most cases, the source of cobalt sensitization exposure was unknown (Alinaghi et al. 2019). Skin sensitization has been confirmed in patch-testing in guinea pigs following initial exposure to 5% cobalt chloride (2.3% cobalt) (Camner et al. 1993). In the local lymph node assay (LLNA), a 3-day dermal exposure resulted in increased proliferation of lymphocytes in rats, mice, and guinea pigs exposed to doses  $\geq 9.1$ ,  $\geq 4.5$ , and 14 mg Co/kg/day as cobalt chloride, respectively (Ikarashi et al. 1992a). Additional LLNA studies in mice have confirmed skin sensitization at  $\geq 12$  mg Co/kg/day as cobalt chloride (Ikarashi et al. 1992b; Mandervelt et al. 1997). Bonefeld et al. (2015) also reported skin sensitization in mice following exposure to 10% cobalt chloride (4.5% cobalt), which resulted in increased ear swelling and proliferation of both B and T lymphocytes when challenged with re-exposure 3 weeks later, compared with unsensitized mice (Bonefeld et al. 2015).

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**2.15 NEUROLOGICAL**

Studies examining neurotoxicity in humans following inhalation exposure to cobalt are limited to a couple of occupational studies evaluating neurotransmitter levels in workers exposed to hard metals. In a year-long prospective cohort from Taiwan of 69 shipyard workers exposed to particulate matter and metal fumes, urinary cobalt levels were not associated with urinary serotonin levels (Lai et al. 2021). In a cross-sectional study of 186 Chinese welders, urinary cobalt levels were not associated with serum dopamine levels (Wu et al. 2023b).

Available intermediate-duration inhalation studies in rodents indicate that exposure to high levels of cobalt caused central nervous system depression, while histopathological damage was only observed at concentrations associated with lethality. A 16- or 17-day intermittent exposure to 20 and 40 mg Co/m<sup>3</sup> 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<sup>3</sup>, respectively (NTP 2014). Hypoactivity was also observed in rats and mice intermittently exposed to cobalt sulfate at concentrations  $\geq 19$  mg Co/m<sup>3</sup> for 16 days; rodents that died at those exposure concentrations showed congestion in the vessels of the brain (NTP 1991). No exposure-related clinical signs or changes in brain weight or histology were seen in F344/N rats or B6C3F1 mice exposed to concentrations up to 11.4 mg Co/m<sup>3</sup> as cobalt sulfate for 13 weeks (Bucher et al. 1990; NTP 1991). Similarly, no exposure-related changes in clinical signs or changes in brain weight or histology were observed in F344/N rats or B6C3F1 mice following exposure to cobalt metal at concentrations up to 5 or 10 mg Co/m<sup>3</sup> for 14 weeks, respectively (NTP 2014).

No neurological effects have been reported at the lower concentrations evaluated in chronic-duration inhalation studies in rodents. No clinical signs of toxicity or histopathological changes in the brain, spinal cord, or peripheral nerves were observed in F344/N rats and B6C3F1 mice following exposure to cobalt sulfate at concentrations up to 1.11–1.14 mg Co/m<sup>3</sup> or at cobalt metal concentrations up to 5 mg Co/m<sup>3</sup> for 105 weeks (Behl et al. 2015; Bucher et al. 1999; NTP 1998, 2014).

No studies were identified that examined neurotoxicity in humans following oral exposure to cobalt.

Neurological effects were reported frequently in animals following acute-duration oral exposure. Mild central nervous system depression was observed in Wistar rats or Swiss-Webster mice exposed once to cobalt sulfide at 32.2 or 22.2 mg Co/kg, respectively, and Swiss-Webster mice exposed once to cobalt chloride at 16 mg Co/kg via gavage (Singh and Junnarkar 1991). Observed effects included decreased

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spontaneous activity, touch response, muscle tone, and respiration; mild hypothermia; and increased pentobarbitone-induced sleeping time. Similar effects that were classified as more severe (moderate in nature) were observed in Wistar rats exposed once to cobalt chloride at 7.8 mg Co/kg via gavage (Singh and Junnarkar 1991). No changes in functional observation battery, cage-side observations, or brain weight or histology were observed in Sprague-Dawley rats exposed to 12.5 mg Co/kg/day for 7 days as cobalt chloride via gavage (Shrivastava et al. 2010). However, neurobehavioral impairments, including decreased motor strength in the hanging wire tasks and decreased motor activity and exploration in an open field, were observed in male Wistar rats following exposure to 67.5 mg Co/kg/day via gavage as cobalt chloride for 7 days (Akinrinde and Adebisi 2019). No learning or memory impairments were noted in the Morris water maze. Neurobehavioral alterations were associated with a 2-fold increase in glial fibrillary acidic protein (GFAP) positive astrocytes, a marker of reactive gliosis, and a 60% increase in acetylcholinesterase (AChE) activity (Akinrinde and Adebisi 2019). Altered exploration in the Y-maze test, impaired memory in the novel object recognition test, and increased anxiety-like behaviors in the elevated plus maze were also observed in Wistar rats exposed to cobalt chloride at 9.9 mg Co/kg/day for 14 days via gavage (Oria et al. 2022). Neurobehavioral alterations were accompanied by reactive gliosis in the hippocampus (increased GFAP-positive astrocytes) and ultrastructural changes in the hippocampus and amygdala. Moderate-to-severe sciatic nerve damage (degeneration of myelinated fibers; Schwann cell degeneration, perineurium disjunction) was observed in Wistar rats exposed to 37 mg Co/kg/day as cobalt chloride via gavage for 7 days (Tanoğlu et al. 2022).

Some intermediate-duration rodent studies have reported altered performance in operant conditioning tasks following oral exposure to cobalt. For example, Sprague-Dawley rats exposed to 20.3 mg Co/kg/day as cobalt chloride for 57 days in water showed enhanced avoidance retention in passive-avoidance testing, as determined by increased latency to step down on an electrified grid after the initial operant training acquisition phase (Bourg et al. 1985). This finding is suggestive of decreased stress tolerance. Findings were not attributed to enhanced nociception in exposed animals, as no differences in analgesic tolerance were observed. Impaired operant conditioning in food-reward based paradigms has also been observed in rats exposed to cobalt chloride at gavage doses of 2.5 mg Co/kg/day for 4–7 months (Krasovskii and Fridlyand 1971) or dietary doses of 20 mg Co/kg/day for 69 days (Nation et al. 1983). Krasovskii and Fridlyand (1971) reported time-dependent increases in conditioned latent reflexes and loss of memory retention from 4 to 7 months. Findings reported by Nation et al. (1983) were milder, showing a reduced rate of lever pressing than controls, but no change in overall number of food reinforcements received (Nation et al. 1983). In contrast to Bourg et al. (1985), no evidence of decreased stress tolerance was observed in the conditioned suppression (shock) task in rats exposed to dietary doses up to 20 mg

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Co/kg/day via diet for 69 days (Nation et al. 1983). It is noted that findings from food-based operant conditioning need to be interpreted with caution, as they may be due to conditioned taste aversion rather than impaired cognitive function (Wellman et al. 1984).

Findings in other intermediate-duration studies are mixed. Increased GFAP-positive brain regions, encephalopathy, and decreased levels of several neurotransmitter levels, including serotonin, norepinephrine, dopamine, and gamma-aminobutyric acid (GABA), were observed in Wistar rats orally exposed to 27 mg Co/kg/day as cobalt chloride for 60 days (Mohamed et al. 2019). In a series of studies by Danzeisen et al. (2020a), no clinical signs of neurotoxicity or exposure-related changes in neurological screening or functional neurological testing were observed in Sprague-Dawley rats following intermediate-duration exposure to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride, 648 mg Co/kg/day as cobalt sulfide, or 734 mg Co/kg/day as cobalt tetroxide. Additionally, no changes in brain weight or histology were observed in Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a). No morphological changes were seen in the brains of Wistar rats treated with 18 mg Co/kg/day for 4 months (Holly 1955). No changes in pain threshold or responses were observed in Wistar rats following oral exposure to 23 mg Co/kg/day as cobalt chloride for 28 days (Umar et al. 2016).

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

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 cobalt is potentially ototoxic (Lee et al. 2016). A 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).

Altered neurotransmission has been reported *ex vivo* in rat tissues following exposure to 6.4 mg Co/kg/day in drinking water as cobalt nitrate for 30 days (Mutafova-Yambolieva et al. 1994; Vassilev et al. 1993). Vassilev et al. (1993) evaluated cumulative concentration-effect curves for carbachol (a cholinergic agonist) ileum and trachea isolated from control or treated rats. Increased sensitivity and

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decreased maximal response to carbachol was observed in isolated ileum of treated rats. Mutafova-Yambolieva et al. (1994) evaluated peripheral sympathetic neurotransmission in isolated vas deferens tissue, a classic model for evaluation of pre- and postjunctional mechanisms of peripheral sympathetic neurotransmission due to its dense sympathetic innervation. Specifically, *in vivo* exposure to cobalt nitrate resulted in increased *ex vivo* adrenoceptor- and purinoceptor-mediated contractile responses of the vas deferens. Due to challenges associated with interpreting the adversity of findings from *ex vivo* studies, these studies are not included in the LSE table. Additionally, these findings may represent changes in the examined organ tissue (e.g., respiratory, gastrointestinal, reproductive tissues) rather than (or in addition to) changes in the neurological system.

**2.16 REPRODUCTIVE**

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

Intermediate-duration inhalation exposure to cobalt produced reproductive effects in some studies; the male rodent appears to be more susceptible than the female. A series of intermediate-duration studies evaluated reproductive endpoints in F344/N rats and B6C3F1 mice following intermittent exposure to either cobalt metal dust or cobalt sulfate for 16–17 days or 13–14 weeks (Bucher et al. 1990; NTP 1991, 2013). Male and female reproductive organ weight were examined at both timepoints, histology was examined at both timepoints for cobalt sulfate but only at 14 weeks for cobalt metal, and estrous cyclicity and sperm morphology and motility evaluated at 13–14 weeks. In the shorter-duration studies (16 days), testicular atrophy, along with a decrease in number of cells in the seminiferous tubules and atypical germinal epithelial cells in the epididymal ducts, were observed in male rats exposed to  $\geq 19.0$  mg Co/m<sup>3</sup> for 16 days (NTP 1991). However, no exposure-related changes in organ weight or histology were observed in female rats or male or female mice exposed to concentrations up to 75.7 mg Co/m<sup>3</sup> as cobalt sulfate (NTP 1991). Similarly, no exposure-related changes in organ weights were observed in rats or mice exposed to concentrations up to 40 mg/m<sup>3</sup> as cobalt metal; however, due to the lack of histological examination at this timepoint, a NOAEL could not be confidently established at this exposure level (NTP 2014). In the longer intermediate-duration studies (13–14 weeks), effects noted included decreased percent motile sperm at cobalt metal concentrations  $\geq 2.5$  mg Co/m<sup>3</sup> in male rats and mice and at cobalt sulfate concentrations  $\geq 1.11$  mg Co/m<sup>3</sup> in male mice (NTP 1991, 2014). Additional effects observed in exposed male rodents included increased relative testes weights in male rats at  $\geq 2.5$  mg Co/m<sup>3</sup> as cobalt metal, decreased absolute testes weight in male mice at  $\geq 5$  mg Co/m<sup>3</sup> as cobalt metal, and a 3-fold

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increase in percent abnormal sperm with testicular atrophy in male mice at 11.4 mg Co/m<sup>3</sup> as cobalt sulfate. In contrast, male rats similarly exposed to cobalt sulfate at concentrations up to 11.4 mg/m<sup>3</sup> for 13 weeks did not show any changes in sperm parameters or reproductive organ weight or histology (NTP 1991). In female rodents, prolonged estrous cycle length was observed in mice exposed to cobalt metal at 10 mg Co/m<sup>3</sup> for 14 weeks or cobalt sulfate at 11.4 mg Co/m<sup>3</sup> for 13 weeks; this effect was not observed in similarly exposed female rats (NTP 1991, 2014). No changes in female reproductive organ weight or histology were observed in either rats or mice at cobalt sulfate concentrations up to 11.4 mg Co/m<sup>3</sup> or cobalt metal concentrations up to 5 or 10 mg Co/m<sup>3</sup>, respectively. In another intermediate-duration inhalation study, no exposure-related histopathological changes in the testes, ovaries, or uterus were observed in Wistar rats intermittently exposed to cobalt tetroxide at concentrations up to 59.31 mg Co/m<sup>3</sup> for 28 days (Burzlaff et al. 2022a).

Reproductive endpoints evaluated in chronic-duration studies were restricted to histological examination of reproductive organs. As observed in intermediate-duration studies, findings indicate that the male reproductive system is more sensitive to cobalt toxicity than the female reproductive system.

Histopathological changes in the testes were observed in male F344/N rats and B6C3F1 mice intermittently exposed to 5 mg Co/m<sup>3</sup> as cobalt metal for 105 weeks (Behl et al. 2015; NTP 2014). In rats, findings were severe, classified as testicular infarcts (complete effacement of parenchyma due to necrosis). Findings in mice were less severe, including minimal-to-mild degeneration of the testicular epithelium. No histopathological changes were observed in female reproductive organs in rats or mice at cobalt metal concentrations up to 5 mg Co/m<sup>3</sup> (Behl et al. 2015; NTP 2014). No histopathological changes in male or female reproductive organs were observed in F344/N rats or B6C3F1 mice following exposure to cobalt sulfate at concentrations up to 1.11 or 1.14 mg Co/m<sup>3</sup>, respectively, for 105 weeks (Bucher et al. 1999; NTP 1998).

Acute-duration oral studies evaluating reproductive effects in animals are limited. The percent of abnormal sperm was increased in a dose-related manner in male Swiss mice orally exposed to doses ranging from 7.089 to 28.37 mg Co/kg/day as cobalt chloride (4.74 to 9.86% abnormal), compared to 2.10% abnormal in controls (Hassan et al. 2006). No exposure-related changes in sperm parameters or male reproductive organ histology were observed in male Sprague-Dawley rats exposed to cobalt chloride at dietary doses up to 20 mg Co/kg/day for 14 days (Corrier et al. 1985).

Several intermediate-duration studies have reported male reproductive effects following oral exposure to cobalt. The lowest dose associated with impaired fertility was reported in male Swiss mice exposed to



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cobalt chloride at  $\geq 6.354$  mg Co/kg/day via drinking water for 12 weeks, resulting in a decreased sperm count and reduced number of viable pregnancies when mated to unexposed females (Elbetieha et al. 2008). Additional effects noted at  $\geq 11.62$  mg Co/kg/day included a decreased percentage of pregnant females, decreased absolute and relative testes weights, increased absolute and relative seminal vesicles weights, decreased testicular sperm count and daily sperm count/testis, and histopathological changes in the testes (necrosis, hypertrophy of Leydig cells, degeneration of spermatogonial cells).

A series of intermediate-duration drinking water studies in CD-1 mice showed duration-dependent testicular effects following exposure to 43.4–58.9 mg Co/kg/day as cobalt chloride for 7–13 weeks (Anderson et al. 1992; Pedigo et al. 1988). Exposure for 7 weeks was not associated with adverse effects on testes weight, histology, sperm count or motility, or fertility. At 9 weeks, decreased absolute (29%) and relative (25%) testes weights were observed, along with morphological changes in the seminiferous tubules, including vacuolation of Sertoli cells and spermatid, reduced thickness of germinal epithelium, and sloughing of germ cells. Severity of effects increased at 11–13 weeks, with decreased absolute (62%) and relative (58%) testes weights, decreased epididymal sperm concentration (85%), decreased motile sperm (71–83%), and severe degeneration of seminiferous tubules characterized by extensive Sertoli and germ cell loss. After 13 weeks, additional findings not observed at earlier timepoints included grossly apparent testicular atrophy and decreased fertility, as measured by a 78% decrease in fertilized ova when mated to unexposed female mice. Testicular weight, histopathological findings, and decreased fertility after the 13-week exposure persisted following a 20-week recovery period (Anderson et al. 1992; Pedigo et al. 1988). Findings at 13 weeks were confirmed in a follow-up study by Anderson et al. (1993) utilizing the same protocol, with a 61% decrease in testicular weight, seminiferous tubule damage and degeneration, and hypercellularity of the interstitial areas. Pedigo et al. (1988) also showed that reproductive effects in male mice were dose-dependent following exposure to cobalt chloride via drinking water for 12 weeks. At  $\geq 23.0$  mg Co/kg/day, adverse effects included decreased absolute (33–74%) and relative (29–70%) testes weights, decreased epididymal sperm concentration (34–92%), and increased serum testosterone levels (5–7-fold). Additional effects observed at the highest dose (72.1 mg Co/kg/day) included decreased percent of motile sperm (58%) and decreased fertility, as measured by a 74% decrease in fertilized ova when mated to unexposed female mice. Similar decreases in fertility (when mated to unexposed females), sperm concentration, and sperm motility have also been observed in male B6C3F1 mice exposed to 58.9 mg Co/kg/day as cobalt chloride in drinking water for 10 weeks (Pedigo and Vernon 1993). In this study, fertilization rates no longer differed from control 6 weeks postexposure.

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For other cobalt compounds, no exposure-related impairments in fertility, mating, or reproductive indices or sperm parameters were observed in male and female Sprague-Dawley rats exposed to gavage doses up to 648 mg Co/kg/day as cobalt sulfide or 734 mg Co/kg/day as cobalt tetroxide for 2 weeks prior to mating through PND 3 (Danzeisen et al. 2020a).

Mollenhauer et al. (1985) demonstrated that exposure to dietary cobalt metal at 20 mg Co/kg/day for 98 days 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. Testicular atrophy and marked decrease in testicular weight (58%) were observed in Sprague-Dawley rats exposed dietary doses of 20 mg Co/kg/day as cobalt chloride for 69 days (Nation et al. 1983). Evidence of testicular damage, including marked degeneration and necrosis of germinal epithelium in 27–90% of seminiferous tubules, a 43% drop in spermatid reserves, and atrophy/marked decreases in testicular weight, have been reported in Sprague-Dawley rats exposed to 16.5–20 mg Co/kg/day as cobalt chloride for 13–14 weeks in food or drinking water (Corrier et al. 1985; Domingo et al. 1984). No changes in serum hormone levels (testosterone, progesterone, estradiol) or testes or prostate weight or histology were observed in male Sprague-Dawley rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a).

Data on female reproductive toxicity following oral exposure to cobalt in animals are limited. No changes in estrous cyclicity, serum hormone levels (testosterone, progesterone, estradiol), or female reproductive organ weight or histology were observed in female rats exposed to gavage doses up to 7.44 mg Co/kg/day as cobalt chloride or 734 mg Co/kg/day as cobalt tetraoxide for 90 days (Danzeisen et al. 2020a).

No studies were identified regarding reproductive effects in animals after dermal 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).

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**2.17 DEVELOPMENTAL**

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

In a controlled human study designed to evaluate the potential for cobalt chloride supplementation to reverse pregnancy-related anemia, all pregnancies were reportedly “normal” with no evidence of “enlargement” of infants for 20 pregnant women exposed to 0.57 mg Co/kg/day for at least 90 days prior to delivery, compared to 55 unexposed controls (Holly 1955). No further details on pregnancy or infant outcomes were provided.

Acute-duration exposure to cobalt during gestation did not produce developmental effects in rats, even at doses associated with maternal toxicity. Maternal exposure to 81 mg Co/kg/day via gavage as cobalt chloride on GDs 8–12 had no effects on fetal growth, mortality, or incidence of external malformations (Seidenberg et al. 1986). Similarly, no effects on fetal growth, survival, or external or internal malformations or variations were found following maternal exposure to doses up to 24.8 mg Co/kg/day as cobalt chloride during GDs 6–15 in Sprague-Dawley rats (Paternian and Domingo 1988). In both studies, maternal toxicity (>20% decreases in body weight gains) were observed.

In contrast to gestation-only studies, gestation plus postnatal exposure studies reported impaired pup development and survival. Impaired pre- and postnatal growth was observed in Wistar rat pups following maternal gavage exposure to cobalt chloride at doses  $\geq 5.4$  mg Co/kg/day from GD 14 through PND 21 (Domingo et al. 1985b). Findings included decreased pup weights >10% on PNDs 1, 4, and 21, as well as mild decreases (<10%) in body length. Higher maternal doses of 22 mg Co/kg/day were associated with decreased postnatal survival, primarily between PNDs 1 and 4 (Domingo et al. 1985b). No gross malformations were observed, and no dose-related changes in hematology, clinical chemistry, or organ weights were reported in pups surviving until PND 21. In a one-generation study in Sprague-Dawley rats, pup weight was decreased by up to 18% on PND 1 and by up to 21% on PND 4 following F0 exposure to 734 mg Co/kg/day as cobalt tetroxide from 2 weeks pre-mating through PND 3 (Danzeisen et al. 2020a). Pup viability at PND 4 was also decreased at this dose (87.6%) compared to controls (100%); however, this finding was attributed by the study authors to the unexplained total loss of one litter (quantitative data were not provided). There were no exposure-related external abnormalities. In Sprague-Dawley rats similarly exposed to cobalt sulfide, no exposure-related changes in pup viability,

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growth, or malformations were observed at gavage doses up to 648 mg Co/kg/day (Danzeisen et al. 2020a).

Gluhcheva et al. (2020) reported various systemic effects in PND 18 mouse pups in a study designed to evaluate potential effects of perinatal exposure to cobalt chloride following maternal exposure to 19 mg Co/kg/day via drinking from GD 19 or 20 through PND 18. Pups showed a 17% decrease in body weight on PND 18, along with reduced relative spleen and kidney weights; relative liver weights were comparable to controls. Histological examinations showed various abnormalities in these organs, including reduced red pulp in the spleen; leukocyte infiltration, mesangial cellularity, and reduced capsular space in the kidney; and leukocyte infiltration, binucleated hepatocytes, abundant Kupffer cells, and apoptotic bodies in the liver. Hematological analysis showed a 17% increase in red blood cell count; hematocrit and hemoglobin levels were comparable to controls. Similar studies have shown serious body weight effects (40% decrease) accompanied by liver, kidney, and brain damage in PND 14 rat pups following maternal exposure to 20 mg Co/kg/day as cobalt chloride from GD 14 to PND 14 (Garoui et al. 2011, 2012, 2013). Observed liver effects included increased plasma levels of ALT and AST of approximately 2-fold and infiltration of mononuclear cells and vascular congestion in the liver (Garoui et al. 2011). Absolute liver weights were also significantly decreased but findings were confounded by significant body weight decreases in pups and lack of relative liver weight data reporting. Observed kidney effects included increased plasma creatinine (31%), decreased urinary creatinine (29%) and urea (47%), reduced relative kidney weight (4%), and vascular congestion with reduction of glomerular space (Garoui et al. 2012). Neurological findings included altered development of cerebellar architecture, including poorly differentiated layers marked by frequent pyknotic cells, fewer overall cells, and an overly developed external granular layer. Pups also showed decreases in the levels of AChE and butyrylcholinesterase (BuChE) in the cerebrum by 33 and 36%, respectively, and in the cerebellum by 33% and 47%, respectively (Garoui et al. 2013).

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

### 2.18 OTHER NONCANCER

A limited number of studies have evaluated endpoints relevant to metabolic syndrome in workers exposed to cobalt. In a prospective cohort that followed 100 male welders over the course of 2 years, urinary cobalt levels were not associated with body mass index, fasting blood glucose, or serum lipids, and an

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inverse (non-adverse) association was observed between urinary cobalt levels and serum adiponectin levels (Wu et al. 2023a). In a cross-sectional study of 769 ferro-manganese refinery workers, current cobalt plasma levels were inversely associated with fasting blood glucose levels; however, once adjusted for multiple metal exposure, the association was no longer significant (Ge et al. 2021).

Studies in rodents indicate that exposure to cobalt may impact glucose homeostasis. Decreased serum glucose was observed in male rats exposed to cobalt metal at concentration  $\geq 1.25$  mg Co/m<sup>3</sup> for 14 weeks; this finding was not observed in similarly exposed female rats at concentrations up to 5 mg Co/m<sup>3</sup> or male or female mice at concentrations up to 10 mg Co/m<sup>3</sup> (NTP 2014). No exposure-related changes in serum glucose were observed in rats or mice exposed to cobalt sulfate at concentrations up to 11.4 mg Co/m<sup>3</sup> for 13 weeks (Bucher et al. 1990; NTP 1991). Following oral exposure, decreased serum glucose was also reported in rats exposed once to 161 mg Co/kg as cobalt chloride via gavage (Domingo and Llobet 1984). Maternal rats exposed to 20 mg Co/kg/day as cobalt chloride in drinking water from GD 14 to PND 14 also showed decreased plasma glucose; however, this may have been secondary to decreased maternal food intake (Garoui et al. 2012). A dose of 18 mg Co/kg/day as cobalt chloride in drinking water for 12–16 days also lowered blood glucose levels in diabetic rat models; however, no exposure-related changes were observed in similarly exposed non-diabetic rats (Saker et al. 1998). In contrast, elevated serum glucose levels were observed in male rats exposed to 12.5 mg Co/kg/day as cobalt chloride via gavage for 7 days (Shrivastava et al. 2008, 2010).

Several oral studies reported decreased food and/or water intake in rodents; in most cases, findings are likely attributable to palatability issues and are not considered evidence of toxicity. 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 16.5 mg Co/kg/day in drinking water as cobalt chloride for 13 weeks decreased water intake, resulting in decreased urine output, in Sprague-Dawley rats (Domingo et al. 1984). Decreased water intake was also reported in rats exposed to 20.3 mg Co/kg/day as cobalt chloride in drinking water for 57 days, 72.1 mg Co/kg/day as cobalt chloride in drinking water for 12 weeks, or 58.9 mg Co/kg/day as cobalt chloride in drinking water for 13 weeks (Bourg et al. 1985; Pedigo et al. 1988). Decreases in both water and food intake were observed in maternal Wistar rats exposed to 20 mg Co/kg/day in drinking water as cobalt chloride for 2 weeks during gestation plus 2 weeks during lactation (Garoui et al. 2011, 2012).

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

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An acute-duration (10 days) subcutaneous exposure in ICR mice to 0.59 mg Co/kg/day as cobalt chloride resulted in increased adipocyte messenger ribonucleic acid (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.

**2.19 CANCER**

IARC classified cobalt metal (without tungsten carbide or other metal alloys) and soluble cobalt (II) salts (cobalt chloride, cobalt sulfate) as probably carcinogenic to humans and cobalt (II) oxide as possibly carcinogenic to humans (IARC 2023). Metal mixtures containing cobalt, including cobalt metal with tungsten carbide and weapons-grade tungsten (with nickel and cobalt) are classified as probably and possibly carcinogenic to humans, respectively (IARC 2006, 2023). IARC (2023) determined that cobalt (II, III) oxide (cobalt tetraoxide), cobalt (II) sulfide, and other cobalt (II) compounds are not classifiable as to their carcinogenicity to humans. NTP determined that cobalt and cobalt compounds that release cobalt ions *in vivo* are reasonably anticipated to be human carcinogens (NTP 2021). The EPA Integrated Risk Information System (IRIS) program is currently conducting an inhalation cancer risk assessment for cobalt and cobalt compounds and has released the protocol for the assessment along with its dose-response methodology (EPA 2022a).

Several retrospective cohort studies have evaluated cancer risk in workers exposed to cobalt (Table 2-9). 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 just the U.S. cohort in this study, which included eight sites, there was no increased lung cancer mortality risk or trends in standardized mortality ratios (SMRs) from long-term exposure to cobalt or from the other metals studied (Marsh et al. 2017a). No sex-related differences in SMRs were observed. While two plants observed excess lung cancer mortality, SMRs did not differ from

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the general population. The study authors stated that the lung cancer risks were higher in females than in males in Germany, the United States, 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 or cumulative exposure to cobalt impacted lung cancer mortality risk.

**Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cancer**

| Reference, study type, and population                                                                                                                        | Exposure concentration                                                                                                                                                                                                                                                                                                  | Outcome evaluated                                                                                                                             | Result                                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| <b>Lasfargues et al. 1994</b><br><br>Retrospective cohort; 709 workers from the hard metal industry; employed for at least 1 year from 1956 to 1989 (France) | Job-exposure matrix (historic air concentrations and urinary cobalt levels)<br><br>Unexposed<br>Low:<br>Air: <0.01 mg Co/m <sup>3</sup><br>Urine: 0.01–0.02 µmol/L<br>Medium:<br>Air: 0.015–0.04 mg Co/m <sup>3</sup><br>Urine: 0.01–0.10 µmol/L<br>High:<br>Air: >0.05 mg Co/m <sup>3</sup><br>Urine: 0.02–0.28 µmol/L | Cancer deaths<br><br>All malignant neoplasms<br><br>Buccal cavity, pharynx, larynx<br><br>Esophagus<br><br>Larynx<br><br>Leukemia<br><br>Lung | ↑ (high)<br><br>↔<br><br>↔<br><br>↔<br><br>↔<br><br>↑ (medium, current smokers)<br>↑ (high, current smokers) |
| <b>Marsh et al. 2017a</b><br><br>Retrospective cohort; 7,304 workers from the hard metal industry (United States)                                            | Average intensity of exposure during a 56-year period, median:<br>0.006 mg Co/m <sup>3</sup><br><br>Cumulative exposure, median:<br>0.020 mg Co-year/m <sup>3</sup>                                                                                                                                                     | Lung cancer deaths                                                                                                                            | ↔                                                                                                            |
| <b>Marsh et al. 2017b</b><br><br>Retrospective cohort; 32,354 workers from the hard metal industry (Austria, Germany, Sweden, United Kingdom, United States) | Average intensity of exposure during a 62-year period, median:<br>0.006 mg Co/m <sup>3</sup><br><br>Cumulative exposure, median:<br>0.020 mg Co-year/m <sup>3</sup>                                                                                                                                                     | Lung cancer deaths                                                                                                                            | ↔                                                                                                            |

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**Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cancer**

| Reference, study type, and population                                                                                                                   | Exposure concentration                                                                                                                                       | Outcome evaluated                                                                                                                                                                         | Result                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| <b>McElvenny et al. 2017</b><br><br>Retrospective cohort; 1,538 workers from the hard metal industry (United Kingdom)                                   | Historical air concentration, median, mg Co/m <sup>3</sup> :<br>1980s: 0.0105<br>1994–2003: 0.01<br>2004–2004: 0.0071                                        | All cancer deaths                                                                                                                                                                         | ↔                                                                                                              |
| <b>Morfeld et al. 2017</b><br><br>Retrospective cohort; 6,865 workers from the hard metal industry (Germany)                                            | Long-term average concentration, median: 0.04 mg Co/m <sup>3</sup><br><br>Cumulative exposure, estimated median (range): 0.16–0.23 mg Co-year/m <sup>3</sup> | Lung cancer mortality risk                                                                                                                                                                | ↔                                                                                                              |
| <b>Moulin et al. 1993; Mur et al. 1987</b><br><br>Retrospective cohort 1,148 workers from an electrochemical plant producing cobalt and sodium (France) | Exposure levels not reported                                                                                                                                 | Lung cancer deaths<br><br>Buccal cavity, pharynx, larynx cancer deaths<br><br>Brain cancer deaths<br><br>Other cancer deaths (gastrointestinal, pancreas, bladder, prostate, blood, bone) | ↑ (1950–1980)<br>↔ (1950–1988)<br><br>↔ (1950–1980)<br>↔ (1950–1988)<br><br>↑ (1950–1988)<br><br>↔ (1950–1988) |
| <b>Moulin et al. 1998</b><br><br>Retrospective cohort; 7,459 workers from the hard metal industry (France)                                              | Measured air levels in workshops, range of geometric means: 0.01825–1.6534 mg Co/m <sup>3</sup>                                                              | Cancer deaths<br>All cancer sites<br><br>Buccal cavity, pharynx<br><br>Larynx<br><br>Esophagus<br><br>Lung<br><br>Pleura<br><br>Bladder                                                   | <br>↔<br><br>↔<br><br>↔<br><br>↔<br><br>↔<br><br>↔                                                             |
| <b>Moulin et al. 2000</b><br><br>Retrospective cohort; 4,897 workers from the hard metal industry (France)                                              | Job-exposure matrix (not reported)                                                                                                                           | Cancer deaths<br>All cancer sites<br><br>Buccal cavity, pharynx<br><br>Larynx<br><br>Esophagus<br><br>Lung                                                                                | <br>↔<br><br>↔<br><br>↔<br><br>↔<br><br>↔                                                                      |



## 2. HEALTH EFFECTS

**Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cancer**

| Reference, study type, and population                                                                                                                                                                   | Exposure concentration                                                                                                                                                                                                           | Outcome evaluated                                                                                                                                                              | Result                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                         |                                                                                                                                                                                                                                  | Pleura                                                                                                                                                                         | ↔                                                                                          |
|                                                                                                                                                                                                         |                                                                                                                                                                                                                                  | Bladder                                                                                                                                                                        | ↔                                                                                          |
|                                                                                                                                                                                                         |                                                                                                                                                                                                                                  | Leukemia                                                                                                                                                                       | ↔                                                                                          |
| <b>Sauni et al. 2017</b><br><br>Retrospective cohort; 955 workers from a cobalt production plant industry (Finland)                                                                                     | Historical air concentration, range of means in mg Co/m <sup>3</sup> (in different departments):<br>1968–1976: 0.017–0.082<br>1977–1986: 0.02–0.10<br>1987–1999: 0.019–0.065<br>2000–2003: 0.017–0.065<br>2004–2014: 0.018–0.075 | All cancer incidence<br><br>Lung cancer incidence                                                                                                                              | ↔<br><br>↔                                                                                 |
| <b>Svartengren et al. 2017</b><br><br>Retrospective cohort; 3,713 workers from the hard metal industry (Sweden)                                                                                         | Historical air concentration 1970–2012, range: 0.0001–2.8 mg Co/m <sup>3</sup><br><br>Quartiles:<br>Q1: ≤0.001<br>Q2: 0.002–0.0038<br>Q3: 0.0039–0.0088<br>Q4: ≥0.0089                                                           | Lung cancer incidence<br><br>Other cancers (lip, larynx, pleura, gastrointestinal, pancreas, prostate, bladder, skin, blood)                                                   | ↑ (Q4)<br><br>↔                                                                            |
| <b>Tüchsen et al. 1996</b><br><br>Retrospective cohort; 874 women occupationally exposed to cobalt-aluminate spinel dye (Factory 1) or cobalt silicate dye (Factory 2) in porcelain factories (Denmark) | Historical air concentration, range: 0.01–1.5 mg Co/m <sup>3</sup>                                                                                                                                                               | Cancer incidence<br>All cancers<br><br>Lung cancer<br><br>Cervix uteri<br><br>Other cancers (gastrointestinal, pancreatic, breast, ovary, kidney, bladder, skin, brain, blood) | ↔<br><br>↑ (all workers)<br>↔ (Factory 1)<br>↑ (Factory 2)<br><br>↑ (all workers)<br><br>↔ |
| <b>Wallner et al. 2017</b><br><br>Retrospective cohort; 1,965 workers from the hard metal industry (Austria)                                                                                            | Historical air concentration, average: 0.05 mg Co/m <sup>3</sup><br><br>Cumulative exposure, average: 0.52 mg Co-year/m <sup>3</sup>                                                                                             | All cancer deaths<br><br>Lung cancer deaths                                                                                                                                    | ↔<br><br>↔                                                                                 |

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**Table 2-9. Results of Epidemiological Studies Evaluating Exposure to Cobalt and Cancer**

| Reference, study type, and population                                                                                 | Exposure concentration                                                                           | Outcome evaluated                                                                                                                                                                | Result                                                    |
|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Westberg et al. 2017a, 2017b</b><br><br>Retrospective cohort; 16,999 workers from the hard metal industry (Sweden) | Historical air concentration (1970–2012), median: 0.01 mg Co/m <sup>3</sup>                      | Lung cancer deaths                                                                                                                                                               | ↔                                                         |
| <b>Wild et al. 2000</b><br><br>Retrospective cohort; 2,216 men, 644 women working in hard metal industry (France)     | Job exposure matrix based on potential exposure to hard metal dust (concentrations not measured) | Cancer deaths                                                                                                                                                                    |                                                           |
|                                                                                                                       |                                                                                                  | All cancer sites                                                                                                                                                                 | ↔                                                         |
|                                                                                                                       |                                                                                                  | Lung cancer                                                                                                                                                                      | ↑ (men, ever smokers)<br>↔ (men, nonsmokers)<br>↔ (women) |
|                                                                                                                       |                                                                                                  | Other cancers (oral cavity or pharynx, larynx, esophagus, stomach, intestine, rectum, liver, pancreas, breast, pleura, bladder, brain, Hodgkin's disease and lymphoma, leukemia) | ↔                                                         |

↑ = association; ↔ = no association; Q = quartile

A retrospective mortality study in workers from a French electrochemical plant producing cobalt and sodium found a small increase in the number of lung cancer deaths between the years of 1950 and 1980 (Mur et al. 1987); however, when the cohort was re-assessed 8 years later, the association was no longer apparent (Moulin et al. 1993). Deaths associated with brain cancer in this cohort was slightly increased from 1950 to 1988 (Moulin et al. 1993). No other cancer deaths were increased in this worker cohort, compared to the general population (SMRs). An increased incidence of lung cancer was also reported in workers in the highest quartile of cobalt exposure ( $\geq 0.0089$  mg/m<sup>3</sup>) from a Swedish cohort of hard metal workers (Svartengren et al. 2017). However, after various analyses looking at exposure intensity, duration, and lag, no clear association with cobalt was observed. In both the French and Swedish cohorts, the study authors noted that the lack of control for smoking status was a major confounding factor. When smoking status was specifically evaluated in a French cohort of hard metal workers, increased lung cancer deaths were observed only in workers exposed to  $\geq 0.015$  mg Co/m<sup>3</sup> who were current smokers, compared

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to the general population (Lasfargues et al. 1994). Lung cancer death rates were not increased in workers who formerly or never smoked. Consistent with this study, an evaluation of 14 French hard metal workshops found an increased rate of lung cancer deaths in male workers exposed to cobalt, compared to the general population, but only if they were “ever smokers” (Wild et al. 2000). The incidence of lung cancer deaths was not elevated in male workers who never smoked or female workers. Across the various departments, male workers with increased risk of lung cancer death were employed in the hard metal production before sintering and maintenance departments. However, workers were exposed to various other compounds, including asbestos, polycyclic aromatic hydrocarbons, silica, nickel compounds, and chromium compounds (Wild et al. 2000).

Other studies evaluating cobalt production facilities or hard metal factories in the United Kingdom and European countries did not find significant exposure-response relationships between cancer incidence or SMRs and occupational exposure to cobalt (McElvenny et al. 2017; Moulin et al. 1998, 2000; Morfeld et al. 2017; Sauni et al. 2017; Wallner et al. 2017; Westberg et al. 2017a). A small retrospective cohort study in Danish female porcelain workers found an increased incidence in lung cancer in workers using cobalt silicate dye, but not in workers using cobalt aluminate dye (Tüchsen et al. 1996). As reported by Prescott et al. (1992), the silicate dye (cobalt-zinc silicate) is semi-soluble, while the cobalt aluminate is insoluble, which may account for the differential finding. Additionally, the contribution of the zinc and silica elements of the semi-soluble dye are unknown. Tüchsen et al. (1996) indicated that findings need to be confirmed in a larger sample size.

No associations were observed between occupational exposure to cobalt and overall cancer risk in a meta-analysis of nine studies (Marsh et al. 2017a; McElvenny et al. 2017; Morfeld et al. 2017; Moulin et al. 1993, 1998, 2000; Sauni et al. 2017; Svartengren et al. 2017; Tüchsen et al. 1996) conducted by Zhang et al. (2021). Similarly, a systematic review and meta-analysis conducted by Holy et al. (2022) determined that there is “insufficient to conclude that there exists an increased risk” of developing any specific type of cancer from exposure to cobalt via occupational exposure, exposure from implanted medical devices (total joint replacements), or a combination thereof.

Chronic-duration inhalation exposure to cobalt produces exposure-related lung tumors in rats and mice, pheochromocytomas in the adrenal glands of rats, and hematopoietic cancers in rats. Chronic intermittent exposure to cobalt sulfate for 105 weeks caused an increased incidence in alveolar/bronchiolar adenoma or carcinoma in F344/N rats and B6C3F1 mice at  $\geq 0.39$  mg Co/m<sup>3</sup> in females and 1.11–1.14 mg Co/m<sup>3</sup> in males (Behl et al. 2015; Bucher et al. 1999; NTP 1998). Benign, complex, or malignant

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pheochromocytoma were also observed in the adrenal glands in males at 0.39 mg Co/m<sup>3</sup> and in females at 1.11 mg Co/m<sup>3</sup>. Increased incidence in alveolar/bronchiolar carcinoma was also observed in male and female F344/N rats and B6C3F1 mice exposed to concentrations  $\geq 1.25$  mg Co/m<sup>3</sup> as cobalt metal for 105 weeks (Behl et al. 2015; NTP 2014). Additional neoplastic changes observed following chronic-duration exposure to cobalt metal in rats included increased incidence of mononuclear cell leukemia in females at  $\geq 1.25$  mg Co/m<sup>3</sup> and bilateral benign pheochromocytoma in males at  $\geq 1.25$  mg Co/m<sup>3</sup> and in females at  $\geq 2.5$  mg Co/m<sup>3</sup> (Behl et al. 2015; NTP 2014).

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

## 2.20 GENOTOXICITY

Available data indicate that cobalt has a low potential as a direct mutagenic agent; however, there is potential for indirect clastogenic and deoxyribonucleic acid (DNA) damaging effects based on findings from both *in vitro* and *in vivo* data. The overall weight of evidence indicates that cobalt and cobalt compounds are nonmutagenic in bacteria, yeast, and mammalian cells. The overall *in vitro* and *in vivo* evidence for the clastogenic potential of cobalt is mixed, with more recent *in vivo* studies (following guidelines with more rigorous criteria) demonstrating the absence of chromosomal damage following exposure to cobalt compounds. While *in vitro* results are mixed for DNA damage following exposure to various cobalt compounds, positive findings *in vivo* from human studies suggest that cobalt compounds have the potential to cause DNA damage, likely via reactive oxygen species. *In vitro* and *in vivo* studies of the genotoxic effects of cobalt are summarized in Tables 2-10 and 2-11, respectively.

**Table 2-10. Genotoxicity of Cobalt *In Vitro***

|                                      |               | Results         |                               |                      |                     |
|--------------------------------------|---------------|-----------------|-------------------------------|----------------------|---------------------|
| Species (test system)                | Endpoint      | With activation | Without activation            | Reference            | Form                |
| Prokaryotic organisms                |               |                 |                               |                      |                     |
| <i>Salmonella typhimurium</i> (TA98) | Gene mutation | –               | –                             | Kirkland et al. 2015 | Cobalt metal powder |
| <i>S. typhimurium</i> (TA98, TA100)  | Gene mutation | –               | +<br>(TA98)<br>+/-<br>(TA100) | NTP 2014             | Cobalt metal        |

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**Table 2-10. Genotoxicity of Cobalt *In Vitro***

| Species (test system)                                       | Endpoint                  | Results                             |                                             | Reference               | Form                        |
|-------------------------------------------------------------|---------------------------|-------------------------------------|---------------------------------------------|-------------------------|-----------------------------|
|                                                             |                           | With activation                     | Without activation                          |                         |                             |
| <i>Escherichia coli</i> (WP2 <i>uvrA</i> /pKM101)           | Gene mutation             | –                                   | –                                           | NTP 2014                | Cobalt metal                |
| <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538) | Gene mutation             | Not tested                          | –                                           | Arlauskas et al. 1985   | Cobalt chloride             |
| <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538) | Gene mutation             | Not tested                          | –                                           | Kanematsu et al. 1980   | Cobalt chloride             |
| <i>S. typhimurium</i> (TA97a)                               | Gene mutation             | –                                   | –                                           | Kirkland et al. 2015    | Cobalt chloride             |
| <i>S. typhimurium</i> (TA98, TA1538)                        | Gene mutation             | –                                   | Not tested                                  | Mochizuki and Kada 1982 | Cobalt chloride             |
| <i>S. typhimurium</i> (TA1537, TA2367)                      | Gene mutation             | Not tested                          | –                                           | Ogawa et al. 1986       | Cobalt chloride             |
| <i>S. typhimurium</i> (TA97)                                | Gene mutation             | Not tested                          | +                                           | Pagano and Zeiger 1992  | Cobalt chloride             |
| <i>S. typhimurium</i> (TA100)                               | Gene mutation             | Not tested                          | –                                           | Tso and Fung 1981       | Cobalt chloride             |
| <i>S. typhimurium</i> (TA98, TA102, TA1535, TA1537)         | Gene mutation             | –                                   | +<br>(TA98, TA1537)<br>–<br>(TA102, TA1535) | Wong 1988               | Cobalt chloride             |
| <i>E. coli</i> (WP2 <i>uvrA</i> pKm 101)                    | Gene mutation             | Not tested                          | –                                           | Arlauskas et al. 1985   | Cobalt chloride             |
| <i>E. coli</i> (B/r WP2 Try)                                | Gene mutation             | Not tested                          | –                                           | Kada and Kanematsu 1978 | Cobalt chloride             |
| <i>E. coli</i> (B/r WP2 try, WP2 <i>hcr try</i> )           | Gene mutation (reversion) | Not tested                          | –                                           | Kanematsu et al. 1980   | Cobalt chloride             |
| <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538) | Gene mutation             | Not tested                          | –                                           | Kanematsu et al. 1980   | Cobalt sulfate              |
| <i>S. typhimurium</i> (TA100)                               | Gene mutation             | –                                   | –                                           | Kirkland et al. 2015    | Cobalt sulfate              |
| <i>S. typhimurium</i> (TA100, TA1535, TA98)                 | Gene mutation             | +<br>(TA100)<br>–<br>(TA1535, TA98) | +<br>(TA100)<br>–<br>(TA1535, TA98)         | NTP 1991                | Cobalt sulfate heptahydrate |

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**Table 2-10. Genotoxicity of Cobalt *In Vitro***

| Species (test system)                                          | Endpoint                  | Results         |                    | Reference             | Form                        |
|----------------------------------------------------------------|---------------------------|-----------------|--------------------|-----------------------|-----------------------------|
|                                                                |                           | With activation | Without activation |                       |                             |
| <i>S. typhimurium</i><br>(TA100, TA1535, TA98)                 | Gene mutation             | +               | +                  | NTP 1998              | Cobalt sulfate heptahydrate |
|                                                                |                           | (TA100)         | (TA100)            |                       |                             |
|                                                                |                           | –               | –                  |                       |                             |
|                                                                |                           | (TA1535, TA98)  | (TA1535, TA98)     |                       |                             |
| <i>S. typhimurium</i><br>(TA100, TA1535, TA98)                 | Gene mutation             | (+)             | –                  | Zeiger et al. 1992    | Cobalt sulfate heptahydrate |
|                                                                |                           | (TA100)         |                    |                       |                             |
|                                                                |                           | –               |                    |                       |                             |
|                                                                |                           | (TA1535, TA98)  |                    |                       |                             |
| <i>E. coli</i><br>(B/r WP2 try, WP2 hcr try)                   | Gene mutation (reversion) | Not tested      | –                  | Kanematsu et al. 1980 | Cobalt sulfate              |
| <i>S. typhimurium</i><br>(TA100, TA1535, TA97, TA98,           | Gene mutation             | –               | –                  | NTP 2018              | Cobalt naphthenate          |
| <i>S. typhimurium</i><br>(TA98, TA100, TA1535, TA1537, TA1538) | Gene mutation             | Not tested      | –                  | Kanematsu et al. 1980 | Cobalt hydroxide            |
| <i>E. coli</i><br>(B/r WP2 try, WP2 hcr try)                   | Gene mutation (reversion) | Not tested      | –                  | Kanematsu et al. 1980 | Cobalt hydroxide            |
| <i>S. typhimurium</i><br>(TA98, TA100, TA1535, TA1537, TA1538) | Gene mutation             | Not tested      | –                  | Kanematsu et al. 1980 | Cobalt carbonate            |
| <i>E. coli</i><br>(B/r WP2 try, WP2 hcr try)                   | Gene mutation (reversion) | Not tested      | –                  | Kanematsu et al. 1980 | Cobalt carbonate            |
| <i>E. coli</i><br>(WP2 <sub>s</sub> λ)                         | DNA damage                | Not tested      | –                  | Rossman et al. 1984   | Cobalt chloride             |
| <i>Bacillus subtilis</i><br>(H17, M45)                         | DNA damage                | Not tested      | (+)                | Kanematsu et al. 1980 | Cobalt chloride             |
| <i>B. subtilis</i><br>(H17, M45)                               | DNA damage                | Not tested      | –                  | Nishioka 1975         | Cobalt chloride             |
| <i>B. subtilis</i><br>(H17, M45)                               | DNA damage                | Not tested      | +                  | Kanematsu et al. 1980 | Cobalt sulfate              |
| <i>B. subtilis</i><br>(H17, M45)                               | DNA damage                | Not tested      | +                  | Kanematsu et al. 1980 | Cobalt hydroxide            |
| <i>B. subtilis</i><br>(H17, M45)                               | DNA damage                | Not tested      | +                  | Kanematsu et al. 1980 | Cobalt carbonate            |
| <b>Eukaryotic organisms</b>                                    |                           |                 |                    |                       |                             |
| <i>Saccharomyces cerevisiae</i><br>(D7)                        | Gene mutation (reversion) | Not tested      | –                  | Fukunaga et al. 1982  | Cobalt chloride             |

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**Table 2-10. Genotoxicity of Cobalt *In Vitro***

| Species (test system)                                        | Endpoint                                        | Results         |                    | Reference                | Form                                       |
|--------------------------------------------------------------|-------------------------------------------------|-----------------|--------------------|--------------------------|--------------------------------------------|
|                                                              |                                                 | With activation | Without activation |                          |                                            |
| <i>S. cerevisiae</i> (D7)                                    | Gene mutation (cross-over)                      | Not tested      | +                  | Fukunaga et al. 1982     | Cobalt chloride                            |
| <i>S. cerevisiae</i> (D7)                                    | Gene mutation (reversion)                       | Not tested      | –                  | Kharab and Singh 1985    | Cobalt chloride                            |
| <i>S. cerevisiae</i> (IL126-1C, IL8-8D, SBTD-2B, DP1-1B/514) | Gene mutation (induction of rho minus mutation) | Not tested      | +                  | Prazmo et al. 1975       | Cobalt chloride                            |
| <i>S. cerevisiae</i> (D7)                                    | Gene mutation (reversion)                       | Not tested      | –                  | Singh 1983               | Cobalt chloride                            |
| <i>S. cerevisiae</i> (D7)                                    | DNA repair (gene conversion)                    | Not tested      | +                  | Fukunaga et al. 1982     | Cobalt chloride                            |
| <i>S. cerevisiae</i> (D7)                                    | DNA repair (gene conversion)                    | Not tested      | +                  | Kharab and Singh 1985    | Cobalt chloride                            |
| <i>S. cerevisiae</i> (D7)                                    | DNA repair (gene conversion)                    | Not tested      | (+)                | Singh 1983               | Cobalt chloride                            |
| <b>Mammalian cells</b>                                       |                                                 |                 |                    |                          |                                            |
| SHE cells                                                    | Cell transformation                             | Not tested      | +                  | Procter and Gamble 1995  | Cobalt sulfate hydrate                     |
| SHE cells                                                    | Cell transformation                             | Not tested      | +                  | Costa et al. 1982        | Cobalt sulfide (crystalline) <sup>a</sup>  |
| SHE cells                                                    | Cell transformation                             | Not tested      | –                  | Costa et al. 1982        | Cobalt sulfide (amorphous) <sup>b</sup>    |
| Mouse lymphoma L5178Y cells                                  | Mutation at the HPRT locus                      | (+)             | –                  | Kirkland et al. 2015     | Cobalt metal powder                        |
| Mouse lymphoma L5178Y cells                                  | Mutation at the HPRT locus                      | –               | –                  | Kirkland et al. 2015     | Cobalt metal powder (extract) <sup>c</sup> |
| Mouse lymphoma cells (L5178Y/TK <sup>+/-</sup> )             | Mutagenic activity                              | Not tested      | –                  | Amacher and Paillet 1980 | Cobalt chloride                            |
| Chinese hamster V79 cells                                    | Mutation at the HPRT locus                      | Not tested      | +                  | Hartwig et al. 1990      | Cobalt chloride                            |
| Chinese hamster V79 cells                                    | Mutation at the HPRT locus                      | Not tested      | (+)                | Hartwig et al. 1991      | Cobalt chloride                            |
| Chinese hamster V79 cells                                    | Mutation at the HPRT locus                      | Not tested      | (+)                | Miyaki et al. 1979       | Cobalt chloride                            |
| Mouse lymphoma L5178Y cells                                  | Mutation at the HPRT locus                      | –               | –                  | Kirkland et al. 2015     | Cobalt sulfate                             |

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**Table 2-10. Genotoxicity of Cobalt *In Vitro***

| Species (test system)                      | Endpoint                   | Results         |                    | Reference                | Form               |
|--------------------------------------------|----------------------------|-----------------|--------------------|--------------------------|--------------------|
|                                            |                            | With activation | Without activation |                          |                    |
| Mouse lymphoma L5178Y cells                | Mutation at the HPRT locus | –               | –                  | Kirkland et al. 2015     | Cobalt sulfide     |
| Mouse lymphoma L5178Y cells                | Mutation at the HPRT locus | –               | –                  | Kirkland et al. 2015     | Cobalt dihydroxide |
| Mouse lymphoma L5178Y cells                | Mutation at the HPRT locus | –               | –                  | Kirkland et al. 2015     | Cobalt tetraoxide  |
| Mouse lymphoma L5178Y cells                | Mutation at the HPRT locus | –               | –                  | Kirkland et al. 2015     | Cobalt oxide       |
| Human lymphocytes                          | Sister chromatid exchange  | Not tested      | +                  | Andersen 1983            | Cobalt chloride    |
| Mouse macrophage p388d1 cells              | Sister chromatid exchange  | Not tested      | +                  | Andersen 1983            | Cobalt chloride    |
| Chinese hamster V79 cells                  | Sister chromatid exchange  | Not tested      | +                  | Hartwig et al. 1991      | Cobalt chloride    |
| Human lymphocytes                          | Chromosomal aberrations    | Not tested      | –                  | Olivero et al. 1995      | Cobalt chloride    |
| Human lung fibroblast cells                | Chromosomal aberrations    | Not tested      | +                  | Smith et al. 2014        | Cobalt chloride    |
| Human bronchial epithelial cells           | Chromosomal aberrations    | Not tested      | +                  | Xie et al. 2016          | Cobalt chloride    |
| Human lung fibroblast cells                | Chromosomal aberrations    | Not tested      | +                  | Smith et al. 2014        | Cobalt oxide       |
| Human lymphocytes                          | Chromosomal aberrations    | Not tested      | –                  | Capomazza and Botta 1991 | Cobalt chloride    |
| Human lymphocytes                          | Chromosomal aberrations    | Not tested      | –                  | Olivero et al. 1995      | Cobalt sulfate     |
| Human lymphocytes                          | Chromosomal aberrations    | Not tested      | –                  | Olivero et al. 1995      | Cobalt nitrate     |
| Human lymphocytes                          | Chromosomal aberrations    | Not tested      | –                  | Paton and Allison 1972   | Cobalt nitrate     |
| Human diploid cells (WI38, MRC5)           | Chromosomal aberrations    | Not tested      | –                  | Paton and Allison 1972   | Cobalt nitrate     |
| Human bronchial epithelial cells           | Chromosomal aberrations    | Not tested      | +                  | Xie et al. 2016          | Cobalt oxide       |
| Human peripheral blood mononucleated cells | Micronuclei                | Not tested      | +                  | De Boeck et al. 2003     | Cobalt metal       |



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**Table 2-10. Genotoxicity of Cobalt *In Vitro***

| Species (test system)                      | Endpoint    | Results         |                    | Reference                | Form                          |
|--------------------------------------------|-------------|-----------------|--------------------|--------------------------|-------------------------------|
|                                            |             | With activation | Without activation |                          |                               |
| Human osteosarcoma cells                   | Micronuclei | Not tested      | +                  | Miller et al. 2001       | Cobalt metal powder           |
| Human lymphocytes                          | Micronuclei | Not tested      | +                  | Van Goethem et al. 1997  | Cobalt metal powder           |
| Human lymphocytes                          | Micronuclei | Not tested      | +                  | Capomazza and Botta 1991 | Cobalt chloride               |
| Human lymphocytes                          | Micronuclei | Not tested      | +                  | Olivero et al. 1995      | Cobalt chloride               |
| Human bronchial epithelial cells           | Micronuclei | Not tested      | +                  | Uboldi et al. 2016       | Cobalt chloride               |
| Mouse fibroblasts (Balb/3T3)               | Micronuclei | Not tested      | –                  | Ponti et al. 2009        | Cobalt chloride               |
| Human lymphocytes                          | Micronuclei | Not tested      | –                  | Olivero et al. 1995      | Cobalt sulfate                |
| SHE cells                                  | Micronuclei | Not tested      | +                  | Gibson et al. 1997       | Cobalt sulfate hydrate        |
| Human lymphocytes                          | Micronuclei | Not tested      | –                  | Olivero et al. 1995      | Cobalt nitrate                |
| Human bronchial epithelial cells           | Micronuclei | Not tested      | +                  | Uboldi et al. 2016       | Cobalt oxide                  |
| Mouse fibroblasts (Balb/3T3)               | Micronuclei | Not tested      | +                  | Ponti et al. 2009        | Cobalt nanoparticles          |
| Human lymphocytes                          | DNA damage  | Not tested      | +                  | De Boeck et al. 1998     | Cobalt metal                  |
| Human peripheral blood mononucleated cells | DNA damage  | Not tested      | –                  | De Boeck et al. 2003     | Cobalt metal                  |
| Human lymphocytes                          | DNA damage  | Not tested      | +                  | Van Goethem et al. 1997  | Cobalt metal powder           |
| Embryonic mouse stem cells                 | DNA damage  | –               | –                  | Derr et al. 2022         | Cobalt metal                  |
| Human lymphocytes                          | DNA damage  | Not tested      | +                  | De Boeck et al. 1998     | Cobalt-tungsten carbide alloy |
| Human lymphocytes                          | DNA damage  | Not tested      | +                  | Van Goethem et al. 1997  | Cobalt-tungsten carbide alloy |
| Human sub mandibular gland ductal cells    | DNA damage  | Not tested      | +                  | Akita et al. 2007        | Cobalt chloride               |
| Human hepatocarcinoma (HepG2) cells        | DNA damage  | Not tested      | +                  | Alarifi et al. 2013      | Cobalt chloride               |

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**Table 2-10. Genotoxicity of Cobalt *In Vitro***

| Species (test system)                            | Endpoint                    | Results         |                    | Reference                 | Form                       |
|--------------------------------------------------|-----------------------------|-----------------|--------------------|---------------------------|----------------------------|
|                                                  |                             | With activation | Without activation |                           |                            |
| Human T lymphocyte (Jurkat) cells                | DNA damage                  | Not tested      | +                  | Caicedo et al. 2008       | Cobalt chloride            |
| Human lymphocytes                                | DNA damage                  | Not tested      | +                  | De Boeck et al. 1998      | Cobalt chloride            |
| Human diploid fibroblasts                        | DNA damage                  | Not tested      | +                  | Hamilton-Koch et al. 1986 | Cobalt chloride            |
| Human HeLa cells                                 | DNA damage                  | Not tested      | +                  | Hartwig et al. 1990       | Cobalt chloride            |
| Human hepatoblastoma cells                       | DNA damage                  | Not tested      | –                  | Kopp et al. 2018          | Cobalt chloride            |
| Human epithelial colorectal adenocarcinoma cells | DNA damage                  | Not tested      | –                  | Kopp et al. 2018          | Cobalt chloride            |
| Human HeLa cells                                 | Inhibition of DNA synthesis | Not tested      | +                  | Painter and Howard 1982   | Cobalt chloride            |
| Human bronchial epithelial cells                 | DNA damage                  | Not tested      | +                  | Uboldi et al. 2016        | Cobalt chloride            |
| Embryonic mouse stem cells                       | DNA damage                  | –               | –                  | Derr et al. 2022          | Cobalt chloride            |
| Mouse fibroblasts (Balb/3T3)                     | DNA damage                  | Not tested      | +                  | Ponti et al. 2009         | Cobalt chloride            |
| CHO cells                                        | DNA damage                  | Not tested      | +                  | Hamilton-Koch et al. 1986 | Cobalt chloride            |
| Embryonic mouse stem cells                       | DNA damage                  | –               | –                  | Derr et al. 2022          | Cobalt sulfide             |
| Embryonic mouse stem cells                       | DNA damage                  | –               | –                  | Derr et al. 2022          | Cobalt carbonate           |
| Embryonic mouse stem cells                       | DNA damage                  | –               | –                  | Derr et al. 2022          | Cobalt dihydroxide         |
| Embryonic mouse stem cells                       | DNA damage                  | –               | –                  | Derr et al. 2022          | Cobalt tetroxide           |
| Human epithelial colorectal adenocarcinoma cells | DNA damage                  | Not tested      | –                  | Kopp et al. 2018          | Cobalt oxide               |
| Human hepatoblastoma cells                       | DNA damage                  | Not tested      | –                  | Kopp et al. 2018          | Cobalt oxide               |
| Human bronchial epithelial cells                 | DNA damage                  | Not tested      | +                  | Uboldi et al. 2016        | Cobalt oxide               |
| Embryonic mouse stem cells                       | DNA damage                  | –               | –                  | Derr et al. 2022          | Cobalt oxide               |
| Human hepatocarcinoma (HepG2) cells              | DNA damage                  | Not tested      | +                  | Alarifi et al. 2013       | Cobalt oxide nanoparticles |

## 2. HEALTH EFFECTS

**Table 2-10. Genotoxicity of Cobalt *In Vitro***

| Species (test system)        | Endpoint   | Results         |                    | Reference         | Form                 |
|------------------------------|------------|-----------------|--------------------|-------------------|----------------------|
|                              |            | With activation | Without activation |                   |                      |
| Mouse fibroblasts (Balb/3T3) | DNA damage | Not tested      | +                  | Ponti et al. 2009 | Cobalt nanoparticles |

<sup>a</sup>Cobalt sulfide typically has a crystalline structure.

<sup>b</sup>An amorphous form of cobalt sulfide was produced by precipitation of the sulfide salt from an ultrapure solution of cobalt chloride in water in the presence of an excess of ammonium sulfide.

<sup>c</sup>Cobalt metal powder was extracted in RPMI 1640 medium containing 5% heat-inactivated horse serum, plus 100 units/mL penicillin, 100 mg/mL streptomycin, 2.5 mg/mL amphotericin B, and 0.5 mg/mL pluronic for 72 hours and then undissolved solid was removed via centrifugation prior to testing.

– = negative result; + = positive result; (+) = weakly positive result; +/- = equivocal (an increase in revertants that is not dose related, not reproducible, or not of sufficient magnitude to support a determination of mutagenicity); CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; HPRT = hypoxanthine-guanine-phosphoribosyltransferase; SHE = Syrian hamster embryo

**Table 2-11. Genotoxicity of Cobalt *In Vivo***

| Species (exposure route) | Endpoint                                       | Results                    | Reference                      | Form            |
|--------------------------|------------------------------------------------|----------------------------|--------------------------------|-----------------|
| <b>Mammals</b>           |                                                |                            |                                |                 |
| Human (occupational)     | Micronuclei (lymphocytes)                      | –                          | De Boeck et al. 2000           | Cobalt dust     |
| Human (occupational)     | DNA damage (lymphocytes)                       | –                          | De Boeck et al. 2000           | Cobalt dust     |
| Human (environmental)    | Oxidative DNA damage (urinary 8-OHdG)          | + (children)<br>– (adults) | Banza Lubaba Nkulu et al. 2018 | Cobalt dust     |
| Human (occupational)     | Oxidative DNA damage (urinary 8-OHdG)          | –                          | De Boeck et al. 2000           | Cobalt dust     |
| Human (occupational)     | Sister chromatid exchanges (lymphocytes)       | +                          | Gennart et al. 1993            | Cobalt metal    |
| Human (occupational)     | DNA damage (mononuclear blood cells)           | +                          | Hengstler et al. 2003          | Cobalt metal    |
| Human (occupational)     | Micronuclei (lymphocytes)                      | +                          | Iarmarcovai et al. 2005        | Cobalt metal    |
| Mice (inhalation)        | Micronuclei (peripheral blood erythrocytes)    | –                          | NTP 2014                       | Cobalt metal    |
| Human (occupational)     | DNA damage (lymphocytes)                       | +                          | Iarmarcovai et al. 2005        | Cobalt metal    |
| Human (occupational)     | Oxidative DNA damage (blood 8-OHdG)            | +                          | Berniyanti et al. 2020         | cobalt metal    |
| Rat (oral)               | Chromosomal aberrations (spermatogonial cells) | –                          | Kirkland et al. 2015           | cobalt chloride |

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**Table 2-11. Genotoxicity of Cobalt *In Vivo***

| Species (exposure route)          | Endpoint                                             | Results | Reference                               | Form                        |
|-----------------------------------|------------------------------------------------------|---------|-----------------------------------------|-----------------------------|
| Mice (oral)                       | Chromosomal aberrations (bone marrow, spermatocytes) | +       | Hassan et al. 2006                      | cobalt chloride             |
| Mice (oral)                       | Chromosomal breaks and aberrations (bone marrow)     | +       | Palit et al. 1991a, 1991b, 1991c, 1991d | cobalt chloride             |
| Hamsters (i.p.)                   | Chromosomal aberrations (bone marrow)                | +       | Farah 1983                              | cobalt chloride             |
| Hamsters (i.p.)                   | Chromosomal aberrations (testicular cells)           | +       | Farah 1983                              | cobalt chloride             |
| Rat (oral)                        | Micronuclei (polychromatic erythrocytes)             | +       | Awoyemi et al. 2017                     | cobalt chloride hexahydrate |
| Mice (i.p.)                       | Micronuclei (bone marrow)                            | +       | Rasgele et al. 2013                     | cobalt chloride             |
| Mice (i.p.)                       | Micronuclei (bone marrow)                            | +       | Suzuki et al. 1993                      | cobalt chloride             |
| Rat (oral)                        | Chromosomal aberrations (bone marrow)                | –       | Kirkland et al. 2015                    | cobalt sulfate              |
| Rat (oral)                        | Chromosomal aberrations (bone marrow)                | –       | Kirkland et al. 2015                    | cobalt oxide                |
| Rat (oral)                        | Chromosomal aberrations (bone marrow)                | –       | Kirkland et al. 2015                    | cobalt tetraoxide           |
| Rat (inhalation)                  | Oxidative DNA damage (lung tissue)                   | –       | Burzlauff et al. 2022a                  | cobalt tetraoxide           |
| Rat (i.p.)                        | Oxidative DNA damage (liver, kidney, lung)           | +       | Kasprzak et al. 1994                    | cobalt acetate              |
| Nonmammalian eukaryotic organisms |                                                      |         |                                         |                             |
| <i>Drosophila melanogaster</i>    | Somatic mutation and recombination                   | +       | Ertuğrul et al. 2020                    | Cobalt chloride             |
| <i>D. melanogaster</i>            | Somatic mutation and recombination                   | +       | Kaya et al. 2002                        | Cobalt chloride             |
| <i>D. melanogaster</i>            | DNA damage (single-strand breaks)                    | +       | Ertuğrul et al. 2020                    | Cobalt chloride             |
| <i>D. melanogaster</i>            | Somatic mutation and recombination                   | +       | Ertuğrul et al. 2020                    | Cobalt nanoparticles        |
| <i>D. melanogaster</i>            | DNA damage (single-strand breaks)                    | +       | Ertuğrul et al. 2020                    | Cobalt nanoparticles        |

– = negative result; + = positive result; 8-OHdG = 8-hydroxydeoxyguanosine; DNA = deoxyribonucleic acid; i.p. = intraperitoneal

**Mutagenicity.** In general, most studies reported that both soluble and poorly soluble/insoluble forms of cobalt were nonmutagenic to *Salmonella typhimurium* with or without metabolic activation (see Table 2-10 for references). However, a few studies reported positive or equivocal results. For cobalt metal, NTP (2014) reported equivocal results without metabolic activation in *S. typhimurium* strain

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TA100 and weak mutagenicity (lacking dose response) in strain TA98 without metabolic activation. Cobalt chloride was mutagenic in strains TA97, TA98, and TA1537 without metabolic activation (Pagano and Zeiger 1992; Wong 1988). Cobalt sulfate was mutagenic in strain TA100 with and without metabolic activation in two NTP studies (NTP 1991, 1998). Zeiger et al. (1992) also reported mutagenicity for cobalt sulfate in strain TA100 with metabolic activation only. Soluble forms of cobalt were nonmutagenic in *Escherichia coli* without metabolic activation (Kanematsu et al. 1980). Cobalt chloride was nonmutagenic in *Saccharomyces cerevisiae* (Fukunaga et al. 1982; Kharab and Singh 1985; Singh 1983), but mutagenic in assays that examined gene cross-over and rho minus mutations (Fukunaga et al. 1982; Prazmo et al. 1975).

Mutations at the hypoxanthine-guanine-phosphoribosyltransferase (HPRT) locus were primarily negative for soluble and poorly soluble/insoluble cobalt forms tested in mouse lymphoma cells with or without metabolic activation (Amacher and Paillet 1980; Kirkland et al. 2015). A weak mutagenic response was reported for cobalt metal powder with metabolic activation in mouse lymphoma cells; however, these results were not reproducible with extracts of the powder, and were therefore not considered to be biologically relevant (Kirkland et al. 2015). Cobalt chloride induced HPRT mutations in Chinese hamster V79 cells without metabolic activation, with weakly positive results reported in two studies (Hartwig et al. 1991; Miyaki et al. 1979).

No *in vivo* mutagenicity data were identified.

**Clastogenicity.** *In vitro* results are mixed for the induction of chromosomal aberrations in various cultured human cells with soluble and poorly soluble/insoluble cobalt forms. Several studies reported negative results for chromosomal aberrations in human lymphocytes and human diploid cells exposed to soluble and poorly soluble/insoluble cobalt forms (Capomazza and Botta 1991; Olivero et al. 1995; Paton and Allison 1972). Conversely, cobalt chloride and cobalt oxide induced dose-dependent chromosomal aberrations in human bronchial epithelial and lung fibroblast cells (Smith et al. 2014; Xie et al. 2016). Increased sister chromatid exchanges were reported for cobalt chloride in human lymphocytes, mouse macrophage cells, and Chinese hamster V79 cells (Andersen 1983; Hartwig et al. 1991). Results for micronuclei induction in mammalian cells are generally positive for cobalt chloride, cobalt metal, and other soluble/insoluble cobalt forms (Capomazza and Botta 1991; De Boeck et al. 2003; Gibson et al. 1997; Miller et al. 2001; Olivero et al. 1995; Ponti et al. 2009; Ubaldi et al. 2016; Van Goethem et al. 1997). Three studies reported negative results for micronuclei induction in mouse fibroblasts and human

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lymphocytes treated with cobalt chloride, cobalt sulfate, or cobalt nitrate (Olivero et al. 1995; Ponti et al. 2009).

*In vivo* findings for clastogenicity of cobalt and cobalt compounds are mixed from both occupational studies in humans and laboratory studies in animals. Sister chromatid exchanges and micronuclei were increased in the lymphocytes of workers occupationally exposed to cobalt metal in the metal powder production and welding industries, respectively (Gennart et al. 1993; Iarmarcovai et al. 2005).

Micronuclei were not increased in the lymphocytes of nonsmoking workers occupationally exposed to cobalt dust from cobalt refineries and hard metal plants (De Boeck et al. 2000). Conversely, micronuclei were elevated in the lymphocytes of cobalt dust-exposed workers who smoked (De Boeck et al. 2000). In laboratory animals, cobalt chloride administered orally in mice and intraperitoneally in hamsters resulted in chromosomal aberrations in bone marrow and reproductive cells (Farah 1983; Hassan et al. 2006; Palit et al. 1991a, 1991b, 1991c, 1991d). However, more recent studies following updated (and more stringent) study guidelines reported that cobalt chloride and various poorly soluble/insoluble cobalt forms administered orally in rats did not induce chromosomal aberrations in bone marrow or spermatogonial cells (Kirkland et al. 2015). NTP (2014) reported negative findings for micronuclei in the peripheral blood erythrocytes of mice following inhalation exposure to cobalt metal. Cobalt chloride induced micronuclei in the polychromatic erythrocytes and bone marrow of orally and intraperitoneally exposed rats and mice, respectively (Awoyemi et al. 2017; Rasgele et al. 2013; Suzuki et al. 1993). However, the increased micronuclei findings in the bone marrow are potentially due to erythropoiesis stimulation, rather than direct genotoxic action of cobalt (Kirkland et al. 2015).

***DNA Interactions and Damage.*** *In vitro* findings in bacteria demonstrated increased DNA damage from exposure to cobalt chloride and poorly soluble/insoluble cobalt forms (Kanematsu et al. 1980). Two studies showed negative results for DNA damage in bacteria treated with cobalt chloride (Nishioka 1975; Rossman et al. 1984). Several studies reported positive findings for DNA damage in human lymphocytes treated with cobalt metal, cobalt metal powder, and cobalt-tungsten carbide alloy (De Boeck et al. 1998; Van Goethem et al. 1997). In contrast, De Boeck et al. (2003) and Derr et al. (2022) did not observe DNA damage in human peripheral blood mononucleated cells or in embryonic mouse stem cells following treatment with cobalt metal. Multiple studies of cobalt chloride revealed DNA damage in cultured human and rodent cells (see Table 2-10 for references). However, more recent studies conducted in cultured human cells and embryonic mouse stem cells treated with cobalt chloride (or poorly soluble/insoluble forms of cobalt) did not result in DNA damage (Derr et al. 2022; Kopp et al. 2018). Positive findings for DNA damage were reported for cobalt oxide, cobalt oxide nanoparticles, and cobalt

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nanoparticles following treatment in cultured human cells and mouse fibroblasts (Alarifi et al. 2013; Ponti et al. 2009; Uboldi et al. 2016). Additional *in vitro* assessments of cobalt chloride were either positive or weakly positive for DNA repair via gene conversion in bacteria (Fukunaga et al. 1982; Kharab and Singh 1985; Singh 1983) and positive for inhibition of DNA synthesis in human HeLa cells (Painter and Howard 1982).

DNA damage and oxidative DNA damage *in vivo* have been demonstrated in mononuclear blood cells, serum, and lymphocytes obtained from workers occupationally exposed to cobalt metal (Berniyanti et al. 2020; Hengstler et al. 2003; Iarmarcovai et al. 2005). De Boeck et al. (2000) reported negative findings for DNA damage and oxidative DNA damage in the lymphocytes and urine, respectively, of nonsmoking workers occupationally exposed to cobalt dust from cobalt refineries and hard metal plants. Conversely, oxidative DNA damage was increased in the lymphocytes of cobalt dust-exposed workers who smoked (De Boeck et al. 2000). Increased levels of a urinary biomarker for oxidative damage (8-hydroxydeoxyguanosine) was also associated with increased urinary cobalt levels in children residing in mining regions of the Democratic Republic of the Congo (D.R. Congo) (Banza Lubaba Nkulu 2018). Similar associations were not observed in adults; however, median urinary cobalt levels in children were nearly 3 times the levels observed in adults. Increased exposure in children may be due to hand-to-mouth activities recognized to occur with greater frequency in children compared to adults; Banza Lubaba Nkulu (2018) did not address this confounding factor.

In *in vivo* studies in animals, cobalt tetroxide administered to rats via inhalation did not result in oxidative damage in lung tissue (Burzlaff et al. 2022a). However, oxidative DNA damage increased in the liver, kidney, and lung of rats following intraperitoneal administration of cobalt acetate (Kasprzak et al. 1994). Positive findings were reported for DNA damage and somatic mutations/recombinations in *Drosophila melanogaster* following exposure to cobalt chloride and cobalt nanoparticles (Ertuğrul et al. 2020; Kaya et al. 2002).

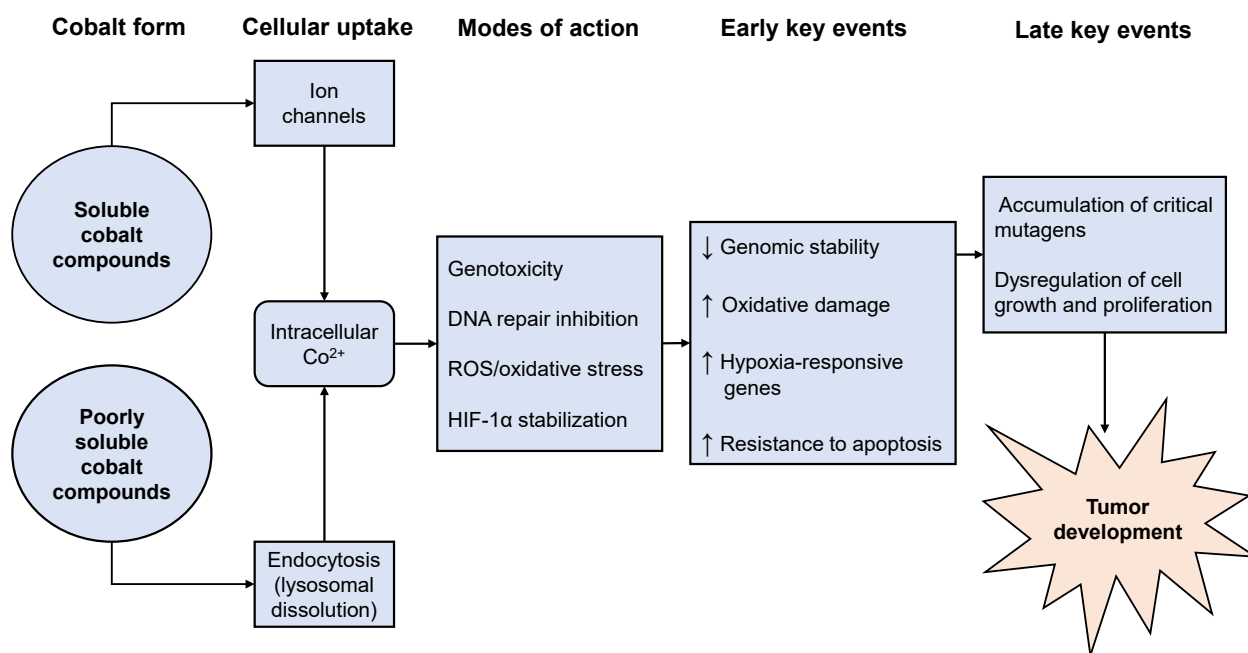
**Cell Transformation.** Cell transformation assays performed in Syrian hamster embryo cells were positive for cobalt sulfate and crystalline cobalt sulfide, while negative results were reported for amorphous cobalt sulfide (Costa et al. 1982; Procter and Gamble 1995). Crystalline is the natural structure for cobalt sulfide; amorphous cobalt sulfide was generated by precipitation of the sulfide salt from an ultrapure solution of cobalt chloride in water in the presence of an excess of ammonium sulfide.

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## 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 through the ion channels or via endocytosis of poorly soluble cobalt compounds. The poorly soluble cobalt compounds are then solubilized in the acidic environment and 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* (Figure 2-4). These include inhibition of DNA repair, genotoxicity, generation of reactive oxygen species (ROS) resulting in oxidative damage, and stabilization of hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), a protein that increases the expression of genes that promote survival of cells when they receive less oxygen (NTP 2016).

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



Source: NTP (2016)



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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 cobalt chloride on PND 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 normal homeostatic degradation of HIF-1 $\alpha$  under normal cellular oxygen conditions; thus, exposure to cobalt can often mimic hypoxic conditions in *in vitro* models (van den Brule et al. 2022; Yuan et al. 2003). This stabilization of HIF-1 $\alpha$  triggers a cascade of cellular responses to hypoxia (despite normoxic conditions). Interaction of cobalt compounds with HIF-1 $\alpha$  is highly dependent upon the bioaccessibility of cobalt; compounds with high intracellular bioaccessibility have a greater potential to stabilize HIF-1 $\alpha$  (cobalt chloride, cobalt sulfate, cobalt nitrate, cobalt oxide, cobalt hydroxide, cobalt acetate, cobalt metal, cobalt hydroxide) compared to compounds with low intracellular bioaccessibility (cobalt carbonate, cobalt sulfide, cobalt tetraoxide) (van den Brule et al. 2022; Verougstraete et al. 2022). Stabilization of HIF-1 $\alpha$  and activation of downstream targets (e.g., erythropoietin) has been proposed as the underlying mechanisms for several cobalt-associated health effects, particularly polycythemia (Hoffmeister et al. 2018; NTP 2016). Hoffmeister et al. (2019) demonstrated single or repeated oral exposure to low doses of cobalt (<1 mg Co/kg/day) increased erythropoietin levels in humans. The testicular degeneration seen as a result of cobalt exposure can be 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). However, repeated low-level exposure to cobalt may lead to increased tolerance of hypoxic conditions via activation of HIF-1 $\alpha$  and its downstream gene targets, facilitating oxygen delivery via angiogenesis, vasodilation, glucose transport, and scavenging of oxygen radicals (Shrivastava et al. 2008).

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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, GPx, 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, 2002). Several authors reported elevated markers of oxidative stress in rats following oral exposure to cobalt associated with toxic effects in various organs, including the heart, intestines, liver, kidney, and brain; some studies demonstrated that co-administration with an antioxidant attenuates toxic effects (Ajibade et al. 2017; Akinrinde et al. 2016a, 2016b, 2016c, 2019; Clyne et al. 2001; Garoui et al. 2011, 2012, 2013; Oria et al. 2022).

**2.22 COBALT NANOPARTICLES**

This section provides a brief overview of cobalt nanoparticle (CoNP) 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 CoNPs were identified. Increased levels of cobalt ions in serum and testes were observed in male rats after *in vivo* exposure of 500 µg/kg body weight 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, 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 ROS 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

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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 had an increase in relative brain, kidney, and liver weights, along with increases in erythrocyte and hemoglobin counts (Ali 2019). Acute-duration inhalation exposure to 2.12 mg/m<sup>3</sup> CoNPs for 4 days (5 hours/day) caused slight damage to respiratory tissues in rats when the lungs were assessed by electron microscopy; no histopathological changes were observed using standard light microscopy (Kyono et al. 1992). No damage was observed after a single 5-hour exposure to 2.72 mg/m<sup>3</sup> CoNPs (Kyono et al. 1992). 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 three rats in the treatment group (Brown et al. 2018). In transgenic mice (gpt delta) that were intratracheally instilled with 50 µg CoNPs per mouse and examined on days 1, 3, 7, and 28 after exposure, toxic effects identified in the respiratory system included lung inflammation, oxidative stress, injury, and cell proliferation, which further resulted in DNA damage and DNA mutation (Wan et al. 2017). Sprague-Dawley rats that underwent subcutaneous implantation of CoNPs 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. Exposures to CoNPs from inhalation, dermal, and oral routes, as well as via prosthetics and therapeutics, need 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

- 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 to 78%. The fraction of ingested cobalt that is absorbed from the gastrointestinal tract depends on an individual's nutritional status, the cobalt dose, and the type of cobalt. The ingested cobalt absorption rates range from 5 to 97%. Absorption rates vary widely among humans. Cobalt may also be absorbed through the skin; absorption through intact skin was <1%, while absorption through abraded skin was almost 80%.
- 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.
- Cobalt is not subject to metabolism by enzymatic pathway but tends to get distributed between organ systems and excreted via urine and feces.
- 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,  $^{57}\text{Co}$  and  $^{60}\text{Co}$ .

#### 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  $>2.5\ \mu\text{m}$  occurs in the upper portion of the airway, whereas particulates  $<2.5\ \mu\text{m}$  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 ( $^{57}\text{Co}$ ) cobalt oxide with

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

geometric mean diameters of 0.8 and 1.7  $\mu\text{m}$ , the average fractional deposition of the smaller particles was 52% and the average fractional deposition of the 1.7  $\mu\text{m}$  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 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 Poulsen (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 2 weeks, 3 months, or 2 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  $\mu\text{m}$  for the 2-week inhalation study, 1.4–2.0  $\mu\text{m}$  for the 3-month study, and 1.5–2.0  $\mu\text{m}$  for the 2-year inhalation study. Lung deposition rates were calculated. For both rats and mice, lung deposition rates generally increased with exposure. The 2-week study used doses of 2.5, 5, 10, and 20  $\text{mg}/\text{m}^3$ . The corresponding lung deposition rates were 1.46, 2.48, 3.12, and 8.91  $\mu\text{g Co}/\text{day}$  for rats and 0.57, 1.25, 1.87, and 2.34  $\mu\text{g Co}/\text{day}$  for mice. For the 3-month and 2-year studies, lung deposition rates were calculated for the following doses: 1.25, 2.5, and 5  $\text{mg}/\text{m}^3$ . The corresponding deposition rates for rats were 1.45, 2.13, and 5.6  $\mu\text{g Co}/\text{day}$  for the compartment with higher absorption rates and 0.018, 0.08, and 0.29  $\mu\text{g Co}/\text{day}$  for the compartment with lower absorption rates. The corresponding deposition rates for mice were 0.87, 1.84, and 1.18  $\mu\text{g Co}/\text{day}$  for the fast compartment and 0.027, 0.075, and 0.22  $\mu\text{g Co}/\text{day}$  for the slow compartment (NTP 2014).

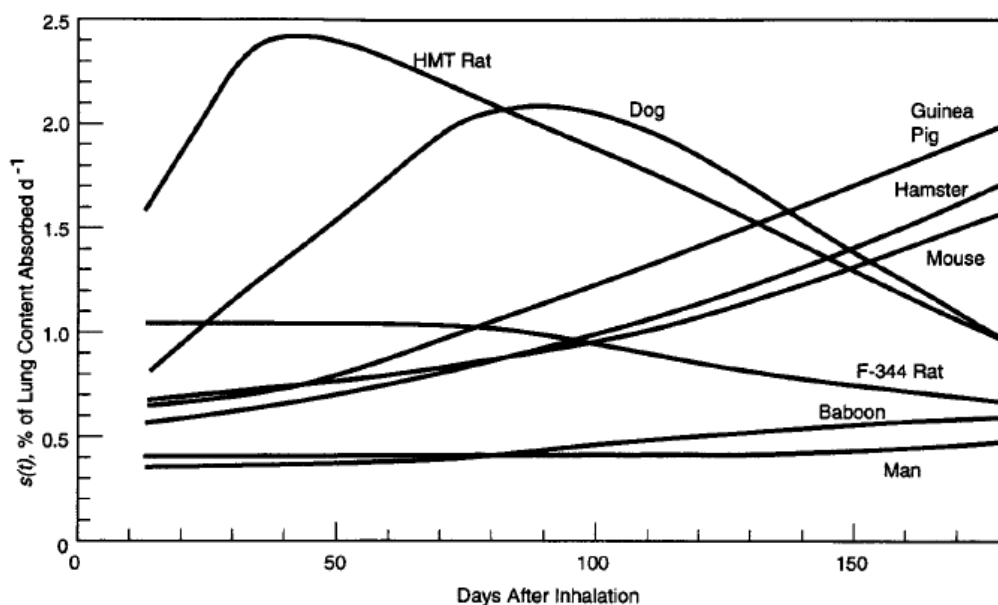
In Syrian golden hamsters exposed to cobalt oxide, absorption was reported to be approximately 27% of inhaled cobalt oxide (particle size, 1–2.5  $\mu\text{m}$ ), with 60% recovered in the gastrointestinal tract, which could reflect mucociliary transport and swallowing of particles (Wehner and Craig 1972). Collier et al. (1991) calculated translocation rates from lungs to blood in rats exposed to  $^{57}\text{Co}$ -labelled cobalt tetraoxide 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 postexposure, with the youngest rats exhibiting the highest rates.

Absorption rates from the lungs into the blood were measured in two interspecies studies using  $^{57}\text{Co}$ -labelled cobalt tetraoxide. Bailey et al. (1989) measured the rate of absorption of  $^{57}\text{Co}$ -labelled cobalt tetraoxide at two different particle sizes (0.8 and 1.7  $\mu\text{m}$ ) in humans, baboons, dogs, hamsters,

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guinea pigs, mice, and three strains of rats (Sprague-Dawley, F344, and HMT). Mice were only exposed to the 0.8  $\mu\text{m}$  size particles. The fraction of cobalt translocated for the 0.8  $\mu\text{m}$  particles was twice that of the 1.7  $\mu\text{m}$  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  $^{57}\text{Co}$ -labelled cobalt tetroxide that was denser and had a smaller specific surface area than the particles in the first study. The particle size used was 0.9  $\mu\text{m}$  (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 to 0.0015%/day for the smaller particles and 0.002 to 0.006%/day for the larger particles (Bailey and Roy 1994; Bailey et al. 1989). Results are summarized in Figures 3-1, 3-2, and 3-3.

**Figure 3-1. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 0.8  $\mu\text{m}$  Porous Cobalt Tetraoxide**

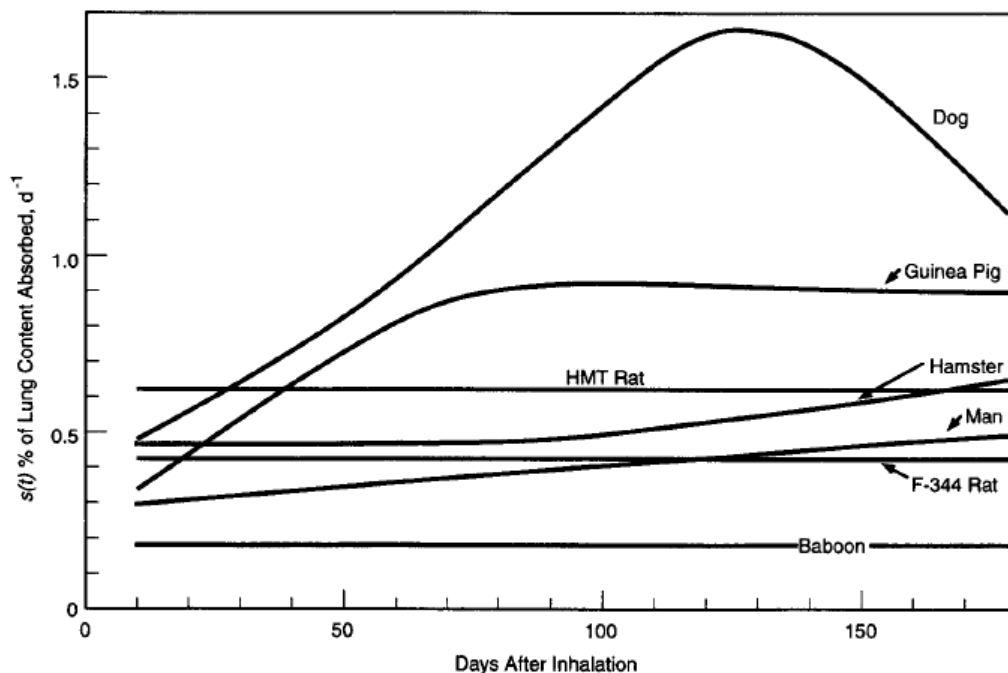


Man = data for humans (male)

Source: Bailey and Roy (1994)

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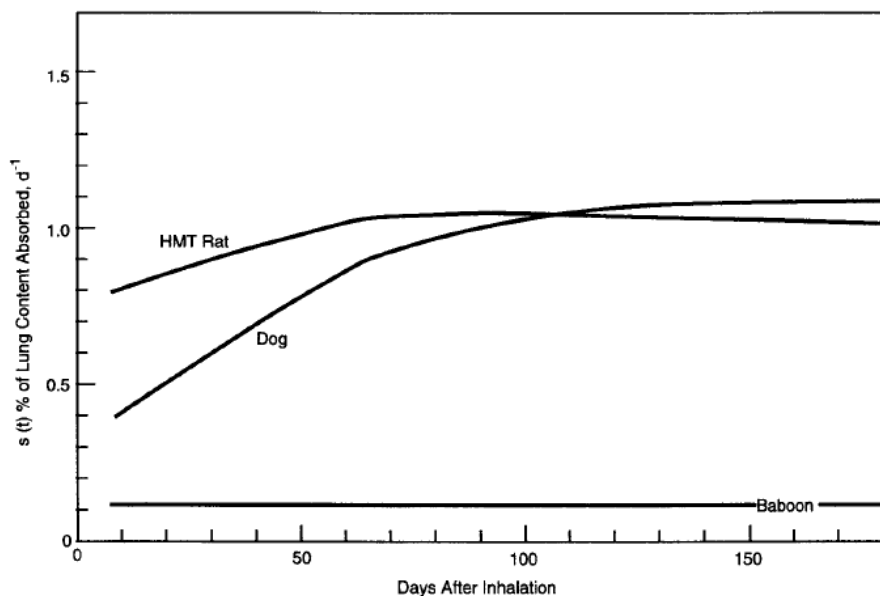
**Figure 3-2. Modeling Indicates Particle Size is Crucial for Absorption of Cobalt from Lungs to Blood after Inhalation Exposure: 1.7  $\mu\text{m}$  Porous Cobalt Tetraoxide**



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  $\mu\text{m}$  Solid Cobalt Tetraoxide**



Source: Bailey and Roy (1994)

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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 that the absorption rates range from 10 to 25% for soluble forms of cobalt administered as a solid and from 20 to 45% for soluble forms of cobalt administered as a liquid (Tvermoes et al. 2015).

Christensen et al. (1993) measured the absorption of both soluble cobalt chloride and insoluble cobalt tetraoxide in 12 male and 11 female volunteers. Based on urinary excretion of cobalt, uptake of cobalt chloride was greater than the uptake of the insoluble cobalt tetraoxide. 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 cobalt 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 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, although 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 (DMT1) (Danzeisen et al. 2020a; Knopfel et al. 2005). Since cobalt and iron share similar characteristics, it is thought that both may compete for uptake by DMT1. DMT1 is involved in transporting iron into the duodenum and is upregulated by iron deficiency or by increased demand for iron (Garlick 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).



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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 2 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<sub>12</sub> via ingestion is about 0.25 mg, of which 50–90% is contained in the liver (IARC 1991).

Absorption studies in rats have reported 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 reported 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, F344 rats, hamsters, or CBA/H mice (Bailey et al. 1989).

Danzeisen et al. (2020a) estimated the bioavailability of cobalt compounds in rats following oral exposure based on substance elution in gastric and intestinal fluids. As reported in human studies, sex differences in bioavailability were reported for cobalt chloride, with slightly higher estimated bioavailability in females (12%) than males (7%). These predictions are lower than estimates in humans (20–45%; Tvermoes et al. 2014), potentially due to differences in study design, including a single bolus administration in the rat study compared to lower doses over a 3-month period in the human study (Danzeisen et al. 2020a). The estimated bioavailabilities of cobalt sulfide and cobalt tetroxide in rats, relative to cobalt chloride, were <0.1%, suggesting that these compounds are not well absorbed (Danzeisen et al. 2020a).

Administration of cobalt chloride (labeled with radioactive <sup>58</sup>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 cobalt chloride was administered in cows' milk. Cobalt (II) glycine complex was absorbed in greater quantities than a cobalt (III) glycine complex (Taylor 1962). Taylor (1962) performed this study to better elucidate the mechanism by which absorption occurs in the gastrointestinal tract.

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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 ( $\leq 60$  days old), reported absorption is 3–15-fold greater than in adult animals (200 days of age) (Naylor and Harrison 1995).

Species differences in estimated absorption following oral exposure 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).

Studies evaluating absorption through dermal exposure are limited. In an assessment of hard metal workers, Klasson et al. (2017) reported a significant correlation with cobalt on the skin and uptake into blood and noted 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 a positive association between cobalt levels in the urine of hard metal workers and measured dermal (index finger) exposure and collected both before and after their work shift. For each doubling of pre- and post-shift dermal levels of cobalt, the median urinary cobalt levels increased by 70 and 32%, respectively. The stronger association between pre-shift dermal levels and urinary cobalt levels, compared to post-shift dermal levels, may reflect ongoing absorption from the previous day's exposure despite end-of-shift hand cleaning, possibly due to unremoved residue. Kettelarij et al. (2018b) collected urine samples over the course of 24 hours (4–11 samples per worker) and collected removable skin contamination sample (via skin wipes) pre- and post-shift, compared to the study by Klasson et al. (2017), which collected urine samples pre- and post-shift and collected samples of skin exposure once. In an experiment to measure absorption through the skin, four subjects held their right hands for 90 minutes in a box filled with either freshly mixed powder (5–15% cobalt) or waste dry powder. Both conditions resulted in an increase of urinary cobalt by an order of magnitude postexposure and continued for 48–60 hours (Scansetti et al. 1994); unlike Kettelarij et al. (2018b), end-of-shift hand washing was not addressed.

Data on absorption of cobalt through human skin are available from a limited number of *ex vitro* studies. Using cobalt powder applied in synthetic sweat, the reported steady-state percutaneous permeation through excised human abdominal skin was  $0.0123 \pm 0.0054 \mu\text{g}/\text{cm}^2/\text{hour}$ , with a lag time of

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1.55±0.71 hours with much of the cobalt remaining in the skin (Leggett 2008). Another study evaluated skin permeation and distribution of cobalt chloride hexahydrate dissolved in ammonium formate buffer solution in full thickness human skin samples (Hagvall et al. 2021). While cobalt accumulated primarily in the stratum corneum (which is ~20 µm thick), with peak intensity at 10 µm beneath the surface of the skin, it did penetrate into the epidermis to a depth of 60 µm.

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  $2.2 \times 10^{-5}$  mg  $^{60}\text{Co/kg}$  as cobalt chloride in 1.4 N HCl through 1 cm<sup>2</sup> of intact or abraded skin of guinea pigs. Absorption measured 3 hours postexposure 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<sub>12</sub>, 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<sub>12</sub> 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 µg/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<sub>2</sub>-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).

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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). In a mother-infant study from the African Copperbelt mining region, in which populations have high environmental exposure to cobalt, a high degree of placental transfer of cobalt from mother to infant was observed, with higher concentrations in umbilical cord blood, compared to maternal cord blood (Kayembe-Kitenge et al. 2023). The levels in paired maternal-cord blood samples were highly correlated, as were maternal-placental and placental-cord samples.

The tissue distribution of cobalt in animals and humans are similar. In dogs exposed to either <sup>60</sup>Co-labelled cobalt oxide or <sup>60</sup>Co-labelled cobalt tetraoxide via inhalation and following translocation from the lung, the highest cobalt concentrations were recorded in the liver, kidney, and skeleton, with <sup>60</sup>Co-labelled cobalt oxide having higher concentrations than <sup>60</sup>Co-labelled cobalt tetraoxide (Barnes et al. 1976). Cobalt oxide is more soluble than <sup>60</sup>Co-labelled cobalt tetraoxide; only 10% of the initial lung burden remained in the lung, compared to 85% for <sup>60</sup>Co-labelled cobalt tetraoxide, 8 days after inhalation exposure (Barnes et al. 1976). Brune et al. (1980) exposed rats to cobalt particles via inhalation for 8 hours/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 <sup>57</sup>Co-labelled cobalt tetraoxide was found mainly in the thoracic tissues 182 days postexposure. Seven days postexposure, the majority of the extrathoracic cobalt tissue distribution was found in the gastrointestinal 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. In dogs exposed to various forms of cobalt oxides, 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).

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In Syrian golden hamsters, the carcass (23%) and gastrointestinal tract (60%) had the most cobalt 24 hours postexposure to Cobalt oxide (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  $\mu\text{g Co/g}$  tissue) in F344/N rats (in decreasing order): lung, liver, kidney, femur, heart, serum, and blood. The tissue cobalt burden ( $\mu\text{g Co/tissue}$ ) 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 that cobalt is distributed by serum and blood (Finley et al. 2013; Tvermoes et al. 2014). Following oral administration of cobalt in volunteers for 31 days, Finley et al. (2013) reported that the rate of uptake for serum cobalt levels was  $1.3 \mu\text{g/L}$  for every  $1.0 \mu\text{g/L}$  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 volunteers. Both Finley et al. (2013) and Tvermoes et al. (2014) reported 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 volunteers who ingested approximately 1 mg cobalt/day of a dietary cobalt supplement. The study authors also reported an increase in percent of cobalt bound from 95 to 99% during the post-dosing time frame. The study authors suggested 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 ( $^{60}\text{CoCl}_2$ ) in rats, Barnaby

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et al. (1968) reported that after 1 day, the liver contained the highest level of cobalt (4% of the radioactivity administered) with <1% in all other organs. However, after 132 days, the highest levels of cobalt were reported in the muscle and skeleton, both <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 and testes (Firriolo et al. 1999). 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. Following a 90-day exposure to 7.44 mg Co/kg/day as cobalt chloride, distribution of cobalt in the tissues was primarily to the liver and kidney (Danzeisen et al. 2020a). Additional distribution was observed to the following organs, in descending order: adrenal gland, pancreas, bone plus bone marrow, ovary, uterus, prostate, brain, lungs, and testes. As expected (since cobalt is a component of vitamin B<sub>12</sub>), low levels of cobalt were observed in most tissues in sham controls.

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 cobalt sulfate in the diet for 8 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 were 100-fold higher than controls in serum, 30-fold higher than controls in the myocardium, and 26-fold higher than controls in the soleus muscle.

Skalny et al. (2021) administered cobalt chloride in drinking water to pregnant mice from 3 days prior to gestation through lactation. At weaning (day 25), the offspring were removed and exposed to cobalt chloride 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 those tissues showed time- and dose-dependent increases. Serum levels were 140-, 194-, 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.

Gluhcheva et al. (2014) showed that cobalt passes through breastmilk and that distribution in mice is dependent upon lifestage. In the study, mouse dams were exposed via drinking water to cobalt chloride hexahydrate at 19 or 31 mg Co/kg/day for 2 or 3 days prior to parturition and throughout the lactation

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period, and pups continued exposure through 90 days of age. Pups were sacrificed at intervals between PNDs 18 and 90. Cobalt accumulation in the liver and kidneys was greater in younger animals, compared to older animals, potentially due to immature enzyme systems. Cobalt distribution to the spleen was comparable across timepoints.

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

Smith et al. (1972) administered intravenous cobalt, as  $^{60}\text{Co}$ , to 23 men and one woman and performed whole-body scans up to 1,018 days postexposure. The results indicated that 10–30% of the cobalt was found in the liver. Jansen et al. (1996) administered  $^{55}\text{Co}$ -labelled cobalt chloride intravenously to two healthy adult human males. The scans showed 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 cobalt chloride intraperitoneally daily for 3 weeks. At the end of exposure, the tissues with the highest cobalt concentrations were the liver and kidney. Two hours after intravenous injection of  $^{57}\text{Co}$ -labelled cobalt chloride 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  $^{55}\text{Co}$ -labelled cobalt chloride in rats (Jansen et al. 1996). After intravenous injection of  $^{60}\text{Co}$ -labelled cobalt chloride 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  $^{60}\text{Co}$ -labelled cobalt chloride in rats. Following intramuscular injection of cobalt mesoporphyrin in rats, the liver and blood had the highest cobalt concentrations, followed by the 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 Section 3.1.2 or to be excreted as detailed in Section 3.1.4

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(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).

Following exposure of humans to physiologically insoluble cobalt compounds (e.g., cobalt metal, cobalt tetraoxide), 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. 1994). The second phase, which involves a macrophage mediated clearance from the lungs, has a half-time of 10–78 days (Beleznyay and Osvay 1994; Mosconi et al. 1994). The third clearance phase, representing long-term clearance from the lungs, has a half-time on the order of years (Bailey et al. 1989; Beleznyay and Osvay 1994; Mosconi et al. 1994; Newton and Rundo 1971).

Following a controlled aerosol exposure in humans, about 40% of the initial lung burden of inhaled <sup>57</sup>Co-labelled cobalt oxide 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 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 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).



**Table 3-1. Peak Translocation and Average Mechanical Clearance Rates (%) After Inhalation of Cobalt Oxide for 180 Days<sup>a</sup>**

| Species (strain) | Percent of lung content cleared per day for 180 days |          |         |          |                                               |
|------------------|------------------------------------------------------|----------|---------|----------|-----------------------------------------------|
|                  | Translocation at peak                                |          |         |          | Average mechanical clearance (%) <sup>b</sup> |
|                  | 0.8 µm                                               | Peak day | 1.7 µm  | Peak day |                                               |
| Human            | 0.45                                                 | 180      | 0.5     | 180      | 0.1                                           |
| Baboon           | 0.6                                                  | 180      | 0.2     | c        | 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     | c        | 0.9                                           |
| Rat (F344)       | 1.1                                                  | 10       | 0.4     | c        | 1                                             |
| Hamster          | 1.8                                                  | 180      | 0.7     | 180      | 0.8                                           |
| Mouse            | 1.7                                                  | 180      | No data | No data  | 1.05                                          |

<sup>a</sup>Cobalt-57 was used as a tracer.

<sup>b</sup>Clearance rates were virtually identical in both particle size groups.

<sup>c</sup>Constant value over 180 days.

Source: Bailey et al. (1989)

Elimination half-lives in rats and mice exposed for 2 weeks to cobalt metal were 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 3 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 phase, a slow phase, had a half-life between 19 and 23 days. For 2-year exposures in rats, dose-dependent rapid clearance phase half-lives were between 1.5 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<sup>3</sup>, 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 2 weeks, the half-lives decreased as the dose increased. Like rats exposed for 3 months, the pulmonary clearance exhibited a two-phase elimination. For mice exposed for 2 years to 1.25, 2.5, and 5 mg/m<sup>3</sup>, 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).

Following inhalation exposure, 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 (Andre et al. 1989;

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Bailey et al. 1989; Collier et al. 1989; Kerfoot 1974; Kreyling et al. 1986, 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 moderately soluble forms, such as cobalt oxide, clearing faster than insoluble forms, such as cobalt tetraoxide (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 cobalt oxide (labeled with  $^{57}\text{Co}$ ) 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<sup>a</sup>**

| Species (strain)     | Mean initial $^{57}\text{Co}$ activity in lung L(3) <sup>b</sup> (kBq) |                   | Lung retention L(90) <sup>c</sup> /L(3) (%) |                   | Lung retention L(180) <sup>d</sup> /L(3) (%) |                   |
|----------------------|------------------------------------------------------------------------|-------------------|---------------------------------------------|-------------------|----------------------------------------------|-------------------|
|                      | 0.8 $\mu\text{m}$                                                      | 1.7 $\mu\text{m}$ | 0.8 $\mu\text{m}$                           | 1.7 $\mu\text{m}$ | 0.8 $\mu\text{m}$                            | 1.7 $\mu\text{m}$ |
| 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               |
| 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           |

<sup>a</sup>Cobalt-57 was used as a tracer.

<sup>b</sup>Lung deposits at Day 3.

<sup>c</sup>Lung deposits at Day 90.

<sup>d</sup>Lung deposits at Day 180.

Source: Bailey et al. (1989)

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 hours of oral administration of radioactive  $^{57}\text{Co}$ - or  $^{60}\text{Co}$ -labelled cobalt chloride, 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%).

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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. Postdosing 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 1-week postdosing. 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 3 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 1 and 2 weeks post oral dosing decreased by 63 and 69%, respectively, in healthy male volunteers who received 0.4 mg cobalt/day for 15 days, indicating that much of the cobalt was rapidly eliminated from the blood postdosing (Tvermoes et al. 2013).

Tvermoes et al. (2014) 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/minute) and women (99 mL/minute) and the differences in urine production volume between men (2,900 mL) and women (1,800 mL). The ratios of urine to serum cobalt concentrations for men and women throughout dosing were 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 (Cobalt Chloride) in Whole Blood and Serum in Humans after Oral Dosing**

|             | First phase                      |                                     | Second phase     |                     |                                     |                  |
|-------------|----------------------------------|-------------------------------------|------------------|---------------------|-------------------------------------|------------------|
|             | Fraction eliminated <sup>a</sup> | 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               |

<sup>a</sup>Over a period of 22–36 days.

Source: Tvermoes et al. (2014)

Animal studies demonstrate that soluble cobalt is excreted through the urine and insoluble cobalt is excreted through the feces. Table 3-4 provides the cumulative urinary and fecal elimination in several species following oral administration of cobalt tetroxide (with a <sup>57</sup>Co tracer) (Bailey et al. 1989). No significant differences in elimination of cobalt tetroxide were found among several species of animals, and >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 postexposure, 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 cobalt tetroxide 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% was excreted in the urine (Kreyling et al. 1986).

**Table 3-4. Summary of Retention and Excretion After Intragastric Administration of Cobalt Tetraoxide Particles (Mean Percentage of Recovered Activity at 7 Days Post Administration)<sup>a</sup>**

| 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    |

**Table 3-4. Summary of Retention and Excretion After Intragastric Administration of Cobalt Tetraoxide Particles (Mean Percentage of Recovered Activity at 7 Days Post Administration)<sup>a</sup>**

| 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  |
| 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 |

<sup>a</sup>Cobalt-57 was used as a tracer.

Source: Bailey et al. (1989)

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. (2020a, 2020b) reported plasma toxicokinetic parameters and fecal and urinary excretion kinetics for different cobalt compounds administered by gavage. The results are presented in Tables 3-5 and 3-6. Values for the maximum plasma concentration ( $C_{\max}$ ), half-life ( $t_{1/2}$ ), and elimination constant ( $K_{el}$ ) were comparable for all three substances (at administered doses), except that  $C_{\max}$  for cobalt tetraoxide was twice as high in male as in female rats. Large differences in estimated oral bioavailability (AUC) due to substance solubility were expected and confirmed. The predominant excretion pathway was via fecal excretion, which decreased with solubility (>80% for cobalt chloride hexahydrate; >95% for cobalt tetraoxide), with some urinary excretion. Excretion levels were highest on day 1 following exposure, with levels on subsequent days at least an order of magnitude lower (Table 3-6).

**Table 3-5. Pharmacokinetic Parameters for Orally Administered Cobalt in Rats**

| Test item                   | Dose level (mg Co/kg) | $C_{\max}$ (mg/L) | $t_{1/2}$ (hours) | $K_{el}$ (1/hour) | $AUC_{0-t \text{ last}}/\text{cobalt dose}$ [(hour mg/L)/(mg/kg)] |
|-----------------------------|-----------------------|-------------------|-------------------|-------------------|-------------------------------------------------------------------|
| Male rats                   |                       |                   |                   |                   |                                                                   |
| Cobalt chloride hexahydrate | 2.48                  | 2.51              | 14.2              | 0.0489            | 20                                                                |
| Cobalt tetraoxide           | 214                   | 2.08              | 17.3              | 0.0402            | 0.18                                                              |
| Cobalt sulfide              | 194                   | 2.01              | 16.8              | 0.0413            | 0.1                                                               |

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**Table 3-5. Pharmacokinetic Parameters for Orally Administered Cobalt in Rats**

| Test item                   | Dose level<br>(mg Co/kg) | C <sub>max</sub><br>(mg/L) | t <sub>1/2</sub><br>(hours) | K <sub>el</sub><br>(1/hour) | AUC <sub>0-t last</sub> /cobalt dose<br>[(hour mg/L)/(mg/kg)] |
|-----------------------------|--------------------------|----------------------------|-----------------------------|-----------------------------|---------------------------------------------------------------|
| <b>Female rats</b>          |                          |                            |                             |                             |                                                               |
| Cobalt chloride hexahydrate | 2.48                     | 2.61                       | 13.7                        | 0.0508                      | 13.7                                                          |
| Cobalt tetraoxide           | 214                      | 1.10                       | 16.1                        | 0.043                       | 0.12                                                          |
| Cobalt sulfide              | 194                      | 2.01                       | 14.9                        | 0.0464                      | 0.1                                                           |

AUC<sub>0-t last</sub> = area under the curve from time (t) zero to t last; C<sub>max</sub> = maximum plasma concentration; K<sub>el</sub> = elimination constant; t<sub>1/2</sub> = half-life

Source: Danzeisen et al. (2020a)

**Table 3-6. Cobalt Levels in Urine and Feces in Rats Following Oral Exposure to Cobalt**

| Substance                   | Dose level<br>(mg Co/kg) | Cobalt concentration in<br>urine (µg Co/L) |       |       | Cobalt concentration in<br>feces (µg Co/g) |       |       |
|-----------------------------|--------------------------|--------------------------------------------|-------|-------|--------------------------------------------|-------|-------|
|                             |                          | Day 1                                      | Day 2 | Day 3 | Day 1                                      | Day 2 | Day 3 |
| Male rats                   |                          |                                            |       |       |                                            |       |       |
| Cobalt chloride hexahydrate | 2.48                     | 9,791                                      | 834   | 239   | 41.11                                      | 3.91  | 1.69  |
| Cobalt tetraoxide           | 220                      | 6,344                                      | 379   | 307   | 5,502.63                                   | 258.5 | 23.33 |
| Female rats                 |                          |                                            |       |       |                                            |       |       |
| Cobalt chloride hexahydrate | 2.48                     | 4,974                                      | 411   | 247   | 47.55                                      | 2.77  | 0.35  |
| Cobalt tetraoxide           | 220                      | 5,158                                      | 572   | 172   | 5,335.27                                   | 233.6 | 6.59  |

Source: Danzeisen et al. (2020b)

Urinary excretion of cobalt increased from a pre-exposure level of 18.1 nmol (1.07 µg) to 38.5 nmol (2.27 µg) 24 hours after exposure in five subjects who were dermally exposed for 1 hour by keeping their hands in a solution containing 1,600 mg Co/L. The maximum amount of cobalt excreted occurred 4–6 hours after exposure in two subjects; 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 cobalt chloride 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.

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In humans with metal-on-metal hip replacements, urinary cobalt levels were 3-fold higher than concentrations in plasma. Cobalt clearance increased from 1.3 mL/minute in the preoperative group to 3.7 mL/minute in the follow-up group; with increasing daily output, the renal clearance in the postoperative group increased from 1.9 to 7.1 mL/minute (Daniel et al. 2010). Smith et al. (1972) reported that 24 hours after intravenous administration of  $^{60}\text{Co}$ -labelled cobalt chloride, 22% of the administered dose was excreted in the urine, 1.8% of the administered dose was excreted in the feces, and >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 1,000 days showed the following half-times and corresponding percentages leaving the body: 0.5 days (44%); 6 days (32%); 60 days (13%); and 800 days (11%). The liver retained an average of 20% of the total body burden from a few days post administration through 1,000 days post injection (Smith et al. 1972).

Paley et al. (1958) reported that 56–73% of the dose was excreted in urine 48 hours after intravenous administration and Kent and McCance (1941) reported that 57% was excreted in 2 weeks. The average urinary excretion of  $^{57}\text{Co}$  in 13 healthy human subjects (9 males and 4 females) during the first 24 hours after intravenous injection of cobalt glycinate was 34%, with no gender differences reported. Following intravenous injection of  $^{57}\text{Co}$  glycinate, the urinary to fecal excretion ratio of 6:1 was measured in one subject over the course of 3 days (Leggett 2008).

Following intravenous injection of cobalt nitrate 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 3-7) (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 cobalt chloride and cobalt nitrate, and both were excreted rapidly from the body (Rosenberg 1993; Talbot and Morgan 1989).

**Table 3-7. Summary of Retention and Excretion of Cobalt Following Injection of Cobalt Nitrate Solution (Mean Percent Recovery)<sup>a</sup>**

| Species (strain) | Whole-body retention on day |     |     | Cumulative urinary excretion on day |    |    | Cumulative fecal excretion on day |     |     |
|------------------|-----------------------------|-----|-----|-------------------------------------|----|----|-----------------------------------|-----|-----|
|                  | 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 (F344)       | –                           | –   | 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  |

<sup>a</sup>Cobalt-57 was used as a tracer.

Source: Bailey et al. (1989)

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 ( $t_{1/2}$  of 3 days) in rats than cobalt chloride, where >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 <sup>60</sup>Co-labelled cobalt chloride and <sup>58</sup>Co-labelled cobalt-cyanocobalamin into rats. After 21 days post administration of <sup>60</sup>Co-labelled cobalt chloride, 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 <sup>58</sup>Co-labelled cobalt-cyanocobalamin in the kidneys was 43.8%, with 12% in the liver. Most of the isotope activity was in the feces. Cumulative excretion over 9 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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). 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 (Clewell 1995).

The International Commission on Radiological Protection (ICRP) developed two models to evaluate the kinetics of cobalt: a Human Respiratory Tract Model (HRTM) (Bailey et al. 2007; ICRP 1994, 1995), and a systemic model (ICRP 2016; Legget 2008). The HRTM simulates the deposition, clearance, and absorption of inhaled particulates. The systemic model simulates the distribution and excretion of cobalt absorbed from the respiratory tract or gastrointestinal tract.

The ICRP (2016) has published HRTM parameter values for absorption of cobalt compounds (Table 3-8). The HRTM assumes that absorption into blood occurs at equivalent rates in all parts of the respiratory tract, except in the anterior nasal passages, where no absorption occurs. Absorption is simulated as a two-stage process that begins with particle dissolution, followed by transfer of dissolved material into blood. Dissolution is simulated as a biphasic process with a rapid phase, fraction  $f_{\text{rapid}}$  dissolving at rate  $k_{\text{rapid}}$  ( $\text{day}^{-1}$ ), and a slow phase, fraction,  $f_{\text{slow}}(1-f_{\text{rapid}})$  dissolving at rate  $k_{\text{slow}}$  ( $\text{day}^{-1}$ ). A fraction of the dissolved material is bound ( $f_{\text{bound}}$ ) and is transferred to blood at rate ( $k_{\text{bound}}$ ). The unbound fraction,  $1-f_{\text{bound}}$ , is transferred instantaneously to blood. In the absence of specific estimates for absorption kinetics, compounds are classified into absorption types F (fast), M (medium), and S (slow).

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**Table 3-8. ICRP (2016) Absorption Parameter Values for Cobalt**

| Type <sup>a</sup>          | Rapid fraction | Slow fraction | Rapid rate (day <sup>-1</sup> ) | Slow rate (day <sup>-1</sup> ) | Bound fraction | Bound rate (day <sup>-1</sup> ) | GI tract absorption fraction <sup>b</sup> |
|----------------------------|----------------|---------------|---------------------------------|--------------------------------|----------------|---------------------------------|-------------------------------------------|
| <b>Inhaled cobalt</b>      |                |               |                                 |                                |                |                                 |                                           |
| Fast (F)                   | 1.0            | 0             | 1                               | NA                             | 0.03           | 0.002                           | 0.1                                       |
| Medium (M)                 | 0.2            | 0.8           | 1                               | 0.005                          | 0.03           | 0.002                           | 0.02                                      |
| Slow (S)                   | 0.01           | 0.99          | 1                               | 1x10 <sup>-4</sup>             | 0.03           | 0.002                           | 0.001                                     |
| <b>Ingested cobalt</b>     |                |               |                                 |                                |                |                                 |                                           |
| Insoluble oxides           |                |               |                                 |                                |                |                                 | 0.05                                      |
| All other cobalt compounds |                |               |                                 |                                |                |                                 | 0.1                                       |

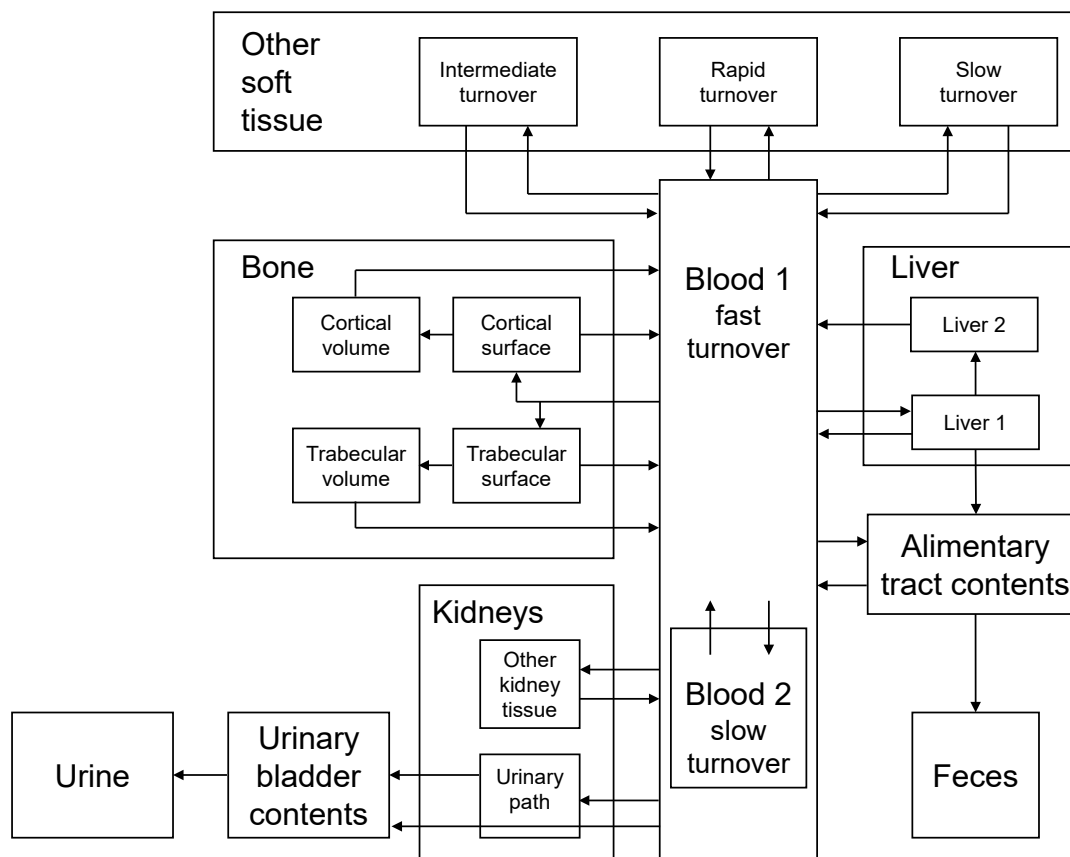
<sup>a</sup>Type F: cobalt chloride, cobalt nitrate; Type M: default for other cobalt compounds in the absence of specific estimates for absorption kinetics; and Type S: cobalt oxide.

<sup>b</sup>Cobalt cleared from the respiratory tract to the GI tract.

GI = gastrointestinal; HRTM = Human Respiratory Tract Model; ICRP = International Commission for Radiological Protection

The ICRP systemic model (Legget 2008; ICRP 2016; ) includes compartments representing blood (central distributing compartment), bladder, bone, gastrointestinal tract, kidney, liver, and other soft tissues (Figure 3-4). The blood compartment includes fast and slow turn-over subcompartments. Transfers of cobalt between blood and tissues occurs to and from the fast turn-over compartment. Other tissue compartments also have subcompartments representing different kinetic pools. Transfers between compartments are governed by first-order rate coefficients (day<sup>-1</sup>). Absorption from the gastrointestinal tract into the fast turn-over compartment of blood is simulated with an absorption fraction. ICRP (2016) assigned absorption fractions of 0.05 for ingested cobalt oxides and 0.1 for all other cobalt compounds.

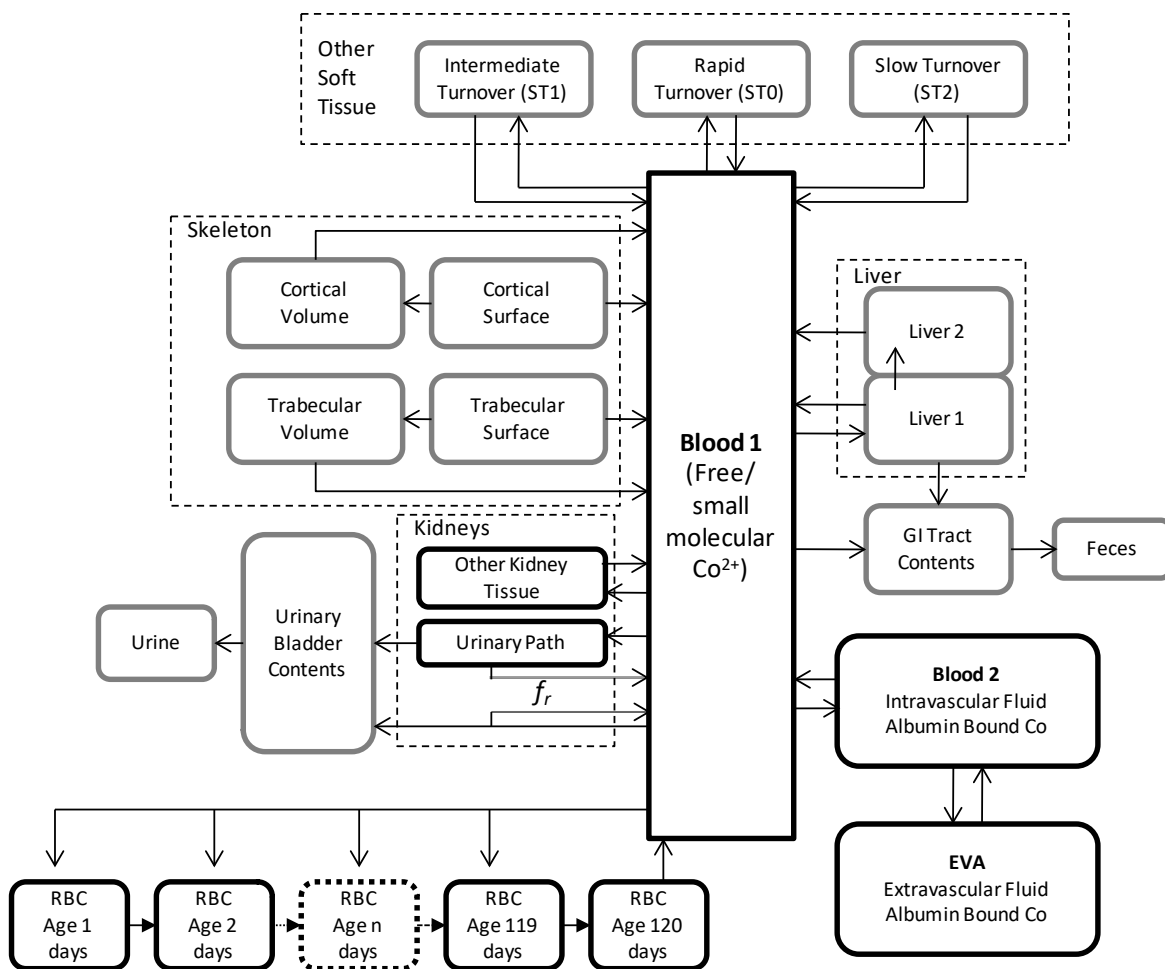
Unice et al. (2012, 2014a, 2014b) modified the Leggett (2008) model in several ways. The Unice et al. (2012) model assigned a central tendency estimate for the gastrointestinal absorption fraction of 0.25, with a minimum of 0.1 and a maximum of 0.35 based on available data for men and women, assumed 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 20 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 15–35% absorption rate (Tvermoes et al. 2013).

**Figure 3-4. Structure of ICRP (2016) Cobalt Systemic Model**

Source: ICRP (2016), with permission from The International Commission on Radiological Protection

Unice et al. (2014a, 2014b) 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  $\text{Co}^{2+}$ , and effect of glomerular filtration rates and free  $\text{Co}^{2+}$  on cobalt excretion. The changes incorporated included increasing the fraction of serum protein bound cobalt from 95% during dosing to 99% postdosing; adding a postdosing 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. (2014a) compared the model output to several data sets including healthy 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 depicts the model design.

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

**Figure 3-5. Structure of Unice et al. (2014b) Cobalt Systemic Model**

Source: Unice et al. (2014b), with permission from Elsevier

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

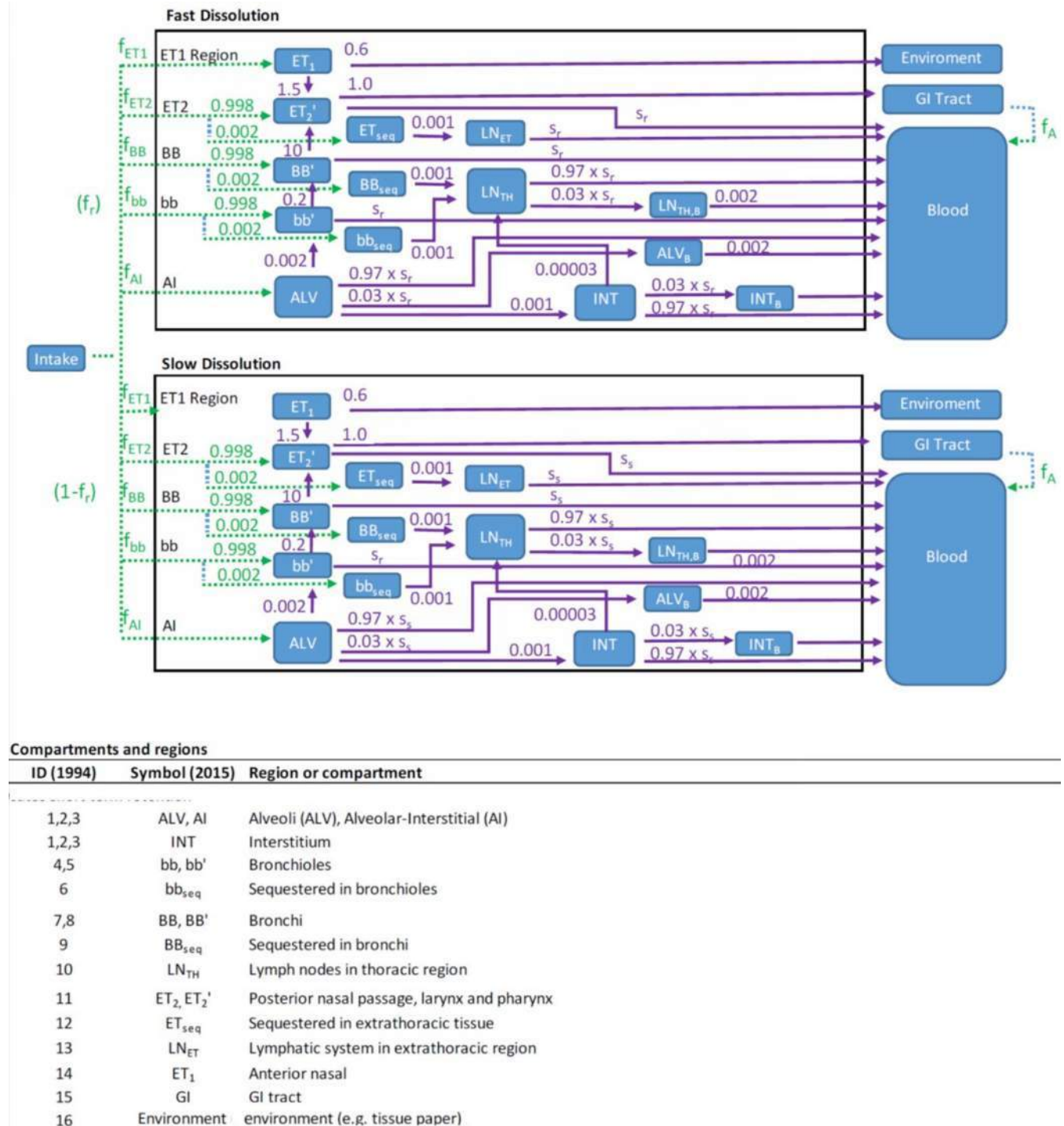
Unice et al. (2020a, 2020b) further updated their cobalt models to include an inhalation pathway based on the ICRP HRTM (Figure 3-6). Their modified ICRP HRTM accounts for particle-size-dependent deposition in the extrathoracic region, both the bronchial and bronchiolar airways, and the alveolar–interstitial region of the lungs. A default particle density of 3 g/cm<sup>3</sup> was used. Other assumptions for most forms of cobalt included moderate respiratory absorption rates (ICRP ‘Type M’), with a rapid fraction of 0.2, rapid dissolution half-life of 17 hours, slow dissolution half-life of 137 days, and absorption fraction from the alimentary tract of 0.02. For the oral absorption component of the model, both ingested dust along with the estimated absorption fraction from the alimentary tract (due to particles clearance from the respiratory tract) were utilized. These oral components were used together with the HRTM in Unice et al. (2020a). 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. 2020a).

### 3.1.6 Animal-to-Human Extrapolations

Retention and clearance of physiologically insoluble <sup>57</sup>Co particles after inhalation 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). While PBPK models are available (Section 3.1.5), they are either restricted to kinetic modeling in humans (ICRP models) or model assumptions for cobalt are based on human data (Unice et al. 2020a). Therefore, they are not suitable for animal-to-human dose extrapolations.

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

Figure 3-6. Updated Model Inhalation



Source: Unice et al. (2020b), with permission from Elsevier

### 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 cobalt tetroxide, 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 postexposure where there were significant differences among all age groups. The study 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 <sup>57</sup>Co-labelled cobalt tetroxide 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 1 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,

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

0.14% of the dose was found in the fetus, 0.19% was found in the chorioallantoic placenta, and 0.22% was found 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 <1% of the maternal dose reached the fetus (Nishimura et al. 1978; Zylicz and Zabłoina 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 (<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 reported low amounts of cobalt in the breast milk. Milk obtained 70 days postexposure from lactating dairy cows contained 0.012% of the exposure dose (Van Bruwaene et al. 1984). Cobalt given intravenously to mother rats as cyanocobalamin was transferred to offspring via the breast milk (1–2%) (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, suffer from sepsis, or have sickle-cell disease could have higher levels of free cobalt in organ tissues due to either a decrease in serum albumin levels or an increase in serum ischemia-modified



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albumin, which 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 the 2003–2012 National Health and Nutrition Examination Survey (NHANES) data 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, 1989). Sensitization to cobalt in hard metal workers causes 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, 1989). Two studies by Potolicchio et al. (1997, 1999) suggested that the presence of a polymorphism (for glutamate 69 in the  $\beta$  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 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).

Developmental effects have not been observed in animals exposed only during gestation, even at maternally toxic oral exposure levels (Paternian and Domingo 1988; Seidenberg et al. 1986). However, effects have been reported in animals following oral exposure during both pre- and postnatal developmental periods, including impaired growth and survival as well as systemic effects similar to those observed in adult animals (e.g., hematological effects) (Danzeisen et al. 2020a; Domingo et al. 1985b; Gluhcheva et al. 2020). Since these findings were examined only in a limited number of studies at a limited number of doses and/or were often observed at doses associated with maternal toxicity or at doses comparable to adult toxicity, it is unknown if the developing fetus or infant will be more susceptible to cobalt toxicity compared to an adult.

Genetic polymorphisms may infer differential susceptibility to risk of cancer from exposure to high levels of cobalt (e.g., occupational exposure). Mateuca et al. (2005) evaluated potential associations between polymorphisms associated with reduced capacity for DNA repair and chromosomal abnormalities (micronucleated mononucleates or binucleates), DNA damage, and oxidative DNA damage (urinary 8-OHdG) in workers exposed to cobalt or hard metal (tungsten-cobalt) and in unexposed controls. Genes evaluated included those involved in base-excision (*hOGG1*, *XRCC1*) and double-strand break (*XRCC3*). The analysis showed that the *XRCC3*<sup>241</sup> and *hOGG1*<sup>1326</sup> variants were associated with increased micronucleated mononucleates in both the exposed workers and the total study population (workers and

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

controls. The Arg/His or His/His *XRCC<sup>1280</sup>* variant was associated with increased DNA damage in the total study population.

### 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 2006).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see <http://www.cdc.gov/exposurereport/>). If available, biomonitoring data for cobalt from this report are discussed in Section 5.6, General Population Exposure.

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 2006). 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 2006). 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 internal dose metrics (e.g., cobalt levels in urine and/or blood), information regarding external exposure levels is typically not available. Typical background levels (geometric mean) of urinary cobalt in humans ranged from 0.32 to 0.42  $\mu\text{g/L}$  and blood cobalt was 0.151  $\mu\text{g/L}$  (Hoet et al. 2013). Elevated levels of cobalt have been measured in the blood after supplementation of inorganic cobalt (Finley et al. 2013; Tvermoes et al. 2013, 2014).

Goldoni et al. (2004) measured cobalt in the exhaled breath of hard metal workers and found cobalt in the exhaled breath at 11.9–741 nanomoles/L, 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).

Wahlqvist et al. (2020) examined the relationships between concurrent inhalation and dermal exposure to cobalt particulates in the air to blood and urine levels 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. Cobalt uptake was higher than expected based on low air concentrations, and the study authors suspected that it was from oral co-exposure from eating with unwashed hands and using oral tobacco products while working. Klasson et al. (2017) also reported associations in hard metal workers between blood cobalt levels and measured cobalt levels in the air and on the skin. Kettelarij et al. (2018b) reported a strong association between measured air levels of cobalt and urinary cobalt levels in hard metal workers. Associations were also observed between cobalt deposits on the skin (measured pre- and post-shift) and urinary cobalt levels; however, the association was stronger pre-shift compared to post-shift, potentially due to continued absorption from the previous workday. Kettelarij et al. (2018b) suggested that these data indicate that urine may be a good biomarker of dermal exposure to cobalt. However, based on low solubility of cobalt dust, and a weaker association between urinary cobalt and post-shift skin cobalt levels despite much higher post-shift skin levels, urinary cobalt levels are more likely reflective of inhalation exposure and potential oral exposure (via hand-to-mouth transfer during eating and/or smoking). Hutter et al. (2016) reported urinary cobalt levels of 200  $\mu\text{g/L}$  at an exposure of 1  $\text{mg/m}^3$  cobalt in air based on scant information (147 air samples, 1,166 urine results for 253/1969 workers, during 27 years). The study authors proposed that results indicated oral co-exposure because urinary

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cobalt was higher in smokers than nonsmokers, based on exposure via the “dust-hand cigarette-mouth path.” Common among these studies was that inhalation exposure dominated the relationship with both blood or urine levels, dermal cobalt was incompletely removed by washing, and the impact of oral co-exposure on dermal uptake assessments was unclear.

Earlier studies reported 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<sup>3</sup> cobalt resulted in blood levels of cobalt of 0.57–0.79 µg/dL and urinary levels of 59–78 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 postexposure, peaking 2–4 hours after the workday 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).

Elevated cobalt levels have also been identified in hair and toenail samples of populations living near a mine tailings repository in Zambia, with mean levels of 0.9 and 1.0 mg/kg, respectively (Nakaona et al. 2020). Levels measured in hair and toenails were positively correlated with each other. According to the study authors, hair and toenail levels were elevated, but they did not correlate with exposures from food or water; levels in the air were not evaluated (Nakaona et al. 2020). Based on available data, it is unclear if either hair or nails are reliable biomarkers of exposure. Elevated cobalt levels were also observed in toenail samples of children living near mine tailings in Western Uganda (2.21 mg/kg), compared to referents living >400 km from the mine (0.49 mg/kg); however, findings were similar between adults living near the mine (0.37 mg/kg) and referents (0.42 mg/kg) (Mwesigye et al. 2016). Mwesigye et al. (2016) noted that presence of dust was prevalent in toenails, even after washing; therefore, toenails may be unreliable biomarkers of exposure via food and water contamination from mine tailings in human populations in which subjects’ feet are frequently directly exposed to contaminated soil. Ren et al. (2020) also noted the importance of thorough and efficient washing strategies when using hair samples for metal(loid) exposure analysis to reduce interference for ambient air pollution. Additionally, care should be taken to prevent the washing technique from stripping cobalt from within the hair and toenails. Seasonal patterns have also been observed for metals and other trace elements in toenails collected in women in the United States, including cobalt, with peak levels observed in summer months (Wojcik et al. 2024). Increased levels in toenail samples (not correlating to increased environmental levels) may be due to changes in footwear in the summer, use of nail polish in warmer months (which may trap trace elements), and/or seasonal variation in nail growth. Regardless of the mechanism, based

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upon these findings, the study authors suggested that studies using toenail concentrations as biomarkers of exposure should correct exposure levels for the season during which the toe clipping were collected.

#### 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 FEV<sub>1</sub> and FVC lung parameters, in particular a decrease in FEV<sub>1</sub>/FVC ratio, plus increased cough, dyspnea, and sputum. The FEV<sub>1</sub> and FVC measures correlated with urinary cobalt concentrations (Gennart and Lauwerys 1990; Kusaka et al. 1986a). Elevated levels of CC16, a lung surfactant protein, is a proposed biomarker for identification of early lung damage in workers with dust and chemical exposures due to its correlation with pulmonary inflammation and epithelial damage (Andersson et al. 2020). Elevated serum CC16 levels were associated with increasing cumulative exposure to inhalable cobalt in Swedish hard metal workers; cumulative exposure levels in this cohort were not associated with decrements in lung function (Andersson et al. 2020).

Oral exposure to cobalt caused increases in hemoglobin and hematocrit in humans (defined as polycythemia by the study authors) (Davis and Fields 1958). Increases in hemoglobin and hematocrit were also observed in animal studies after inhalation exposure (NTP 1991, 1998, 2014). 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 study authors, polycythemia and reduced iodide uptake were reported (Finley et al. 2012a). Additionally, monitoring of cobalt-specific changes in serum antibodies (IgE and IgA) could indicate that sensitization to cobalt occurred (Bencko et al. 1983; Shirakawa et al. 1988, 1989). More research is needed in this area to identify biomarkers of effect after exposure to cobalt as changes in respiratory function, 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 cobalt chloride 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

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

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 cobalt chloride exposure on tissue distribution of metal ions in immature mice (see Section 3.12 for details on the experiment). A time- and dose-dependent effect by cobalt chloride on tissue levels of copper, iron, manganese, and zinc was reported. The study authors suggested that exposure to cobalt alters essential mineral metabolism. Moshtaghi 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  $\beta$  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 ribonucleic acid (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; GSH metabolism and steroidogenesis; and xenobiotic metabolism (Glahn et al. 2008).

Radioactive cobalt-57, in combination with bleomycin, is used in cancer treatment as a therapeutic agent (Goodwin and Meares 1976; Hansen et al. 1976; Kapstad 1978, 1979; Li et al. 2018). 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). However, bleomycin has been associated with adverse effects (hair loss, emesis, weight loss, pneumonitis, fibrosis, and loss of lung diffusion capacity for carbon monoxide) (Li et al. 2018).

Cobalt chelators have been tested in rats to evaluate their mitigation potential in reducing the toxic effects of cobalt (Baker and Czarnecki-Maulden 1987; Domingo et al. 1983; Llobet et al. 1988). In rats previously exposed to cobalt, urinary excretion of cobalt was increased by treatment with GSH and diethylenetriaminepentaacetic acid and fecal excretion of cobalt was increased by treatment with EDTA

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and 2,3-dimercaptosuccinic acid. Treatment with N-acetyl-L-cysteine (NAC) increased both urinary and fecal excretion of cobalt. The amino acid, cysteine, also reportedly reduced the toxicity of cobalt in chicks (Baker and Czarnecki-Maulden 1987). British anti-Lewisite bound to hyaluronic acid (BAL-HA) has also been shown to be an effective chelator *in vitro*; this particular chelator was developed to reduce toxicity of cobalt ions in synovial fluid following metal-on-metal joint replacement surgeries (Ude et al. 2023).

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.

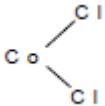
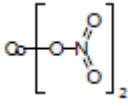
Hard metal dusts, consisting of 5–10% cobalt with the balance being tungsten carbide, were considerably more toxic than cobalt or tungsten carbide particles alone (Harding 1950). The increase in toxicity could be the result of the oxidation of cobalt metal to ionic cobalt, which results in increased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

## 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,  $^{59}\text{Co}$ . The other known isotopes of cobalt are not naturally occurring. Most of the radioactive forms have masses of 47–58 and 60–77 (NNDC 2023). The radioactive properties of cobalt isotopes are maintained in the United States by the National Nuclear Data Center.  $^{60}\text{Co}$ , the most common radioisotope, is formed by the neutron activation of stable  $^{59}\text{Co}$ , has a 5.27-year half-life.  $^{60}\text{Co}$  is radioactive and emits beta particles (mean beta-energy 96.41 keV; total intensity 100%) and gamma radiation (1,173 keV 99.85%, 1,332 keV 99.98%) (NNDC 2023) forming a stable nickel isotope ( $^{60}\text{Ni}$ ). 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 used to detect internal flaws in metals (Clark 2023; Gregersen 2023). The cobalt isotopes  $^{57}\text{Co}$ ,  $^{58}\text{Co}$ , and  $^{60}\text{Co}$  are byproducts of nuclear reactor operations. Cobalt isotopes have half-lives that are specific to the isotope, and range from seconds to years (Clark 2023; NNDC 2023). Information regarding the chemical identity of cobalt and selected cobalt compounds is presented in Table 4-1.

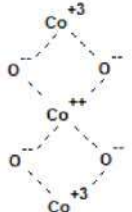
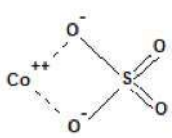
**Table 4-1. Chemical Identity of Cobalt and Selected Cobalt Compounds**

| Characteristic                          | Cobalt                                                         | Cobalt (II) chloride                                                                         | Cobalt (II) nitrate                                                                           |
|-----------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Synonym(s) and Registered trade name(s) | Cl 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                                                             | $\text{CoCl}_2$                                                                              | $\text{Co}(\text{NO}_3)_2$                                                                    |
| SMILES                                  | Co                                                             | <chem>Cl[Co]Cl</chem>                                                                        | <chem>[N+](=O)([O-])[O-].[N+](=O)([O-])[O-].[Co+2]</chem>                                     |
| Chemical structure                      | Co                                                             |           |          |
| CAS registry number                     | 7440-48-4                                                      | 7646-79-9 (anhydrous)                                                                        | 10141-05-6 (anhydrous)                                                                        |



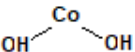
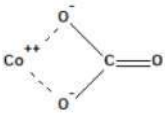
## 4. CHEMICAL AND PHYSICAL INFORMATION

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

| Characteristic                          | Cobalt (II) oxide                                                                                                | Cobalt tetroxide                                                                                                                                                                               | Cobalt (II) sulfate                                                                                                                            |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Synonym(s) and Registered trade name(s) | Cobalt monoxide; Cobalt Black; Zaffre; Oxocobalt; cobaltous oxide; Mmonocobalt 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 <sub>3</sub> O <sub>4</sub>                                                                                                                                                                 | CoSO <sub>4</sub>                                                                                                                              |
| SMILES                                  | O=[Co]                                                                                                           | [O-2].[O-2].[O-2].[O-2].[Co+2].[Co+3].[Co+3]                                                                                                                                                   | [O-]S(=O)(=O)[O-].[Co+2]                                                                                                                       |
| 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; sulfanylidencobalt; cobalt sulphide; cobalto monosulfide; cobalt (2+) sulfide; cobaltous sulfide | Arsanylidynecobalt; cobalt monoarsenide; cobalt (III) arsenide                                                                                                                                 |                                                                                                                                                |
| Chemical formula                        | CoS                                                                                                              | CoAs                                                                                                                                                                                           |                                                                                                                                                |
| SMILES                                  | S=[Co]                                                                                                           | [Co]#[As]                                                                                                                                                                                      |                                                                                                                                                |
| Chemical structure                      | S=Co                                                                                                             | Co≡As                                                                                                                                                                                          |                                                                                                                                                |
| CAS registry number                     | 1317-42-6                                                                                                        | 27016-73-5                                                                                                                                                                                     |                                                                                                                                                |

## 4. CHEMICAL AND PHYSICAL INFORMATION

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

| Characteristic                          | Cobalt (II) hydroxide                                                             | Cobalt (II) carbonate                                                                                                                                                                          |
|-----------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Synonym(s) and Registered trade name(s) | Cobaltous hydroxide; cobalt hydroxide; cobalt (2+) hydroxide                      | Cobalt carbonate; cobalt (2+) carbonate; cobalt carbonate (1:1); cobalt (II) carbonate hydrate; carbonic acid, cobalt (2+) salt; cobalt spar; cobalt monocarbonate; carbonic acid, cobalt salt |
| Chemical formula                        | Co(OH) <sub>2</sub>                                                               | CoCO <sub>3</sub>                                                                                                                                                                              |
| SMILES                                  | [OH-].[OH-].[Co+2]                                                                | C(=O)([O-])[O-].[Co+2]                                                                                                                                                                         |
| Chemical structure                      |  |                                                                                                             |
| CAS registry number                     | 21041-93-0                                                                        | 513-79-1                                                                                                                                                                                       |

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

Sources: NLM (2023a, 2023b, 2023c, 2023d, 2023e, 2023f, 2023g, 2023h, 2023i, 2023j)

**4.2 PHYSICAL AND CHEMICAL PROPERTIES**

Cobalt is a magnetic, hard, gray metal that is resistant to oxidation (Haynes 2015; Lenntech 2023). While it can be brittle, it is also ductile and somewhat malleable, and its natural magnetic properties are enhanced by alloying with other metals. Cobalt's physical and chemical properties make it ideal for a variety of applications. Cobalt exists in nature mainly as cobalt (II) with a +2 oxidation state and, to a lesser extent, cobalt (III) in the +3 oxidation state. Cobalt may also display oxidation states of +4, +1, and -1. The most common and stable ionic species is cobalt (II). Both cobalt (II) and cobalt (III) can form stable complexes (NTP 2016). 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. Cobalt is also an essential trace element found in vitamin B<sub>12</sub>. In biological systems, the chemistry of cobalt is facilitated by various enzymes that can cycle cobalt ions between cobalt (III), cobalt (II), and cobalt (I) species (NTP 2016; Osman et al. 2021).

Cobalt (III) is a strong oxidizer and accepts electron easily in aqueous solutions to form cobalt (II) (ionization potentials:  $\text{Co}^{3+}/2^{+}=+1.8\text{V}$ ;  $\text{Co}^{2+}/\text{Co}_{(s)}=-0.28$ ) (Haynes 2015; Lenntech 2023). Metallic cobalt does not react with water at room temperature; however, reactions with acids produce hydrogen gas (Clark 2023).

## 4. CHEMICAL AND PHYSICAL INFORMATION

Information regarding physical and chemical properties of cobalt and cobalt compounds is presented in Table 4-2.

**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 <sup>a</sup>                                                           | 129.8 <sup>a</sup>                                                                                             | 182.9 <sup>a</sup>                   |
| Color                    | Gray, silvery bluish-white <sup>a,b</sup>                                     | Blue <sup>a</sup>                                                                                              | Pale red <sup>a</sup>                |
| Physical state           | Solid <sup>c</sup>                                                            | Solid                                                                                                          | Solid <sup>g</sup>                   |
| Melting point            | 1,495°C <sup>a</sup>                                                          | 737°C <sup>a</sup>                                                                                             | Decomposes at 100–105°C <sup>g</sup> |
| Boiling point            | 2,927°C <sup>a</sup>                                                          | 1,049°C <sup>a</sup>                                                                                           | No data                              |
| Density at 20°C/4°C      | 8.9 g/cm <sup>3a</sup>                                                        | 3.36 g/cm <sup>3a</sup>                                                                                        | 2.49 g/cm <sup>3a</sup>              |
| Odor                     | Odorless <sup>c</sup>                                                         | Slight sharp odor <sup>f</sup>                                                                                 | Odorless <sup>g</sup>                |
| 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 <sup>f</sup>                                                                                  | Soluble in water <sup>g</sup>        |
| Organic solvent(s)       | Soluble in dilute acids; readily soluble in dilute nitric acid <sup>a,d</sup> | Soluble in alcohols, acetone, ether, glycerol, and pyridine <sup>f</sup>                                       | No data                              |
| Partition coefficients:  |                                                                               |                                                                                                                |                                      |
| Log K <sub>ow</sub>      | No data                                                                       | No data                                                                                                        | No data                              |
| Log K <sub>oc</sub>      | No data                                                                       | No data                                                                                                        | No data                              |
| Vapor pressure:          |                                                                               |                                                                                                                |                                      |
| At 726 mmHg and 85°C     | 2.09x10 <sup>-10</sup> mmHg <sup>a</sup>                                      | No data                                                                                                        | No data                              |
| Approximately            | 0 mmHg <sup>c</sup>                                                           | 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 <sup>3e</sup>                                                | No data                                                                                                        | No data                              |
| Explosive limits         | No data                                                                       | Reacts violently with alkali metals such as potassium or sodium causing fire and explosion hazard <sup>f</sup> | No data                              |

## 4. CHEMICAL AND PHYSICAL INFORMATION

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

| Property                 | Cobalt (II) oxide                      | Cobalt tetroxide                                              | Cobalt (II) sulfate                        |
|--------------------------|----------------------------------------|---------------------------------------------------------------|--------------------------------------------|
| Molecular weight         | 74.932 <sup>a</sup>                    | 240.8 <sup>a</sup>                                            | 155 <sup>a</sup>                           |
| Color                    | Gray <sup>a</sup>                      | Black <sup>a</sup>                                            | Red <sup>a</sup>                           |
| Physical state           | Solid <sup>a</sup>                     | Solid <sup>a</sup>                                            | Solid <sup>h</sup>                         |
| Melting point            | 1,830°C <sup>a</sup>                   | Decomposes at 900°C <sup>a</sup>                              | >700°C <sup>a</sup>                        |
| Boiling point            | No data                                | No data                                                       | No data                                    |
| Density at 20°C/4°C      | 4.63 g/cm <sup>3a</sup>                | 6.11 g/cm <sup>3a</sup>                                       | 3.71 g/cm <sup>3a</sup>                    |
| Odor                     | No data                                | No data                                                       | Odorless <sup>i</sup>                      |
| 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 <sup>a</sup>        | Insoluble in water <sup>a</sup>                               | 330 g/L at 20°C <sup>h</sup>               |
| Organic solvent(s)       | Soluble in acid solutions <sup>a</sup> | Soluble in acid solutions and alkaline solutions <sup>a</sup> | 1.04 g/11 mL methanol at 18°C <sup>h</sup> |
| Partition coefficients:  |                                        |                                                               |                                            |
| Log K <sub>ow</sub>      | No data                                | No data                                                       | No data                                    |
| Log K <sub>oc</sub>      | 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                                    |

## 4. CHEMICAL AND PHYSICAL INFORMATION

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

| Property                 | Cobalt (II) sulfide                    | Cobalt arsenide         |
|--------------------------|----------------------------------------|-------------------------|
| Molecular weight         | 90.998 <sup>a</sup>                    | 133.855 <sup>a</sup>    |
| Color                    | Black <sup>a</sup>                     | No data                 |
| Physical state           | Solid <sup>a</sup>                     | Solid <sup>a</sup>      |
| Melting point            | 1,117°C <sup>a</sup>                   | 1,180°C <sup>a</sup>    |
| Boiling point            | No data                                | No data                 |
| Density at 20°C/4°C      | 5.45 g/cm <sup>3a</sup>                | 8.22 g/cm <sup>3a</sup> |
| 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 <sup>a</sup>        | No data                 |
| Organic solvent(s)       | Soluble in acid solutions <sup>a</sup> | No data                 |
| Partition coefficients:  |                                        |                         |
| Log K <sub>ow</sub>      | No data                                | No data                 |
| Log K <sub>oc</sub>      | 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                 |

## 4. CHEMICAL AND PHYSICAL INFORMATION

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

| Property                 | Cobalt (II) hydroxide                         | Cobalt (II) carbonate                   |
|--------------------------|-----------------------------------------------|-----------------------------------------|
| Molecular weight         | 92.948 <sup>a</sup>                           | 118.942 <sup>a</sup>                    |
| Color                    | Blue-green crystals <sup>a</sup>              | Pink crystals <sup>a</sup>              |
| Physical state           | Solid <sup>a</sup>                            | Solid <sup>a</sup>                      |
| Melting point            | ~160°C <sup>a</sup> (decomposes) <sup>a</sup> | 280°C (decomposes) <sup>a</sup>         |
| Boiling point            | No data                                       | No data                                 |
| Density at 20°C/4°C      | 3.60 g/cm <sup>3a</sup>                       | 4.2 g/cm <sup>3a</sup>                  |
| 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                    | Slightly soluble in water <sup>a</sup>        | 0.00014 g/100g H <sub>2</sub> O at 20°C |
| Organic solvent(s)       | Soluble in acid solutions <sup>a</sup>        | Insoluble in ethanol                    |
| Partition coefficients:  |                                               |                                         |
| Log K <sub>ow</sub>      | No data                                       | No data                                 |
| Log K <sub>oc</sub>      | 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                                 |

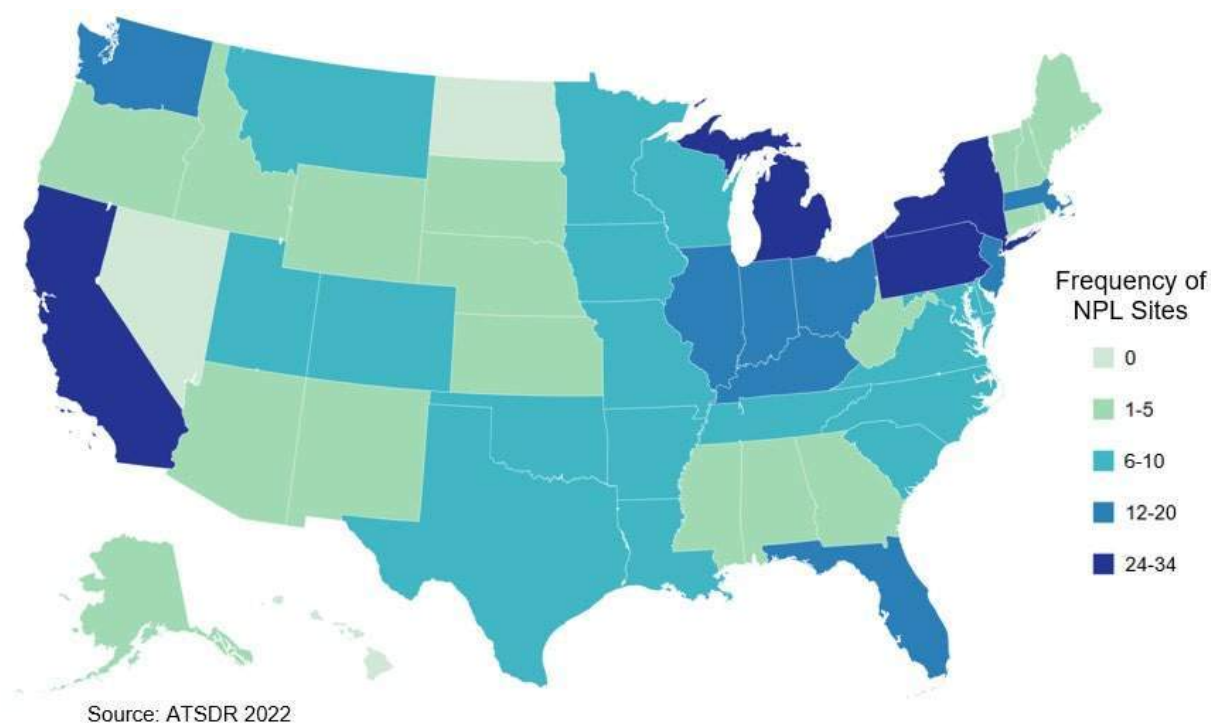
<sup>a</sup>Haynes 2015.<sup>b</sup>Browning 1969.<sup>c</sup>NIOSH 2019b.<sup>d</sup>O'Neil 2013.<sup>e</sup>EPA 2000.<sup>f</sup>NLM 2023bc.<sup>g</sup>NLM 2023c.<sup>h</sup>NLM 2023f.<sup>i</sup>NLM 2023f.

## CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.1 OVERVIEW

Cobalt has been identified in at least 431 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which cobalt has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 426 are located within the United States, 1 is located in the Virgin Islands, 1 is located in Guam, and 3 are located in Puerto Rico (not shown).

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



- In the United States, cobalt is produced from deposits as a byproduct of other metals. Cobalt is used in several commercial, industrial, and military applications. The leading use is in rechargeable batteries, followed by superalloys; 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.

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- 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  $<0.002 \mu\text{g}/\text{m}^3$  (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 such as 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 following industries can be exposed to higher levels of cobalt via airborne dust and direct contact: hard metal production or processing (tool production, grinding, etc.); coal mining; metal mining, smelting, and refining; lithium-cobalt battery production or recycling (including electric vehicle batteries); cobalt dyes and paints; and cobalt chemical production. Populations living near these industrial sites might also be exposed to higher levels of cobalt.

Cobalt occurs naturally in the earth's crust. Due to this, it occurs naturally in seawater, in some surface water and groundwater, and in deep-sea polymetallic nodules of the Atlantic, Indian, and Pacific Oceans (Smith and Carson 1981; USGS 2023). Elevated levels of cobalt in soil and water may also result from anthropogenic activities such as the mining and processing of cobalt-bearing ores, application of cobalt-containing sludge or phosphate fertilizers to soil, and disposal of cobalt-containing wastes. Elevated levels of cobalt in the air are a combination of both natural and anthropogenic sources. Natural atmospheric sources include windblown soil, seawater spray, volcanic eruptions, and forest fires. Anthropogenic contributions include atmospheric releases and subsequent deposition from the burning of fossil fuels and waste, 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). The emissions from natural sources are estimated to slightly exceed those from manufactured sources.

Cobalt compounds are nonvolatile, 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  $>2 \mu\text{m}$  (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



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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; DOE 1984; King 1988; McLaren et al. 1986; Schnitzer 1969; Smith and Carson 1981) while decreasing in the presence of hydroxyl and carboxyl groups or iron and manganese oxides (Medyńska-Juraszek et al. 2020). 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<sup>3</sup>. In several open-ocean environments, geometric mean concentrations ranged from 0.0004 to 0.08 ng/m<sup>3</sup> (Chester et al. 1991). However, in source areas, cobalt levels may exceed 10 ng/m<sup>3</sup>; the highest average cobalt concentration recorded was 48 ng/m<sup>3</sup> 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

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water is  $<1\text{--}2\text{ }\mu\text{g/L}$ , although levels as high as  $107\text{ }\mu\text{g/L}$  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  $20\text{--}25\text{ mg/kg}$  (Abbasi et al. 1989; Greathouse and Craun 1978; Merian 1985; Smith and Carson 1981). Most soils contain  $1\text{--}40\text{ mg cobalt/kg}$ ; the average cobalt concentration in U.S. soils is  $7.2\text{ mg/kg}$  (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  $800\text{ mg/kg}$  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  $11\text{ }\mu\text{g/day}$ . 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 33<sup>rd</sup> most abundant element in the earth's crust, averaging approximately  $17.3\text{ ppm}$  (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 ( $\text{Cu}(\text{Co},\text{Ni})_2\text{S}_4$ ), pentlandite ( $(\text{Fe},\text{Ni},\text{Co})_9\text{S}_8$ ), linnaeite ( $\text{Co}_3\text{S}_4$ ), siegenite ( $(\text{Co},\text{Ni})_3\text{S}_4$ ), skutterudite ( $(\text{Co},\text{Fe},\text{Ni})\text{As}_{2-3}$ ), safflorite ( $(\text{Co},\text{Fe})\text{As}_2$ ), cobaltite ( $\text{CoAsS}$ ), glaucodot ( $(\text{Co},\text{Fe},\text{Ni})\text{AsS}$ ), erythrite ( $\text{Co}_3(\text{AsO}_4)_2\cdot 8\text{H}_2\text{O}$ ), heterogenite ( $\text{CoO}(\text{OH})$ ), and asbolane ( $(\text{Ni},\text{Co})_{2-x}\text{Mn}(\text{o},\text{OH})_4\cdot n\text{H}_2\text{O}$ ) (USGS 2017). Common cobalt ores include cobaltite, smaltite, chloranthite, and

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linnaeite (Clark 2023). The world's reserves of cobalt total an estimated 8.3 million tons, with the largest cobalt reserves in the D.R. Congo (Kinshasa; 4 million tons), Australia (1.5 million tons), Indonesia (0.6 million tons), Cuba (0.5 million tons), the Philippines (0.26 million tons), and Russia (0.25 million tons); all other countries combined have a total estimated reserve of 0.61 million tons (USGS 2023). In the United States, there is an estimated 0.06 million tons of cobalt resources (USGS 2023). The majority of U.S. cobalt deposits are in Minnesota, Alaska, California, Michigan, Montana, Oregon, and Pennsylvania where cobalt is produced as a byproduct of another metal. Cobalt mines were once operational in both Idaho and Missouri. Missouri produces cobalt directly from historic mine tailings (USGS 2023), while Idaho is operationally ready to mine cobalt ore (Jervois 2024). The U.S. supply of cobalt is mostly imports and secondary scrap materials (USGS 2023). In 2022, an estimated 1,900 metric tons of the U.S. cobalt supply were from scrap. Mining production increased between 2018 and 2022, with cobalt production of 480, 500, 600, 650, and 800 metric tons in 2018, 2019, 2020, 2021, and 2022, respectively (USGS 2023). 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).

Cobalt is mined using a combination of conventional underground and open pit methods (Farjana et al. 2019) as well as by land and seabed mining of polymetallic nodules (Ou et al. 2023). 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 copper-cobalt 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).

Tables 5-1 and 5-2 summarize information on companies that reported the production, import, or use of cobalt or cobalt compounds, respectively, for the Toxics Release Inventory (TRI) in 2022 (TRI22 2024). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

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

| State <sup>a</sup> | Number of facilities | Minimum amount on site in pounds <sup>b</sup> | Maximum amount on site in pounds <sup>b</sup> | Activities and uses <sup>c</sup>      |
|--------------------|----------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------------|
| AL                 | 7                    | 10,000                                        | 99,999                                        | 8, 12                                 |
| AR                 | 2                    | 10,000                                        | 99,999                                        | 8                                     |
| AZ                 | 5                    | 1,000                                         | 999,999                                       | 8, 11                                 |
| CA                 | 17                   | 0                                             | 999,999                                       | 2, 3, 7, 8, 11, 12                    |
| CO                 | 2                    | 10,000                                        | 99,999                                        | 11                                    |
| CT                 | 10                   | 0                                             | 999,999                                       | 8, 11, 12                             |
| FL                 | 3                    | 100                                           | 99,999                                        | 8                                     |
| GA                 | 7                    | 1,000                                         | 49,999,999                                    | 8, 12                                 |
| IA                 | 4                    | 10,000                                        | 999,999                                       | 8, 14                                 |
| ID                 | 2                    | 10,000                                        | 99,999                                        | 1, 5, 12                              |
| IL                 | 10                   | 1,000                                         | 9,999,999                                     | 7, 8                                  |
| IN                 | 25                   | 1,000                                         | 9,999,999                                     | 1, 5, 7, 8, 9, 11, 12, 13, 14         |
| KS                 | 10                   | 1,000                                         | 9,999,999                                     | 8, 12, 14                             |
| KY                 | 5                    | 100                                           | 999,999                                       | 2, 3, 7, 8, 11, 12                    |
| LA                 | 2                    | 10,000                                        | 99,999                                        | 8, 10                                 |
| MA                 | 12                   | 100                                           | 999,999                                       | 1, 5, 8, 9, 11, 12                    |
| ME                 | 2                    | 1,000                                         | 99,999                                        | 8                                     |
| MI                 | 17                   | 0                                             | 9,999,999                                     | 2, 3, 5, 7, 8, 9, 11, 12, 14          |
| MN                 | 7                    | 100                                           | 999,999                                       | 8                                     |
| MO                 | 6                    | 1,000                                         | 999,999                                       | 8                                     |
| MS                 | 4                    | 10,000                                        | 999,999                                       | 8                                     |
| NC                 | 12                   | 0                                             | 9,999,999                                     | 1, 2, 3, 4, 7, 8, 9, 12               |
| NE                 | 1                    | 1,000                                         | 9,999                                         | 8                                     |
| NH                 | 3                    | 1,000                                         | 9,999                                         | 2, 3, 8, 11, 12                       |
| NJ                 | 6                    | 100                                           | 999,999                                       | 2, 3, 4, 8, 9, 11, 12                 |
| NV                 | 2                    | 10,000                                        | 999,999                                       | 1, 3, 4, 7, 8, 12                     |
| NY                 | 12                   | 1,000                                         | 9,999,999                                     | 2, 3, 7, 8, 9, 12, 14                 |
| OH                 | 30                   | 0                                             | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 14 |
| OK                 | 5                    | 1,000                                         | 9,999,999                                     | 1, 5, 8, 13, 14                       |
| OR                 | 5                    | 10,000                                        | 99,999                                        | 2, 3, 7, 12                           |
| PA                 | 28                   | 100                                           | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13 |
| PR                 | 2                    | 1,000                                         | 99,999                                        | 8                                     |
| SC                 | 9                    | 1,000                                         | 999,999                                       | 2, 3, 6, 7, 8                         |
| SD                 | 1                    | 1,000                                         | 9,999                                         | 8                                     |
| TN                 | 8                    | 1,000                                         | 999,999                                       | 2, 3, 4, 5, 6, 7, 8, 9, 12            |
| TX                 | 12                   | 0                                             | 999,999                                       | 1, 4, 5, 8, 11, 12                    |
| UT                 | 1                    | 10,000                                        | 99,999                                        | 8                                     |
| VA                 | 3                    | 0                                             | 999,999                                       | 2, 3, 4, 8, 12                        |
| WI                 | 21                   | 1,000                                         | 999,999                                       | 7, 8, 10                              |

## 5. POTENTIAL FOR HUMAN EXPOSURE

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

| State <sup>a</sup> | Number of facilities | Minimum amount on site in pounds <sup>b</sup> | Maximum amount on site in pounds <sup>b</sup> | Activities and uses <sup>c</sup> |
|--------------------|----------------------|-----------------------------------------------|-----------------------------------------------|----------------------------------|
| WV                 | 2                    | 100,000                                       | 999,999                                       | 2, 3, 7, 8                       |

<sup>a</sup>Post office state abbreviations used.<sup>b</sup>Amounts on site reported by facilities in each state.<sup>c</sup>Activities/uses:

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

Source: TRI22 2024 (Data are from 2022)

**Table 5-2. Facilities that Produce, Process, or Use Cobalt Compounds**

| State <sup>a</sup> | Number of facilities | Minimum amount on site in pounds <sup>b</sup> | Maximum amount on site in pounds <sup>b</sup> | Activities and uses <sup>c</sup>           |
|--------------------|----------------------|-----------------------------------------------|-----------------------------------------------|--------------------------------------------|
| AK                 | 2                    | 10,000                                        | 999,999                                       | 1, 5, 12, 13, 14                           |
| AL                 | 10                   | 0                                             | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 10, 13, 14         |
| AR                 | 5                    | 1,000                                         | 999,999                                       | 1, 2, 3, 5, 7, 8, 9, 12                    |
| AZ                 | 11                   | 100                                           | 999,999                                       | 1, 3, 5, 7, 8, 9, 10, 11, 12, 13           |
| CA                 | 16                   | 1,000                                         | 999,999                                       | 1, 2, 3, 5, 7, 8, 9, 10, 12, 14            |
| CO                 | 2                    | 0                                             | 99,999                                        | 1, 13                                      |
| CT                 | 1                    | 10,000                                        | 99,999                                        | 8                                          |
| DE                 | 1                    | 10,000                                        | 99,999                                        | 8                                          |
| FL                 | 5                    | 1,000                                         | 999,999                                       | 1, 2, 3, 4, 5, 8, 9, 13, 14                |
| GA                 | 7                    | 1,000                                         | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 13, 14             |
| IA                 | 7                    | 10,000                                        | 99,999                                        | 2, 3, 7                                    |
| ID                 | 2                    | 1,000                                         | 99,999                                        | 1, 2, 3, 4, 5, 7, 9, 12, 13, 14            |
| IL                 | 21                   | 100                                           | 999,999                                       | 1, 3, 5, 6, 7, 8, 9, 10, 12, 13            |
| IN                 | 15                   | 0                                             | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14  |
| KS                 | 5                    | 1,000                                         | 99,999                                        | 1, 5, 6, 7, 8, 9, 10, 12                   |
| KY                 | 11                   | 1,000                                         | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 10, 12, 13            |
| LA                 | 20                   | 0                                             | 9,999,999                                     | 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14 |
| ME                 | 1                    | 0                                             | 99                                            | 1, 5                                       |
| MI                 | 17                   | 0                                             | 9,999,999                                     | 1, 2, 3, 4, 5, 7, 8, 10, 12, 13, 14        |
| MN                 | 6                    | 1,000                                         | 999,999                                       | 1, 2, 5, 7, 8, 9, 10, 12, 13               |
| MO                 | 4                    | 100                                           | 9,999                                         | 1, 5, 9, 13                                |
| MS                 | 8                    | 1,000                                         | 99,999                                        | 1, 2, 3, 5, 6, 7, 8, 9, 10, 13, 14         |
| MT                 | 3                    | 10,000                                        | 999,999                                       | 1, 3, 4, 5, 6, 12, 13, 14                  |
| NC                 | 8                    | 1,000                                         | 99,999                                        | 1, 5, 6, 7, 9, 12, 14                      |

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-2. Facilities that Produce, Process, or Use Cobalt Compounds**

| State <sup>a</sup> | Number of facilities | Minimum amount on site in pounds <sup>b</sup> | Maximum amount on site in pounds <sup>b</sup> | Activities and uses <sup>c</sup>              |
|--------------------|----------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| ND                 | 5                    | 100                                           | 99,999                                        | 1, 3, 5, 10, 12, 13, 14                       |
| NE                 | 2                    | 1,000                                         | 9,999                                         | 1, 5, 7, 12                                   |
| NJ                 | 3                    | 10,000                                        | 999,999                                       | 7, 10                                         |
| NM                 | 4                    | 100                                           | 99,999                                        | 1, 3, 4, 5, 9, 11, 12, 13, 14                 |
| NV                 | 13                   | 0                                             | 999,999                                       | 1, 2, 3, 4, 7, 8, 12, 13, 14                  |
| NY                 | 3                    | 10,000                                        | 99,999                                        | 7, 14                                         |
| OH                 | 24                   | 0                                             | 9,999,999                                     | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14     |
| OK                 | 9                    | 0                                             | 999,999                                       | 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14        |
| OR                 | 2                    | 1,000                                         | 9,999                                         | 8                                             |
| PA                 | 24                   | 0                                             | 9,999,999                                     | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14     |
| SC                 | 19                   | 100                                           | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 |
| TN                 | 19                   | 100                                           | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14     |
| TX                 | 34                   | 0                                             | 999,999                                       | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14         |
| UT                 | 3                    | 1,000                                         | 99,999                                        | 1, 5, 8, 10                                   |
| VA                 | 3                    | 10,000                                        | 99,999                                        | 1, 3, 5, 6, 7, 10                             |
| WA                 | 2                    | 10,000                                        | 999,999                                       | 2, 3, 4, 7, 10, 11                            |
| WI                 | 5                    | 0                                             | 99,999                                        | 7, 8, 10, 12                                  |
| WV                 | 7                    | 1,000                                         | 99,999                                        | 1, 3, 4, 5, 8, 9, 12, 13, 14                  |
| WY                 | 1                    | 1,000                                         | 9,999                                         | 1, 5                                          |

<sup>a</sup>Post office state abbreviations used.<sup>b</sup>Amounts on site reported by facilities in each state.<sup>c</sup>Activities/uses:

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

Source: TRI22 2024 (Data are from 2022)

**5.2.2 Import/Export**

According to the U.S. Geological Survey (USGS 2023), an estimated 13,600 metric tons of cobalt were imported into the United States in 2022. 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).

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Cobalt exports in the United States ranged from 3,430 to 6,960 metric tons between 2018 and 2021; exports in 2022 are estimated to be 5,100 metric tons (USGS 2023).

**5.2.3 Use**

In 2019, the estimated apparent consumption of cobalt in the United States 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 (USGS 2020). Cobalt is also an important component in energy storage for sustainable and alternative energies, which are on the rise world-wide, including solar photovoltaics, wind turbines, fuel cells, and nuclear reactors (Karduri 2023; Sovacool et al. 2020). In the United States, the need for cobalt to support production of electric vehicles is expected to increase considerably over the next few decades in order to support the U.S. mandate to phase out fossil fueled activities from 2023 to 2050 (WH 2021a, 2021b). The U.S. DOE (2023) classifies cobalt as a "critical" energy resource. However, since most cobalt mining processes occur outside of the United States, development of alternate technology (such as lithium iron phosphate or lithium iron-manganese-phosphate batteries) would decrease dependency on the D.R. Congo and China for cobalt supply (DOE 2023).

Another major use for cobalt is production of superalloys (USGS 2020). Other uses include cemented carbides and diamond tools; controlled-expansion; and corrosion- and wear-resistant alloys, high-speed and strong yet ductile steels, and magnets. Uses of cobalt metal and compounds also 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, vitamin B<sub>12</sub>, and protective catalysts for corrosive and biofouling environments (Sun et al. 2022; USGS 2019; Wang et al. 2022a). 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). In 2019, 46% of cobalt consumed in the United States was used in superalloys (mainly for aircraft gas turbine engines), 9% in cemented carbides for cutting and wear-

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resistant applications, 14% in various metallic applications, and 31% in various chemical applications (USGS 2020).

Cobalt compounds are used as catalysts during the manufacture of PET plastics and PET/polycarbonate blends (Kovacheva-Ninova et al. 2018; Pereira et al. 2007). In sustainable chemistry research, cobalt oxides, cobalt phosphide, and cobalt-molybdenum are being evaluated as potential catalysts in the chemical recycling of PET and polybutylene terephthalate (PBT) (Fuentes et al. 2019; Wang et al. 2022b; Wu et al. 2021).

Some artist pastels contain cobalt as a pigment (Brock and Stopford 2003). The colors of some cobalt compounds (sometimes complexed with other metals) in dyes and pigments are blue (cobalt aluminate), pink/violet (cobalt phosphate, cobalt magnesium), green (cobalt nickel zinc titanite, cobalt chromite, cobalt titanate), blue-green (cobalt hydroxide), and blue-black (cobalt tetraoxide) (Anaissi et al. 2020; Haynes 2015; Müller et al. 2012). Cobalt aluminum oxide nanoparticles are used in pigments and inks (Brown et al. 2018).

#### 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). Wastewater 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 (EPA 2023a, 2023b, 2023c). However, in May 2023, EPA's position was that recycling lithium-ion batteries returns valuable critical minerals to the economy. EPA now allows them to be managed under



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streamlined hazardous waste management standards for universal waste until they reach a destination facility for recycling or to be discarded (EPA 2023e).

### 5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ  $\geq 10$  full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022b).

#### 5.3.1 Air

Estimated releases of 7,480 pounds (~3.39 metric tons) of cobalt to the atmosphere from 320 domestic manufacturing and processing facilities in 2022, accounted for about 1.28% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-3.

Estimated releases of 33,253 pounds (~15.08 metric tons) of cobalt compounds to the atmosphere from 367 domestic manufacturing and processing facilities in 2022, accounted for about 0.66% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-4.

**Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt<sup>a</sup>**

| State <sup>c</sup> | RF <sup>d</sup> | Reported amounts released in pounds per year <sup>b</sup> |                    |                 |                   |                    |                      | Total release         |                  |
|--------------------|-----------------|-----------------------------------------------------------|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
|                    |                 | Air <sup>e</sup>                                          | Water <sup>f</sup> | UI <sup>g</sup> | Land <sup>h</sup> | Other <sup>i</sup> | On-site <sup>j</sup> | Off-site <sup>k</sup> | On- and off-site |
|                    |                 |                                                           |                    |                 |                   |                    |                      |                       |                  |
| AL                 | 7               | 607                                                       | 11                 | 0               | 20,035            | 18,400             | 20,616               | 18,438                | 39,054           |
| AR                 | 2               | 0                                                         | 0                  | 0               | 33                | 0                  | 0                    | 33                    | 33               |
| AZ                 | 5               | 34                                                        | 0                  | 0               | 147,000           | 0                  | 147,034              | 1                     | 147,034          |
| CA                 | 17              | 90                                                        | 19                 | 0               | 41,416            | 122                | 28,160               | 13,486                | 41,646           |
| CO                 | 2               | 0                                                         | 0                  | 0               | 41,000            | 0                  | 41,000               | 0                     | 41,000           |

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**Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt<sup>a</sup>**

| State <sup>c</sup> | RF <sup>d</sup> | Reported amounts released in pounds per year <sup>b</sup> |                    |                 |                   |                    |                      |                       |                  |
|--------------------|-----------------|-----------------------------------------------------------|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
|                    |                 | Air <sup>e</sup>                                          | Water <sup>f</sup> | UI <sup>g</sup> | Land <sup>h</sup> | Other <sup>i</sup> | Total release        |                       |                  |
|                    |                 |                                                           |                    |                 |                   |                    | On-site <sup>j</sup> | Off-site <sup>k</sup> | On- and off-site |
| CT                 | 10              | 85                                                        | 269                | 0               | 751               | 1,020              | 99                   | 2,026                 | 2,125            |
| FL                 | 3               | 344                                                       | 2                  | 0               | 0                 | 17                 | 344                  | 19                    | 363              |
| GA                 | 7               | 156                                                       | 38                 | 0               | 287               | 566                | 158                  | 889                   | 1,047            |
| IA                 | 4               | 27                                                        | 0                  | 0               | 3                 | 0                  | 28                   | 3                     | 31               |
| ID                 | 2               | 4                                                         | 0                  | 0               | 46,400            | 0                  | 46,404               | 0                     | 46,404           |
| IL                 | 9               | 157                                                       | 6                  | 0               | 21                | 1,078              | 157                  | 1,105                 | 1,262            |
| IN                 | 25              | 2,151                                                     | 197                | 0               | 11,884            | 24                 | 13,167               | 1,089                 | 14,256           |
| KS                 | 10              | 319                                                       | 1                  | 0               | 357               | 8                  | 324                  | 361                   | 685              |
| KY                 | 5               | 7                                                         | 2                  | 0               | 765               | 0                  | 7                    | 767                   | 774              |
| LA                 | 2               | 0                                                         | 200                | 9,700           | 0                 | 0                  | 9,900                | 0                     | 9,900            |
| MA                 | 12              | 188                                                       | 42                 | 0               | 1,943             | 5,302              | 228                  | 7,248                 | 7,476            |
| ME                 | 2               | 43                                                        | 0                  | 0               | 0                 | 6                  | 43                   | 6                     | 49               |
| MI                 | 17              | 569                                                       | 109                | 0               | 535               | 1,465              | 569                  | 2,109                 | 2,678            |
| MN                 | 7               | 95                                                        | 0                  | 0               | 1,294             | 0                  | 95                   | 1,294                 | 1,390            |
| MO                 | 6               | 259                                                       | 0                  | 0               | 91,179            | 0                  | 91,433               | 5                     | 91,438           |
| MS                 | 4               | 7                                                         | 90                 | 0               | 0                 | 0                  | 97                   | 0                     | 97               |
| NC                 | 11              | 33                                                        | 214                | 0               | 16,310            | 151                | 16,298               | 409                   | 16,708           |
| NE                 | 1               | 95                                                        | 0                  | 0               | 18                | 0                  | 95                   | 18                    | 113              |
| NH                 | 3               | 6                                                         | 0                  | 0               | 1,226             | 2                  | 6                    | 1,228                 | 1,234            |
| NJ                 | 6               | 124                                                       | 6                  | 0               | 9,427             | 58                 | 124                  | 9,491                 | 9,615            |
| NV                 | 2               | 2                                                         | 7                  | 0               | 255               | 0                  | 2                    | 262                   | 264              |
| NY                 | 12              | 108                                                       | 24                 | 0               | 415               | 635                | 112                  | 1,070                 | 1,182            |
| OH                 | 30              | 608                                                       | 221                | 0               | 13,295            | 206                | 5,929                | 8,402                 | 14,331           |
| OK                 | 5               | 0                                                         | 0                  | 0               | 0                 | 0                  | 0                    | 0                     | 0                |
| OR                 | 5               | 392                                                       | 23                 | 0               | 27,039            | 261                | 23,370               | 4,345                 | 27,715           |
| PA                 | 28              | 224                                                       | 54                 | 0               | 9,187             | 28,372             | 268                  | 37,570                | 37,838           |
| PR                 | 2               | 0                                                         | 0                  | 0               | 5                 | 0                  | 0                    | 5                     | 5                |
| SC                 | 9               | 119                                                       | 56                 | 0               | 7,333             | 0                  | 140                  | 7,369                 | 7,509            |
| SD                 | 1               | 0                                                         | 0                  | 0               | 0                 | 0                  | 0                    | 0                     | 0                |
| TN                 | 8               | 137                                                       | 104                | 0               | 6,795             | 0                  | 147                  | 6,889                 | 7,036            |
| TX                 | 12              | 55                                                        | 20                 | 0               | 3,025             | 390                | 64                   | 3,426                 | 3,490            |
| UT                 | 1               | 8                                                         | 0                  | 0               | 0                 | 0                  | 8                    | 0                     | 8                |
| VA                 | 3               | 11                                                        | 5                  | 0               | 0                 | 90                 | 11                   | 95                    | 106              |
| WI                 | 21              | 128                                                       | 787                | 0               | 6,869             | 195                | 128                  | 7,851                 | 7,979            |

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**Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt<sup>a</sup>**

| Reported amounts released in pounds per year <sup>b</sup> |                 |                  |                    |                 |                   |                    |                      |                       |                  |
|-----------------------------------------------------------|-----------------|------------------|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
| State <sup>c</sup>                                        | RF <sup>d</sup> | Air <sup>e</sup> | Water <sup>f</sup> | UI <sup>g</sup> | Land <sup>h</sup> | Other <sup>i</sup> | Total release        |                       |                  |
|                                                           |                 |                  |                    |                 |                   |                    | On-site <sup>j</sup> | Off-site <sup>k</sup> | On- and off-site |
| WV                                                        | 1               | 290              | 156                | 0               | 0                 | 0                  | 290                  | 156                   | 446              |
| Total                                                     | 320             | 7,480            | 2,666              | 9,700           | 506,103           | 58,369             | 446,853              | 137,465               | 584,318          |

<sup>a</sup>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.

<sup>b</sup>Data in TRI are maximum amounts released by each facility.

<sup>c</sup>Post office state abbreviations are used.

<sup>d</sup>Number of reporting facilities.

<sup>e</sup>The sum of fugitive and point source releases are included in releases to air by a given facility.

<sup>f</sup>Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

<sup>g</sup>Class I wells, Class II-V wells, and underground injection.

<sup>h</sup>Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

<sup>i</sup>Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.

<sup>j</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>k</sup>Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI22 2024 (Data are from 2022)

**Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt Compounds<sup>a</sup>**

| Reported amounts released in pounds per year <sup>b</sup> |                 |                  |                    |                 |                   |                    |                      |                       |                  |
|-----------------------------------------------------------|-----------------|------------------|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
| State <sup>c</sup>                                        | RF <sup>d</sup> | Air <sup>e</sup> | Water <sup>f</sup> | UI <sup>g</sup> | Land <sup>h</sup> | Other <sup>i</sup> | Total release        |                       |                  |
|                                                           |                 |                  |                    |                 |                   |                    | On-site <sup>j</sup> | Off-site <sup>k</sup> | On- and off-site |
| AK                                                        | 2               | 1                | 85                 | 0               | 227,428           | 0                  | 227,514              | 0                     | 227,514          |
| AL                                                        | 10              | 834              | 16,074             | 0               | 83,008            | 657                | 16,837               | 83,736                | 100,572          |
| AR                                                        | 5               | 68               | 9                  | 0               | 92,501            | 4,720              | 92,282               | 5,017                 | 97,299           |
| AZ                                                        | 11              | 751              | 835                | 0               | 442,697           | 0                  | 442,198              | 2,085                 | 444,283          |
| CA                                                        | 16              | 73               | 27                 | 0               | 236,674           | 3,663              | 232,934              | 7,502                 | 240,436          |
| CO                                                        | 2               | 8                | 4                  | 0               | 171               | 0                  | 183                  | 0                     | 183              |
| CT                                                        | 1               | 125              | 0                  | 0               | 0                 | 0                  | 125                  | 0                     | 125              |
| DE                                                        | 1               | 0                | 0                  | 0               | 0                 | 129                | 0                    | 129                   | 129              |
| FL                                                        | 5               | 0                | 0                  | 0               | 34,000            | 6,800              | 0                    | 40,800                | 40,800           |
| GA                                                        | 7               | 62               | 0                  | 0               | 5,800             | 4,949              | 5,862                | 4,949                 | 10,811           |
| IA                                                        | 7               | 238              | 0                  | 0               | 0                 | 20,230             | 238                  | 20,230                | 20,468           |
| ID                                                        | 2               | 1                | 0                  | 0               | 220               | 0                  | 217                  | 4                     | 221              |

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**Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt Compounds<sup>a</sup>**

| State <sup>c</sup> | RF <sup>d</sup> | Reported amounts released in pounds per year <sup>b</sup> |                    |                 |                   |                    |                      |                       |                  |
|--------------------|-----------------|-----------------------------------------------------------|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
|                    |                 | Air <sup>e</sup>                                          | Water <sup>f</sup> | UI <sup>g</sup> | Land <sup>h</sup> | Other <sup>i</sup> | Total release        |                       | On- and off-site |
|                    |                 |                                                           |                    |                 |                   |                    | On-site <sup>j</sup> | Off-site <sup>k</sup> |                  |
| IL                 | 20              | 1,887                                                     | 1,083              | 24              | 86,981            | 116,656            | 86,095               | 120,536               | 206,632          |
| IN                 | 15              | 307                                                       | 52                 | 0               | 118,348           | 1,372              | 96,344               | 23,735                | 120,078          |
| KS                 | 5               | 75                                                        | 7                  | 0               | 4                 | 2,662              | 84                   | 2,663                 | 2,748            |
| KY                 | 11              | 190                                                       | 285                | 0               | 85,361            | 1,644              | 80,620               | 6,859                 | 87,479           |
| LA                 | 20              | 1,174                                                     | 7,079              | 558             | 110,978           | 960                | 97,534               | 23,215                | 120,749          |
| MD                 | 1               | 0                                                         | 0                  | 0               | 0                 | 0                  | 0                    | 0                     | 0                |
| ME                 | 1               | 14                                                        | 0                  | 0               | 211               | 0                  | 14                   | 211                   | 225              |
| MI                 | 16              | 96                                                        | 64                 | 0               | 472,069           | 1,055              | 455,318              | 17,967                | 473,285          |
| MN                 | 6               | 92                                                        | 27                 | 0               | 531               | 329                | 119                  | 860                   | 978              |
| MO                 | 4               | 128                                                       | 0                  | 0               | 4,436             | 0                  | 4,564                | 0                     | 4,564            |
| MS                 | 8               | 236                                                       | 126                | 43,551          | 29,439            | 6,970              | 51,191               | 29,131                | 80,322           |
| MT                 | 3               | 40                                                        | 0                  | 0               | 357,589           | 0                  | 357,629              | 0                     | 357,629          |
| NC                 | 8               | 47                                                        | 48                 | 0               | 42,178            | 258                | 42,208               | 323                   | 42,531           |
| ND                 | 4               | 1,063                                                     | 0                  | 0               | 55,676            | 0                  | 43,691               | 13,048                | 56,739           |
| NE                 | 2               | 0                                                         | 0                  | 0               | 0                 | 0                  | 0                    | 0                     | 0                |
| NH                 | 1               | 0                                                         | 0                  | 0               | 0                 | 0                  | 0                    | 0                     | 0                |
| NJ                 | 3               | 1                                                         | 483                | 0               | 1,049             | 25,325             | 1                    | 26,857                | 26,857           |
| NM                 | 4               | 53                                                        | 1                  | 0               | 57,140            | 7,716              | 57,194               | 7,716                 | 64,910           |
| NV                 | 9               | 12,785                                                    | 222                | 0               | 831,345           | 1                  | 815,886              | 28,468                | 844,354          |
| NY                 | 3               | 402                                                       | 2                  | 0               | 194               | 12                 | 403                  | 206                   | 610              |
| OH                 | 24              | 1,655                                                     | 601                | 11,843          | 145,843           | 74,865             | 110,249              | 124,558               | 234,807          |
| OK                 | 9               | 63                                                        | 13                 | 0               | 26,368            | 1,545              | 20,436               | 7,553                 | 27,990           |
| OR                 | 2               | 0                                                         | 322                | 0               | 29                | 0                  | 0                    | 351                   | 351              |
| PA                 | 24              | 2,691                                                     | 1,811              | 0               | 45,795            | 3,458              | 30,314               | 23,440                | 53,754           |
| SC                 | 19              | 138                                                       | 33,550             | 0               | 106,481           | 2,586              | 129,842              | 12,913                | 142,755          |
| TN                 | 19              | 423                                                       | 4,857              | 0               | 118,740           | 501                | 117,825              | 6,697                 | 124,522          |
| TX                 | 35              | 5,677                                                     | 1,000              | 302             | 514,596           | 11,366             | 505,008              | 27,933                | 532,941          |
| UT                 | 3               | 261                                                       | 5                  | 0               | 16,205            | 0                  | 16,461               | 10                    | 16,471           |
| VA                 | 3               | 12                                                        | 1,851              | 0               | 0                 | 775                | 1,636                | 1,002                 | 2,638            |
| VT                 | 1               | 0                                                         | 0                  | 0               | 0                 | 0                  | 0                    | 0                     | 0                |
| WA                 | 2               | 11                                                        | 7                  | 0               | 191               | 10,030             | 18                   | 10,220                | 10,238           |
| WI                 | 5               | 67                                                        | 0                  | 0               | 376               | 7,435              | 111                  | 7,767                 | 7,878            |
| WV                 | 7               | 868                                                       | 46                 | 0               | 208,840           | 340                | 183,754              | 26,340                | 210,094          |

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**Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Cobalt Compounds<sup>a</sup>**

| Reported amounts released in pounds per year <sup>b</sup> |                 |                  |                    |                 |                   |                    |                      |                       |                  |
|-----------------------------------------------------------|-----------------|------------------|--------------------|-----------------|-------------------|--------------------|----------------------|-----------------------|------------------|
| State <sup>c</sup>                                        | RF <sup>d</sup> | Air <sup>e</sup> | Water <sup>f</sup> | UI <sup>g</sup> | Land <sup>h</sup> | Other <sup>i</sup> | Total release        |                       |                  |
|                                                           |                 |                  |                    |                 |                   |                    | On-site <sup>j</sup> | Off-site <sup>k</sup> | On- and off-site |
| WY                                                        | 1               | 637              | 0                  | 0               | 11,473            | 0                  | 12,110               | 0                     | 12,110           |
| Total                                                     | 367             | 33,253           | 70,577             | 56,279          | 4,570,965         | 319,008            | 4,335,051            | 715,031               | 5,050,082        |

<sup>a</sup>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.

<sup>b</sup>Data in TRI are maximum amounts released by each facility.

<sup>c</sup>Post office state abbreviations are used.

<sup>d</sup>Number of reporting facilities.

<sup>e</sup>The sum of fugitive and point source releases are included in releases to air by a given facility.

<sup>f</sup>Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

<sup>g</sup>Class I wells, Class II-V wells, and underground injection.

<sup>h</sup>Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

<sup>i</sup>Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.

<sup>j</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>k</sup>Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI22 2024 (Data are from 2022)

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). That balance could change due to increasing cobalt production and recycling to support electric vehicle battery production and recycling to meet the U.S. mandate to phase out fossil fueled activities from 2023 to 2050 (WH 2021a, 2021b). Shen et al. (2021) reported that dust containing cobalt, among eight target metals, is the main source of heavy metal exposure for residents around battery factories.

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-

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containing alloys, and industries that use, process, or recycle cobalt metal and compounds. Loven et al. (2023) identified that cobalt represented 0.1% of the metals in airborne particle emissions generated during recycling of waste from electrical and electronic equipment, but cobalt was essentially absent in emissions from metal scrap and cable recycling. 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 and 100–700 mg/m<sup>3</sup>, respectively. Gasoline contains <0.1 mg cobalt/kg and catalytic converters may contain cobalt; therefore, emissions from vehicular exhaust may also be 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 0.44–1.11 µg/g dry tobacco (Fresquez et al. 2013). Therefore, smoking is a potential source of atmospheric cobalt that could impact indoor air quality.

**5.3.2 Water**

Estimated releases of 2,666 pounds (~1.21 metric tons) of cobalt to surface water from 320 domestic manufacturing and processing facilities in 2022, accounted for about 0.46% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI22 2024). These releases are summarized in Table 5-3.

Estimated releases of 70,577 pounds (~32.01 metric tons) of cobalt compounds to surface water from 367 domestic manufacturing and processing facilities in 2022, accounted for about 1.40% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). These releases are summarized in Table 5-4.

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. Cobalt production in the United States is primarily 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

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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). Clean-up efforts in 1994–1995 resulted in reduced dissolved and particulate cobalt levels; however, suspended particles still remained high as of 2005, compared to levels in the lower Hudson River near New York City (Mackie et al. 2007). 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.

**5.3.3 Soil**

Estimated releases of 506,103 pounds (~229.56 metric tons) of cobalt to soil from 320 domestic manufacturing and processing facilities in 2022, accounted for about 87% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 9,700 pounds (~4.40 metric tons), constituting about 2% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-3.

Estimated releases of 4,570,965 pounds (~2,073.35 metric tons) of cobalt compounds to soil from 367 domestic manufacturing and processing facilities in 2022, accounted for about 91% of the estimated total environmental releases from facilities required to report to the TRI (TRI22 2024). An additional 56,279 pounds (~25.53 metric tons), constituting about 1% of the total environmental emissions, were released via underground injection (TRI22 2024). These releases are summarized in Table 5-4.

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 mining and processing of cobalt-bearing ores, application of cobalt-containing sludge or phosphate fertilizers to soil, disposal of cobalt containing wastes, and atmospheric deposition from activities such as burning of fossil fuels, smelting, and metal refining (Smith and Carson 1981).

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Release of  $^{60}\text{Co}$  from an inactive therapy machine resulted in likely the largest release of radioactive material in the history of North America. In December 1983, maintenance workers at a hospital in Juarez, Mexico scrapped a medical machine containing about 6,000 pellets of  $^{60}\text{Co}$ , with a total source activity of approximately 16.6 TBq (terabecquerels) (UNSCEAR 2011). It was estimated that the release was probably the worst spill of radioactive material in North America, exposing the public to gamma radiation 100 times more intense than that at Three Mile Island in 1979 (Marshall 1984). The scrapped medical machine and its radioactive material were sold to a local scrapyard and eventually to steel foundries in Mexico and the United States. The foundries began processing the contaminated material and incorporating the metal into construction materials, such as steel rebar, which was shipped throughout North America. The accident was discovered when a truck carrying the contaminated rebar passed the entrance of Los Alamos National Laboratories in New Mexico, setting off radiation detectors and alarms (UNSCEAR 2011).

## 5.4 ENVIRONMENTAL FATE

### 5.4.1 Transport and Partitioning

**Air.** Finely ground cobalt dust is auto explosive, but cobalt compounds are nonvolatile; 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  $>2\text{ }\mu\text{m}$  (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  $12\text{ }\mu\text{m}$ . The mass median diameter of cobalt in the ambient atmosphere is about  $2.6\text{ }\mu\text{m}$  (Milford and Davidson 1985). Golomb et al. (1997) reported 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  $58\text{ }\mu\text{g}/\text{m}^2\text{-year}$ , of which  $47\text{ }\mu\text{g}/\text{m}^2\text{-year}$  was dry deposition and  $12\text{ }\mu\text{g}/\text{m}^2\text{-year}$  was wet deposition. Total cobalt deposition flux at a site in the Rhone delta in southern France in 1988–1989 was  $0.42\pm0.23\text{ kg}/\text{km}^2\text{-year}$ , with  $0.15\text{ kg}/\text{km}^2\text{-year}$  in the form of wet deposition (Guieu et al. 1991).



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**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  $^{60}\text{Co}$  was released into the Conowingo Reservoir, an impoundment of the lower Susquehanna River, <20% of the radionuclide was trapped in the reservoir sediment (<1% of that would remain after >38 years due to radioactive decay), and the rest was thought to have been transported downstream and into the Chesapeake Bay (McLean and Summers 1990).  $^{60}\text{Co}$  was not detected in environmental samples of publicly-relevant surface and drinking water, fish, sediment, air particulates, milk, and food products in the Chesapeake Bay area (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 ( $^{60}\text{Co}$ , 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;

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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 ultraviolet (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  $^{60}\text{Co}$  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 montmorillonite. 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  $\text{CoOH}^+$ . 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

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from the southeastern United States with soil pH values of 3.9–6.5, 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 EDTA, that 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; DOE 1988; NRC 1981). The mobility of cobalt was assessed in two soils from the Cabriole 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  $\leq 4$  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 study 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

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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. Cobalt speciation was evaluated during typical roasting recycling of lithium-ion batteries; cobalt was changed into sulfide, phosphate, and complex oxides (Takaya et al. 2023). 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, greater quantities would be expected 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 ( $\text{Cl}^-$ ,  $\text{OH}^-$ ,  $\text{CO}_3^{2-}$ ,  $\text{HCO}_3^-$ ,  $\text{SO}_4^{2-}$ ), pH, and redox potential (Eh). Watanabe et al. (2023) reported that free Co(II) decreased by ~80% in the presence of humic substances in water. 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  $\text{Co}^{2+}$  species in fresh water to follow the order:  $\text{free Co}^{+2} \geq \text{CoCO}_3 > \text{CoHCO}_3^+ \gg \text{cobalt sulfate} \geq \text{Co} \cdot \text{humic acid}$ . However, the mole percent of various cobalt species in a Welsh lake was found to be free  $\text{Co}^{+2}$ , 76%;  $\text{CoCO}_3$ , 9.8%;  $\text{CoHCO}_3^+$ , 9.6%; humate complexes, 4.0%; and cobalt sulfate, 0.4%. The rank order of species concentration in seawater was estimated to be:  $\text{CoCO}_3 > \text{free Co}^{+2} > \text{cobalt sulfate} \geq \text{CoHCO}_3^+$  (Mantoura et al. 1978). In another model, the speciation of cobalt was completely different with  $\text{CoCl}^+ > \text{free Co}^{+2} > \text{CoCO}_3 > \text{cobalt sulfate}$  (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 ( $\text{HCO}_3^-$  and  $\text{CO}_3^{2-}$ ) and constituted about 70% of dissolved cobalt, while the free  $\text{Co}^{2+}$  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  $\text{Co}^{2+}$ . The proportion, but not the concentration, of cobalt that exists as

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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 cobalt chloride 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  $^{60}\text{Co}$  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  $\text{H}^+$  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  $\text{B}_{12}$ , which contains cobalt, is synthesized by 58 species of seven genera of bacteria as well as blue-green algae and actinomycetes (mold-like bacteria). Consequently, vitamin  $\text{B}_{12}$  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  $\text{B}_{12}$ .

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  $\text{B}_{12}$ . 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  $\text{CO}_2$  partial pressure, and generally low redox potential; sulfide concentrations are in the range of  $10^{-4}$ – $10^{-3}$  mol/L. The solubility of cobalt is controlled by the solubility

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of cobalt sulfide ( $\log K_1$  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  $^{60}\text{Co(III)}$  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  $^{60}\text{Co(II)}$  forms for lengthy periods in the environment (Leonard et al. 1993a, 1993b). Studies indicate that several processes occur to the cobalt (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. Cobalt was found to bind to different species in arid calcareous soil around a nonferrous metal smelting area in the order of: residual (76.0%) > bound to organic matter (10.3%) > bound to easily reducible oxides (7.1%) > bound to reducible oxides (5.1%) > bound to carbonates (1.3%) (Chu et al. 2022). 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%; iron/manganese 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).  $\text{Co}^{2+}$  may also be oxidized to  $\text{Co}^{3+}$  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 (DOE 1984; Schnitzer 1969; Smith and Carson 1981).  $^{60}\text{Co}$  that is disposed of in shallow land trenches have sometimes been found to migrate more rapidly than expected from the

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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).

Bioaccumulation factors for cobalt of 0.19–1.43 were calculated from cobalt concentrations in soil and wheat crops. The samples were collected from areas with industrial and mining activities, and plots were irrigated with groundwater, sewage water, or industrial water. The highest bioconcentration factor (BCF) was observed in crops irrigated with industrial wastewater, but that water gave the lowest transfer factor from shoot to grain. The resulting hazard index was virtually the same for all three sources of water, and the grain concentrations were within permissible levels (Chen et al. 2021).

### 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 5-5 shows the limit of detections typically achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-6.

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**Table 5-5. Lowest Limit of Detection for Cobalt Based on Standards<sup>a</sup>**

| 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 <sup>3</sup> (fine element)<br>1.08 ng/m <sup>3</sup> (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 |

<sup>a</sup>Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

**Table 5-6. Summary of Environmental Levels of Cobalt**

| Media                | Low        | High           | For more information |
|----------------------|------------|----------------|----------------------|
| Outdoor air (ppbv)   | 0.000016   | 0.005          | Section 5.5.1        |
| Surface water (ppb)  | <1         | 1,806          | Section 5.5.2        |
| Groundwater (ppb)    | <1         | 424            | Section 5.5.2        |
| Drinking water (ppb) | <1         | 107            | Section 5.5.2        |
| Ocean water (pg/L)   | 0.078      | 71             | Section 5.5.2        |
| Food (ppb)           | 0.02       | 0.86           | Section 5.5.4        |
| Soil                 | 0.15 mg/kg | 15,000,000 ppb | Section 5.5.3        |

Detections of cobalt in air, water, and soil at NPL sites are summarized in Table 5-7.

**Table 5-7. Cobalt Levels in Water, Soil, and Air of National Priorities List (NPL) Sites**

| Medium      | Median <sup>a</sup> | Geometric mean <sup>a</sup> | Geometric standard deviation <sup>a</sup> | Number of quantitative measurements | NPL sites |
|-------------|---------------------|-----------------------------|-------------------------------------------|-------------------------------------|-----------|
| Water (ppb) | 41.5                | 64.7                        | 12.5                                      | 126                                 | 67        |
| Soil (ppb)  | 15,000              | 17,200                      | 5.63                                      | 203                                 | 100       |
| Air (ppbv)  | 0.0215              | 0.0109                      | 11.3                                      | 4                                   | 3         |

<sup>a</sup>Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.



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## 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 (AQS). Data from 2016–2020 are summarized in Table 5-8. Mean cobalt levels in ambient air are generally  $<0.002 \mu\text{g}/\text{m}^3$  (EPA 2020). Annual concentrations of cobalt in ambient air samples are provided in Table 5-9 (EPA 2023d).

**Table 5-8. Percentile Distribution of Annual Mean Cobalt (TSP) Concentrations ( $\mu\text{g}/\text{m}^3$ ) Measured in Ambient Air Locations Across the United States**

| Year | Number of U.S. locations | 25 <sup>th</sup> | 50 <sup>th</sup> | 75 <sup>th</sup> | 95 <sup>th</sup> | 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

**Table 5-9. Summary of Annual Concentration of Cobalt (ppbv) Measured in Ambient Air Samples at Locations Across the United States<sup>a</sup>**

| Year                                                         | Number of monitoring locations | Number of samples | Average of the arithmetic mean at all locations | Maximum concentration |
|--------------------------------------------------------------|--------------------------------|-------------------|-------------------------------------------------|-----------------------|
| Total solid particulates                                     |                                |                   |                                                 |                       |
| 2022                                                         | 464                            | 1                 | 0.00040                                         | 0.0039                |
| 2021                                                         | 575                            | 18                | 0.00063                                         | 0.0044                |
| 2020                                                         | 624                            | 31                | 0.00051                                         | 0.005                 |
| 2019                                                         | 22                             | 921               | 0.00054                                         | 0.003                 |
| 2018                                                         | 26                             | 1,265             | 0.00034                                         | 0.008                 |
| Particulate matter $\leq 10 \mu\text{m}$ (PM <sub>10</sub> ) |                                |                   |                                                 |                       |
| 2022                                                         | 203                            | 9                 | 0.104                                           | 1.38                  |
| 2021                                                         | 1,180                          | 12                | 0.102                                           | 1.5                   |
| 2020                                                         | 1,194                          | 14                | 0.117                                           | 2.4                   |
| 2019                                                         | 15                             | 887               | 0.101                                           | 5.83                  |
| 2018                                                         | 16                             | 988               | 0.105                                           | 3.63                  |

<sup>a</sup>24-hour sampling period at standard temperature and pressure.

Source: EPA 2023d

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At the South Pole, cobalt levels of  $0.00049 \pm 0.00015$  ng/m<sup>3</sup> 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<sup>3</sup> (Chester et al. 1991). The average annual PM<sub>10</sub> (particles with diameters  $\leq 10$   $\mu$ m) cobalt concentration at Nahant, Massachusetts (near Boston) in 1992–1993 was 1.7 ng/m<sup>3</sup> (Golomb et al. 1997). Half of the cobalt was contained in fine particles ( $< 2.5$   $\mu$ m) and half in coarse particles (2.5–10  $\mu$ m). The mean cobalt level in southern Norway in 1985–1986 (n=346) was 0.10 ng/m<sup>3</sup> with 35% of the samples falling below the detection limit of 0.04 ng/m<sup>3</sup> (Amundsen et al. 1992). Atmospheric cobalt levels in industrial settings may exceed 10 ng/m<sup>3</sup>. The highest recorded average cobalt concentration in air was 48 ng/m<sup>3</sup> 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  $1.0 \times 10^4$ – $1.7 \times 10^6$  ng/m<sup>3</sup> (Barceloux 1999; IARC 1991).

### 5.5.2 Water

The EPA maintains a Water Quality Portal (WQP) database that aggregates monitoring data from the National Water Information System (NWIS) and STORage and RETrieval (STORET) system. A summary of the data for ambient surface and groundwater across the United States and at Superfund sites and wastewaters sampled from recent years are reported in Tables 5-10, 5-11, and 5-12 (WQP 2023).

**Table 5-10. Summary of Concentrations of Cobalt (ppb) Measured in Surface and Groundwater Samples Across the United States<sup>a</sup>**

| Year                             | Average | Maximum concentration | Number of samples <sup>b</sup> | Percent detected |
|----------------------------------|---------|-----------------------|--------------------------------|------------------|
| Surface water (total cobalt)     |         |                       |                                |                  |
| 2023                             | 4.0     | 35.2                  | 56                             | 91               |
| 2022                             | 1.4     | 443                   | 1,806                          | 69               |
| 2021                             | 4.8     | 430                   | 1,147                          | 29               |
| 2020                             | 1.6     | 59                    | 974                            | 25               |
| 2019                             | 14.8    | 420                   | 1,196                          | 28               |
| 2018                             | 23.0    | 1,100                 | 1,072                          | 28               |
| Surface water (dissolved cobalt) |         |                       |                                |                  |
| 2023 <sup>a</sup>                | 0.49    | 23                    | 230                            | 100              |
| 2022                             | 0.72    | 100                   | 864                            | 82               |
| 2021                             | 0.76    | 68                    | 898                            | 83               |
| 2020                             | 0.83    | 60                    | 851                            | 70               |
| 2019                             | 1.9     | 140                   | 1,226                          | 65               |

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**Table 5-10. Summary of Concentrations of Cobalt (ppb) Measured in Surface and Groundwater Samples Across the United States<sup>a</sup>**

| Year                           | Average | Maximum concentration | Number of samples <sup>b</sup> | Percent detected |
|--------------------------------|---------|-----------------------|--------------------------------|------------------|
| 2018                           | 1.5     | 180                   | 1,525                          | 60               |
| Groundwater (total cobalt)     |         |                       |                                |                  |
| 2023 <sup>a</sup>              | 22.5    | 95.6                  | 19                             | 32               |
| 2022                           | 7.8     | 142                   | 191                            | 40               |
| 2021                           | 10.8    | 102                   | 424                            | 21               |
| 2020                           | 18.2    | 191                   | 383                            | 22               |
| 2019                           | 13.1    | 140                   | 424                            | 24               |
| 2018                           | 15.7    | 143                   | 511                            | 24               |
| Groundwater (dissolved cobalt) |         |                       |                                |                  |
| 2023a                          | 3.1     | 95.7                  | 97                             | 67               |
| 2022                           | 2.0     | 141                   | 867                            | 34               |
| 2021                           | 26.5    | 8,660                 | 2,324                          | 26               |
| 2020                           | 15.2    | 389                   | 2,509                          | 27               |
| 2019                           | 1.2     | 84.5                  | 1,218                          | 44               |
| 2018                           | 1.6     | 98.3                  | 1,136                          | 42               |

<sup>a</sup>As of September 14, 2023.<sup>b</sup>Samples collected from the U.S. Geological Survey Water Science Center monitoring sites and other state environmental departments in over 30 U.S. States.

Source: WQP 2023

**Table 5-11. Summary of Concentrations of Cobalt (ppb) Measured in Surface and Groundwater Samples at Superfund Sites**

| Year                              | Average | Maximum concentration | Number of samples | Percent detected |
|-----------------------------------|---------|-----------------------|-------------------|------------------|
| Bonita Peak Mining Superfund Site |         |                       |                   |                  |
| Surface water (total cobalt)      |         |                       |                   |                  |
| 2021                              | 32.5    | 233                   | 236               | 61               |
| 2020                              | 41.4    | 166                   | 153               | 86               |
| 2019                              | 43.6    | 148                   | 15                | 100              |
| 2018                              | 20.2    | 198                   | 581               | 73               |
| Surface water (dissolved cobalt)  |         |                       |                   |                  |
| 2021                              | 25      | 226                   | 238               | 75               |
| 2020                              | 32.8    | 154                   | 103               | 97               |
| 2019                              | 34.8    | 133                   | 15                | 100              |
| 2018                              | 17.9    | 195                   | 581               | 82               |
| Groundwater (total cobalt)        |         |                       |                   |                  |
| 2021                              | 1.81    | 1.81                  | 2                 | 50               |

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**Table 5-11. Summary of Concentrations of Cobalt (ppb) Measured in Surface and Groundwater Samples at Superfund Sites**

| Year                             | Average | Maximum concentration | Number of samples | Percent detected |
|----------------------------------|---------|-----------------------|-------------------|------------------|
| Groundwater (dissolved cobalt)   |         |                       |                   |                  |
| 2021                             | 81.6    | 1,900                 | 61                | 61               |
| Midnite Mine Superfund Site      |         |                       |                   |                  |
| Surface water (total cobalt)     |         |                       |                   |                  |
| 2022                             | 290     | 2,060                 | 31                | 58               |
| 2021                             | 138     | 1,180                 | 33                | 91               |
| 2020                             | 225     | 2,100                 | 33                | 88               |
| 2019                             | 489     | 5,670                 | 34                | 62               |
| 2018                             | 330     | 1,230                 | 33                | 52               |
| Surface water (dissolved cobalt) |         |                       |                   |                  |
| 2022                             | 387     | 6,450                 | 82                | 51               |
| 2021                             | 198     | 7,140                 | 87                | 91               |
| 2020                             | 201     | 5,260                 | 89                | 73               |
| 2019                             | 400     | 5,330                 | 84                | 60               |
| 2018                             | 298     | 5,790                 | 87                | 61               |

Source: WQP 2023

**Table 5-12. Summary of Concentrations of Cobalt (ppb) Measured in Wastewater Samples Across the United States**

| Year                | Average | Maximum concentration | Number of samples | Percent detected |
|---------------------|---------|-----------------------|-------------------|------------------|
| Industrial effluent |         |                       |                   |                  |
| 2020–2022           | –       | –                     | 2                 | 0                |
| 2019                | 1.6     | 2                     | 8                 | 63               |
| 2018                | 1       | 1                     | 4                 | 25               |
| Municipal waste     |         |                       |                   |                  |
| 2020–2022           | –       | –                     | –                 | –                |
| 2019                | 1       | 1                     | 27                | 4                |
| 2018                | 1       | 1                     | 11                | 9                |

Source: WQP 2023

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

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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<sub>12</sub> 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 (Flatén 1991).

The mean concentrations of cobalt in rain are 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

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(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 33<sup>rd</sup> 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

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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).

In soil samples monitored over a 2-year period near industrial and mining sites in Pakistan, samples irrigated with industrial water had the highest cobalt concentrations detected (1.01–1.20 mg/kg), while the lowest concentrations (0.15–0.30 mg/kg) were observed in soils irrigated with groundwater or sewage water (Chen et al. 2021). Cobalt levels in soils near mining sites in the D.R. Congo are much higher with concentrations of 116–311 mg/kg (Cheyns et al. 2014; Michée et al. 2023). Reported mean soil concentrations in regions distant from mining operations in the D.R. Congo were 20 mg/kg (Cheyns et al. 2014).

Sediment and soil monitoring data were available for cobalt in the EPA's WQP database and are reported in Tables 5-13, 5-14, and 5-15. Because it is a natural component of the earth's crust, cobalt was frequently detected, and the averages and ranges generally agree with reported background concentration ranges. In 2020, the high reported average and maximum concentrations in soil were reported from monitoring in South Dakota, which were likely impacted by mining operation located in the state. In 2022, the high reported average and maximum concentrations in sediments were reported from monitoring in Washington, which were likely impacted by mining operation at the Midnite Mine located in Washington.

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**Table 5-13. Summary of Concentrations of Cobalt (ppb) Measured in Sediment Samples Across the United States**

| Year range | Average | Maximum concentration | Number of samples | Percent detected |
|------------|---------|-----------------------|-------------------|------------------|
| 2022       | 22,240  | 192,000               | 15                | 100              |
| 2021       | 6,303   | 83,000                | 137               | 96               |
| 2020       | 5,370   | 31,000                | 376               | 81               |
| 2019       | 9,621   | 45,000                | 590               | 69               |
| 2018       | 7,604   | 35,000                | 255               | 60               |

Source: WQP 2023

**Table 5-14. Summary of Concentrations of Cobalt (ppb) Measured in Soil Samples Across the United States**

| Year range | Average   | Maximum concentration | Number of samples | Percent detected |
|------------|-----------|-----------------------|-------------------|------------------|
| 2022       | 7,340     | 23,00                 | 15                | 100              |
| 2021       | 17,800    | 24,000                | 10                | 100              |
| 2020       | 1,358,897 | 15,000,000            | 39                | 100              |
| 2019       | 6,089     | 24,700                | 122               | 99               |
| 2018       | 7,430     | 13,000                | 13                | 100              |

Source: WQP 2023

**Table 5-15. Summary of Concentrations of Cobalt (ppb) Measured in Soil and Sediment Samples at Superfund Sites**

| Year                              | Average | Maximum concentration | Number of samples | Percent detected |
|-----------------------------------|---------|-----------------------|-------------------|------------------|
| Bonita Peak Mining Superfund Site |         |                       |                   |                  |
| Soil                              |         |                       |                   |                  |
| 2021                              | 16,780  | 217,000               | 192               | 80               |
| 2018                              | 8,599   | 126,000               | 97                | 100              |
| Sediment                          |         |                       |                   |                  |
| 2018                              | 14,501  | 85,900                | 122               | 100              |

Source: WQP 2023

**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



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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. In wheat samples collected from seven industrial and mining sites in Pakistan where fields were irrigated with various water sources with cobalt concentrations ranging from 0.15 to 1.20 mg/kg, cobalt concentrations in the wheat grain samples ranged from 0.12 to 0.57 mg/kg (Chen et al. 2021).

Cobalt concentrations have been reported in various aquatic animals and seabirds. Concentrations of cobalt in biota sampled from 2018 to 2022 across the United States and compiled in the WQP database are reported in Table 5-16 (WQP 2023). 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 of 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

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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 carpio* and from 0.045 to 0.062 µg/g dry weight for *Barbus plebejus* (Barlas 1999).

**Table 5-16. Summary of Concentrations of Cobalt (ppb) Measured in Biota Samples Across the United States**

| Organism <sup>a</sup>                                | Average | Maximum concentration | Number of samples | Percent detected |
|------------------------------------------------------|---------|-----------------------|-------------------|------------------|
| 2022                                                 | 298     | 795                   | 37                | 86               |
| <i>Catostomus latipinnis</i>                         | 208.3   | 686                   | 9                 | 100              |
| <i>Salmo trutta</i>                                  | 422.5   | 678                   | 2                 | 100              |
| <i>Oncorhynchus mykiss</i>                           | 222.8   | 328                   | 12                | 58               |
| <i>Pantosteus discobolus</i>                         | 490.3   | 795                   | 7                 | 100              |
| <i>Catostomus commersonii</i>                        | 203.5   | 272                   | 4                 | 100              |
| <i>C. commersonii</i> ; <i>Catostomus discobolus</i> | 473.0   | 473                   | 1                 | 100              |
| <i>C. commersonii</i> ; <i>C. latipinnis</i>         | 268.5   | 393                   | 2                 | 100              |
| 2021                                                 | 5,651   | 1,219,000             | 3,567             | 88               |
| Taxon unknown                                        | 2,900.0 | 2,900                 | 1                 | 100              |
| Vertebrata                                           | 252.5   | 276                   | 4                 | 100              |
| <i>Ameiurus natalis</i>                              | 30.5    | 38.8                  | 3                 | 67               |
| <i>Coregonus clupeaformis</i>                        | 24.2    | 30.1                  | 6                 | 33               |
| 2020                                                 | 313.7   | 6,700                 | 162               | 65               |
| Taxon unknown                                        | 1,907.7 | 6700                  | 13                | 100              |
| <i>Mylocheilus caurinus</i>                          | 57.0    | 112                   | 32                | 63               |
| <i>Catostomus macrocheilus</i>                       | 93.5    | 287                   | 24                | 92               |
| <i>O. mykiss</i>                                     | 159.7   | 604                   | 13                | 54               |
| <i>Ptychocheilus oregonensis</i>                     | 47.7    | 123                   | 60                | 48               |
| <i>Catostomus catostomus</i>                         | 102.6   | 198                   | 14                | 64               |
| <i>Oncorhynchus clarkii</i>                          | 282.0   | 824                   | 6                 | 83               |
| 2019                                                 | 57.3    | 243                   | 185               | 49%              |
| <i>M. caurinus</i>                                   | 60.9    | 85                    | 24                | 33               |
| <i>Salvelinus confluentus</i>                        | 33.4    | 62                    | 8                 | 63               |
| <i>O. mykiss</i>                                     | 39.5    | 41                    | 5                 | 40               |
| <i>P. oregonensis</i>                                | 40.6    | 54                    | 38                | 37               |
| <i>Lepomis megalotis</i>                             | 33.6    | 60                    | 14                | 43               |
| <i>C. macrocheilus</i>                               | 83.0    | 243                   | 23                | 96               |
| <i>Oncorhynchus nerka</i>                            | 43.5    | 90                    | 23                | 48               |
| <i>Lepomis macrochirus</i>                           | 39.6    | 39.6                  | 4                 | 25               |
| <i>Prosopium williamsoni</i>                         | 58.0    | 58                    | 2                 | 50               |
| <i>Richardsonius balteatus</i>                       | 53.9    | 89                    | 16                | 50               |

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**Table 5-16. Summary of Concentrations of Cobalt (ppb) Measured in Biota Samples Across the United States**

| Organism <sup>a</sup>            | Average | Maximum concentration | Number of samples | Percent detected |
|----------------------------------|---------|-----------------------|-------------------|------------------|
| <i>Semotilus atromaculatus</i>   | 37.0    | 42.1                  | 4                 | 50               |
| <i>A. natalis</i>                | 108.0   | 108                   | 1                 | 100              |
| <i>Lepomis cyanellus</i>         | 39.5    | 42.9                  | 4                 | 50               |
| <i>C. commersonii</i>            | 67.4    | 74.3                  | 4                 | 75               |
| <i>Perca flavescens</i>          | 49.0    | 68                    | 6                 | 33               |
| <i>O. clarkii</i>                | 86.0    | 139                   | 2                 | 100              |
| <i>Hybognathus nuchalis</i>      | 153     | 153                   | 1                 | 100              |
| 2018                             | 14      | 25.6                  | 19                | 21               |
| <i>L. macrochirus</i>            | 9.19    | 9.19                  | 2                 | 50               |
| <i>Micropterus dolomieu</i>      | 11.3    | 11.3                  | 1                 | 100              |
| <i>Lepomis megalotis</i>         | 25.6    | 25.6                  | 3                 | 33               |
| <i>Cyprinus carpio</i>           | 10      | 10                    | 3                 | 33               |
| <i>Chironomidae</i> <sup>b</sup> | 818     | 10,700                | 61                | 93               |

<sup>a</sup>Only organisms with >5% sample detection listed.

<sup>b</sup>Organism from Bonita Peak Mining Superfund Site.

Source: WQP 2023

Khan et al. (2022) examined the accumulation of heavy metals over a 3-month period in *Poecilia reticulata* in a laboratory aquarium study using five types of industrial wastes: chemical sludge, chemical sludge-ash, boulder slag, converter slag, and marble waste powder with cobalt concentrations of 130.00, 243.21, 50.32, 115.00, and 9.49 mg/kg, respectively. A significantly higher accumulation of cobalt was observed in fish exposed to sludge, sludge-ash, and converter slag. Concentrations of cobalt in the aquariums prepared with chemical sludge, chemical sludge-ash, boulder slag, converter slag, and marble waste powder were approximately 4.09, 8.12, 1.33, 1.51, and 3.82 mg/kg, respectively. Concentrations of cobalt in fish tissues at the end of the study were approximately 4.60, 8.62, 1.59, 1.93, and 3.92 mg/kg, respectively. The control tank and control fish cobalt concentrations were 0.001 and 0.01 mg/kg, respectively.

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

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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 containing 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 can be released into bottled water stored in transparent PET plastic containers containing cobalt acetate as an anti-yellowing agent, with concentrations increasing with prolonged storage at 20°C (Dogan and Cebi 2019). For example, cobalt levels in a 5-L bottle after 2 and 12 months of storage were 0.05 and 0.70 µg/L, respectively. Small amounts of cobalt (0.01175–0.02150 µg/L) also leached into hot water (100°C) that was stored in disposable fast-food container products such as paper cups, plastic cups, plastic bags, and plastic bowls for 15 minutes (Zeng et al. 2023). Most containers tested were made from transparent polypropylene; however, some products also contained polyethylene and polystyrene. This particular combination of products, temperature, and duration was selected to simulate a take-out food scenario with hot food or freshly boiled liquid.

Cobalt levels in food from the Copperbelt mining region of D.R. Congo are much higher than non-mining regions (Cheyns et al. 2014). Food items with the highest concentrations in the mining regions included leafy vegetables (46 µg/g dry weight), beans (22 µg/g dry weight), cassava leaves (12 µg/g dry weight), fruit vegetable (12 µg/g dry weight), and sweet potato leaves (6.5 µg/g dry weight). Concentrations for

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the same food items from non-mining regions were 1.2, 0.84, 1.5, 0.58, and 1.1  $\mu\text{g/g}$  dry weight, respectively.

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. The estimated average intake of cobalt of the U.S. population has been reported as 0.005–0.04 mg Co/day, the U.K. estimated population intake is reported as 0.012 mg/day, and the estimated population intakes in Canada and France have been reported as 0.011 and 0.029 mg Co/day, respectively (EFSA 2009; EPA 1980). 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  $<0.002$   $\mu\text{g}/\text{m}^3$  (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  $<2.0$   $\mu\text{g/L}$ ; however, values as high as 107  $\mu\text{g/L}$  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  $\leq 2.6$   $\mu\text{g}$ ; this could increase to 10  $\mu\text{g}$  for those living in areas with the highest cobalt levels (Meranger et al. 1981). Low levels of cobalt ( $\leq 1.30$   $\mu\text{g/L}$ ) have been detected in water stored at room temperature in transparent PET, with higher cobalt levels detected in smaller containers (0.5 versus 5 L) stored for a longer duration (12 versus 2 months) (Dogan and Cebi 2019). Small amounts of cobalt ( $<0.03$   $\mu\text{g/L}$ ) may leach into hot beverages stored in plastic or paper to-go containers (Zeng et al. 2023).

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Very low levels of cobalt present in some finished waters are not expected to be an exposure concern when showering. Cobalt is not expected to volatilize from water; therefore, there is no potential for vapor inhalation exposure during showering and bathing. Furthermore, dermal exposure is not expected to be a concern. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts dermal exposure based on showering and bathing. These data, along with human activity patterns, are used to calculate a daily time-weighted average (TWA) exposure concentrations from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to [showermodel@cdc.gov](mailto:showermodel@cdc.gov). Using water levels discussed in Section 5.5.2, Reasonable Maximum Exposure (RME) levels for potential dermal exposure to cobalt were calculated for different exposure groups (Table 5-17).

**Table 5-17. Reasonable Maximum Exposure of Cobalt for Daily Administered Dermal Dose in  $\mu\text{g}/\text{kg}/\text{day}$  for the Target Person**

| Exposure group                   | Dermal               |
|----------------------------------|----------------------|
| Birth–<1 year                    | 0.00012              |
| 1–<2 years                       | 0.00011              |
| 2–<6 years                       | $9.9 \times 10^{-5}$ |
| 6–<11 years                      | $8.1 \times 10^{-5}$ |
| 11–<16 years                     | $6.6 \times 10^{-5}$ |
| 16–<21 years                     | $6.1 \times 10^{-5}$ |
| Adult                            | $5.9 \times 10^{-5}$ |
| Pregnant and breastfeeding women | $5.9 \times 10^{-5}$ |

Source: ATSDR 2023

General population exposure to cobalt from food is highly variable and normally higher than intake from drinking water. In a study published in 1980, the cobalt intake from food was estimated to be 5.0–40.0  $\mu\text{g}/\text{day}$  (EPA 1980). The Panel on Additives and Products or Substances used in Animal Feed reported a worst-case calculation for cobalt intake by humans of 14  $\mu\text{g}/\text{day}$  based on approximate cobalt concentrations in animal products (EFSA 2009). Small amounts of cobalt (<0.03  $\mu\text{g}/\text{L}$ ) may leach into hot foods stored in plastic or paper take-out containers (Zeng et al. 2023).

In a 2020 study, children's weekly intake of cobalt from snacks was estimated to be 0.69  $\mu\text{g}/\text{kg}$ , equivalent to about 1.5  $\mu\text{g}/\text{day}$  (Gao et al. 2020). The greatest dietary contributors were flour products (0.16 mg/kg; 23.59%), bean products (0.15 mg/kg; 22.38%), and preserved fruit (0.1 mg/kg; 14.18%). In an earlier study, the daily cobalt intake, including food, water, and beverages of two men that were

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followed for 50 weeks was much higher, 310 and 470  $\mu\text{g}$  (Smith and Carson 1981). 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 healthy 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). The estimated average daily cobalt intake from the diet in Canada was 11  $\mu\text{g/day}$ ; the intake varied from 4 to 15  $\mu\text{g/day}$  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  $\mu\text{g/day}$  (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. A long-term (2013–2018) total diet study of the Japanese population determined that the average intake was 0.17  $\mu\text{g Co/kg/day}$  (12  $\mu\text{g/day}$  for a 70-kg person), with comparable intakes for total mercury and lead. The food concentrations ( $\mu\text{g Co/g}$ ) were greatest in seasonings (0.0075), pulses (0.0056), sugars and confectionaries (0.0033), green vegetables (0.0023), fish and shellfish (0.0022), and mushrooms and seaweed (0.0021) (Watanabe et al. 2022).

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 Camean et al. (1998), the low levels of cobalt presently found in beer do not make a significant contribution to the total cobalt intake in heavy beer drinkers. The average concentration of cobalt measured in coffee varieties of Brazil, Ethiopia, Kenya, Columbia, and India origin sampled from the Jordanian Market in 2019 was 0.76  $\mu\text{g/g}$ , with a range of 0.27–0.97  $\mu\text{g/g}$ ; highest levels were measured in coffee from India (Albals et al. 2021). The daily estimated intake was 1.52  $\mu\text{g Co}$  based on 1 cup/day (2 g of group coffee in 50 mL of tap water). Roasted coffee had higher levels of cobalt (0.97  $\mu\text{g/g}$ ) than green coffee (0.71  $\mu\text{g/g}$ ) or half-roasted coffee (0.67  $\mu\text{g/g}$ ) (Albals et al. 2021).

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

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with metallic items mimicking daily contact, average skin doses were 0.7–1.1  $\mu\text{g}/\text{cm}^2$  (Midander et al. 2014). Midander et al. (2014) concluded that short, repetitive contact with metallic items could be harmful. Bregnbak et al. (2015b) also found that leather was the most frequent exposure source causing dermatitis after non-occupational use of cobalt-containing tools. Eleven water-based acrylic paint colors (lemon yellow, viridian, scarlet, titanium white, burnt umber, yellow ochre, ultramarine, phthalocyanine blue, emerald green, vermilion, and burnt sienna) intended for school-age children purchased from a local shop in Riyadh, Saudi Arabia were all found to have cobalt concentrations ranging from 1.04  $\mu\text{g}/\text{g}$  in titanium white to 14.09  $\mu\text{g}/\text{g}$  in burnt umber (Khan et al. 2021). 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 800–1,250 ppm cobalt (Bregnbak et al. 2017; Thyssen et al. 2013). Cobalt was detected in 100% of preschool children's clothing samples analyzed from China, India, South Korea, and Southeast Asia. Cobalt concentrations ranged from 0.0176 to 4.64 mg/kg, with a median value of 0.089 mg/kg. Cobalt is likely introduced to fabrics as a catalyst or antimicrobial agent during manufacturing. Significantly higher concentrations of cobalt were observed in clothing samples of non-pure cotton fabrics (Chen et al. 2022). Zhang et al. (2022) measured concentrations of cobalt in various polyethylene, propylene, polyurethane, plush, and wooden toys and reported levels ranging from not detected to 2,610 ng/g; both detection rates and detection levels were highest in plush toys. 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<sup>2</sup>/hour from the wrist support and as much as 0.07 ng/cm<sup>2</sup>/hour 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 top of the glazed surface of hand-painted China, a study was conducted to see whether these metals are released from the paint 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  $\mu\text{g}/\text{mL}$  of cobalt and 10 released 0.020–2.9  $\mu\text{g}/\text{mL}$ . 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



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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  $<0.5$  to  $253.33 \mu\text{g/g}$ , 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  $>10 \mu\text{g/g}$  of cobalt were mainly darker pigmented colors like brown, gray, and black. Face paints for both adults and children produced in China, Spain, the United Kingdom, and the United States were analyzed and found to contain up to  $5.5 \mu\text{g/g}$  cobalt (Corazza et al. 2009). Lipstick contained concentrations up to  $1.30 \mu\text{g/g}$  (Corazza et al. 2009; Liu et al. 2013; Sneyers et al. 2009). Concentrations of cobalt in skin creams ranged from  $0.00013$  to  $2.2 \mu\text{g}$  (Bocca et al. 2007; Onwordi et al. 2011; Sneyers et al. 2009). Average cobalt concentrations of  $4.4 \mu\text{g/g}$  were reported in various cosmetic face paints used in China. Out of 91 paint samples tested, 11.0% contained cobalt at levels  $>10 \mu\text{g/kg}$ . Cobalt was detected in 73.3 and 91.7% of white and yellow paints, respectively, and in 100% of nude, red, green, blue, brown, and black paint samples. Cobalt was detected at levels  $>10 \mu\text{g/kg}$  in 7.1, 7.7, 15.4, 37.5, and 71.4% of red, green, blue, brown, and black paints, respectively (Wang et al. 2020). Cobalt concentrations in facial and powdered cosmetic pigments (Unipure yellow LC 182, Unipure Violet LC 581, and Unipure Black LC 990) ranged from  $4.1$  to  $9.4 \mu\text{g/g}$ . In dissolution tests of these facial and powdered cosmetic pigments with artificial sweat solutions, it was observed that cobalt was not released into the sweat-soluble fraction (Wang et al. 2022a).

Cobalt concentrations were analyzed in tattoo ink samples in Italy in 2019 via inductively coupled plasma mass spectrometry. Cobalt was identified in True Black from Solong Tattoo (China) using a proprietary pigment class ( $0.28 \mu\text{g/g}$ ), Mario's Blue from Solong Tattoo (China) using a proprietary pigment class ( $0.14 \mu\text{g/g}$ ), and Grape Violet from Solong Tattoo (China) using a proprietary pigment class ( $0.14 \mu\text{g/g}$ ). Cobalt was not detected in Light Red from Eternal Ink (USA) using CI 12475 (Pigment Red 170), Golden Yellow from Solong Tattoo (China) using a proprietary pigment class, Light Green from Solong Tattoo (China) using a proprietary pigment class, or Snow White from Solong Tattoo (China) using a proprietary pigment class (Battistini et al. 2020); those colors are not typically associated with cobalt compound colorants.

Higher urinary cobalt concentrations were related to older housing built before 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).

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Urinary cobalt (uncorrected and creatinine-corrected) was measured in the U.S. general population during NHANES 1999–2018 and blood cobalt was measured in 2015–2018 (CDC 2022). Table 5-18 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 5-19 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 5-20 shows the geometric mean and selected percentiles of blood cobalt in the U.S. population from NHANES 2015–2016 and 2017–2018.

In an evaluation of pregnant and delivering women conducted in Spain from March 2016 to March 2017, maternal blood and urine samples and cord blood samples were collected and analyzed (Bocca et al. 2019). Maternal blood samples (n=48) in the first trimester had cobalt levels of 0.1–0.8 µg/L, which was similar to cobalt levels in blood samples (n=40) collected at delivery (0.1–0.9 µg/L). Cobalt levels in cord blood sampled (n=31) at delivery ranged from 0.1 to 0.6 µg/L. Cobalt levels in non-creatinine-adjusted maternal urine samples collected in the first, second, and third trimesters were 0.1–2.3, 0.1–3.2, and 0.1–3.4 µg/L, respectively. In creatinine-adjusted maternal urine samples collected in the first, second, and third trimesters, cobalt levels were 0.1–6.5, 0.1–6.2, and 0.1–6.9 µg/L, respectively. These levels were similar to previous study results in pregnant women from South Africa, Western Australia, and North Norway, with maternal blood concentrations of 0.1–0.6 µg/L, a cord blood concentration of 0.27 µg/L, and a maternal urine concentration of 1.17 µg/L (Bocca et al. 2019). Maternal blood and urine concentrations were positively associated with intake of seafood and fresh cheese using Spearman's correlations; however, this association was not observed using a multiple linear regression analysis (Bocca et al. 2020). In a study of pregnant women in Puerto Rico from 2011 to 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). Reported urinary and blood values in Ashrap et al. (2020) were in the NHANES 90<sup>th</sup> and 90<sup>th</sup>–95<sup>th</sup> percentiles, respectively, for Hispanics in Tables 5-18 and 5-20. 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 were 0.52–0.61 in maternal serum of Polish mothers with fetuses with neonatal abnormalities and 0.24–0.27 µg/L in amniotic fluid (Kocylowski et al. 2019).

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**Table 5-18. Geometric Mean and Selected Percentiles of Urinary Cobalt (in µg/L) for the U.S. Population from NHANES**

|             | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) |                     |                     |                    | Sample size |
|-------------|--------------|-------------------------|-------------------------------|---------------------|---------------------|--------------------|-------------|
|             |              |                         | 50 <sup>th</sup>              | 75 <sup>th</sup>    | 90 <sup>th</sup>    | 95 <sup>th</sup>   |             |
| Total       |              |                         |                               |                     |                     |                    |             |
|             | 2011–2012    | 0.326 (0.309–0.344)     | 0.323 (0.306–0.347)           | 0.543 (0.510–0.577) | 0.860 (0.800–0.979) | 1.27 (1.09–1.45)   | 2,504       |
|             | 2013–2014    | 0.391 (0.373–0.411)     | 0.408 (0.382–0.435)           | 0.687 (0.662–0.713) | 1.04 (0.976–1.09)   | 1.35 (1.23–1.48)   | 2,664       |
|             | 2015–2016    | 0.414 (0.394–0.435)     | 0.434 (0.415–0.455)           | 0.687 (0.658–0.725) | 1.06 (0.983–1.12)   | 1.53 (1.34–1.71)   | 3,061       |
|             | 2017–2018    | 0.424 (0.398–0.451)     | 0.437 (0.412–0.451)           | 0.710 (0.673–0.756) | 1.16 (1.07–1.27)    | 1.61 (1.37–1.83)   | 2,808       |
| Age group   |              |                         |                               |                     |                     |                    |             |
| 3–5 years   | 2015–2016    | 0.426 (0.397–0.456)     | 0.466 (0.410–0.512)           | 0.739 (0.662–0.833) | 1.08 (0.947–1.25)   | 1.55 (1.23–2.07)   | 486         |
|             | 2017–2018    | 0.472 (0.410–0.542)     | 0.526 (0.448–0.627)           | 0.854 (0.749–0.917) | 1.22 (1.04–1.52)    | 1.64 (1.34–1.78)   | 403         |
| 6–11 years  | 2011–2012    | 0.397 (0.356–0.442)     | 0.452 (0.361–0.510)           | 0.704 (0.616–0.772) | 1.00 (0.846–1.38)   | 1.42 (1.00–1.78)   | 399         |
|             | 2013–2014    | 0.447 (0.411–0.487)     | 0.479 (0.408–0.522)           | 0.789 (0.718–0.877) | 1.05 (0.991–1.33)   | 1.55 (1.14–1.84)   | 402         |
|             | 2015–2016    | 0.534 (0.494–0.577)     | 0.599 (0.525–0.636)           | 0.886 (0.773–0.948) | 1.20 (0.992–1.40)   | 1.63 (1.20–2.05)   | 379         |
|             | 2017–2018    | 0.519 (0.459–0.586)     | 0.559 (0.474–0.642)           | 0.877 (0.787–0.942) | 1.45 (1.18–1.83)    | 1.88 (1.57–2.21)   | 333         |
| 12–19 years | 2011–2012    | 0.416 (0.358–0.484)     | 0.429 (0.341–0.527)           | 0.700 (0.622–0.806) | 1.12 (0.960–1.30)   | 1.56 (1.16–1.96)   | 390         |
|             | 2013–2014    | 0.549 (0.462–0.653)     | 0.602 (0.491–0.701)           | 0.936 (0.783–1.05)  | 1.43 (1.08–1.75)    | 1.76 (1.49–3.07)   | 451         |
|             | 2015–2016    | 0.571 (0.527–0.620)     | 0.604 (0.535–0.659)           | 0.892 (0.840–1.08)  | 1.48 (1.32–1.74)    | 1.92 (1.57–2.23)   | 402         |
|             | 2017–2018    | 0.516 (0.488–0.545)     | 0.583 (0.514–0.656)           | 0.879 (0.835–0.948) | 1.33 (1.20–1.39)    | 1.49 (1.39–1.65)   | 364         |
| ≥20 years   | 2011–2012    | 0.307 (0.288–0.327)     | 0.308 (0.289–0.328)           | 0.491 (0.457–0.534) | 0.800 (0.695–0.940) | 1.16 (0.984–1.36)  | 1,715       |
|             | 2013–2014    | 0.367 (0.349–0.386)     | 0.382 (0.357–0.410)           | 0.647 (0.614–0.673) | 0.930 (0.882–1.04)  | 1.23 (1.17–1.34)   | 1,811       |
|             | 2015–2016    | 0.385 (0.364–0.408)     | 0.403 (0.379–0.427)           | 0.638 (0.599–0.666) | 0.949 (0.877–1.06)  | 1.41 (1.21–1.66)   | 1,794       |
|             | 2017–2018    | 0.401 (0.371–0.433)     | 0.409 (0.384–0.438)           | 0.650 (0.619–0.702) | 1.08 (0.981–1.20)   | 1.61 (1.27–1.88)   | 1,708       |
| Sex         |              |                         |                               |                     |                     |                    |             |
| Males       | 2011–2012    | 0.317 (0.299–0.336)     | 0.316 (0.293–0.339)           | 0.496 (0.452–0.547) | 0.715 (0.659–0.798) | 0.963 (0.858–1.03) | 1,262       |
|             | 2013–2014    | 0.380 (0.355–0.407)     | 0.414 (0.374–0.452)           | 0.641 (0.604–0.684) | 0.883 (0.820–0.951) | 1.11 (1.04–1.26)   | 1,318       |
|             | 2015–2016    | 0.397 (0.376–0.420)     | 0.434 (0.405–0.466)           | 0.651 (0.609–0.692) | 0.860 (0.815–0.954) | 1.08 (0.960–1.19)  | 1,524       |
|             | 2017–2018    | 0.419 (0.375–0.468)     | 0.427 (0.388–0.466)           | 0.679 (0.611–0.738) | 1.03 (0.906–1.15)   | 1.47 (1.20–1.88)   | 1,381       |

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**Table 5-18. Geometric Mean and Selected Percentiles of Urinary Cobalt (in µg/L) for the U.S. Population from NHANES**

|                       | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) |                     |                     |                  | Sample size |
|-----------------------|--------------|-------------------------|-------------------------------|---------------------|---------------------|------------------|-------------|
|                       |              |                         | 50 <sup>th</sup>              | 75 <sup>th</sup>    | 90 <sup>th</sup>    | 95 <sup>th</sup> |             |
| Females               | 2011–2012    | 0.335 (0.310–0.361)     | 0.340 (0.308–0.382)           | 0.591 (0.554–0.643) | 1.07 (0.891–1.20)   | 1.49 (1.30–1.74) | 1,242       |
|                       | 2013–2014    | 0.402 (0.374–0.432)     | 0.398 (0.366–0.438)           | 0.741 (0.701–0.789) | 1.16 (1.06–1.23)    | 1.5 (1.36–1.75)  | 1,346       |
|                       | 2015–2016    | 0.432 (0.397–0.469)     | 0.433 (0.391–0.489)           | 0.752 (0.675–0.865) | 1.33 (1.20–1.43)    | 1.82 (1.54–2.13) | 1,537       |
|                       | 2017–2018    | 0.428 (0.391–0.469)     | 0.446 (0.410–0.487)           | 0.760 (0.694–0.835) | 1.26 (1.19–1.33)    | 1.61 (1.47–1.79) | 1,427       |
| <b>Race/ethnicity</b> |              |                         |                               |                     |                     |                  |             |
| Mexican American      | 2011–2012    | 0.350 (0.322–0.381)     | 0.350 (0.307–0.377)           | 0.550 (0.490–0.598) | 0.891 (0.721–1.18)  | 1.41 (1.14–2.08) | 317         |
|                       | 2013–2014    | 0.415 (0.378–0.456)     | 0.439 (0.400–0.482)           | 0.686 (0.610–0.766) | 0.918 (0.866–1.09)  | 1.15 (1.06–1.56) | 453         |
|                       | 2015–2016    | 0.469 (0.431–0.511)     | 0.488 (0.431–0.558)           | 0.777 (0.688–0.852) | 1.21 (1.01–1.42)    | 1.81 (1.32–2.14) | 585         |
|                       | 2017–2018    | 0.431 (0.397–0.468)     | 0.437 (0.410–0.474)           | 0.708 (0.626–0.815) | 1.14 (0.997–1.27)   | 1.39 (1.23–1.70) | 435         |
| Non-Hispanic black    | 2011–2012    | 0.340 (0.311–0.373)     | 0.333 (0.304–0.358)           | 0.519 (0.489–0.576) | 0.909 (0.790–0.986) | 1.44 (1.06–1.60) | 669         |
|                       | 2013–2014    | 0.468 (0.410–0.535)     | 0.471 (0.402–0.561)           | 0.796 (0.691–0.877) | 1.26 (1.03–1.39)    | 1.5 (1.35–1.67)  | 581         |
|                       | 2015–2016    | 0.461 (0.422–0.503)     | 0.478 (0.436–0.513)           | 0.740 (0.660–0.845) | 1.20 (0.956–1.40)   | 1.52 (1.34–1.85) | 671         |
|                       | 2017–2018    | 0.470 (0.443–0.499)     | 0.476 (0.430–0.514)           | 0.718 (0.657–0.806) | 1.26 (1.04–1.55)    | 1.86 (1.29–2.35) | 639         |
| Non-Hispanic white    | 2011–2012    | 0.320 (0.295–0.348)     | 0.320 (0.296–0.357)           | 0.543 (0.485–0.591) | 0.858 (0.750–0.995) | 1.2 (1.03–1.35)  | 820         |
|                       | 2013–2014    | 0.374 (0.349–0.401)     | 0.387 (0.345–0.429)           | 0.681 (0.638–0.723) | 1.02 (0.930–1.10)   | 1.34 (1.21–1.56) | 985         |
|                       | 2015–2016    | 0.402 (0.374–0.432)     | 0.422 (0.386–0.454)           | 0.675 (0.627–0.734) | 1.00 (0.938–1.11)   | 1.49 (1.24–1.71) | 924         |
|                       | 2017–2018    | 0.411 (0.372–0.454)     | 0.428 (0.391–0.446)           | 0.702 (0.640–0.759) | 1.11 (0.958–1.33)   | 1.57 (1.31–1.89) | 918         |
| All Hispanic          | 2011–2012    | 0.338 (0.321–0.357)     | 0.326 (0.306–0.350)           | 0.530 (0.490–0.583) | 0.891 (0.763–1.14)  | 1.41 (1.10–1.81) | 573         |
|                       | 2013–2014    | 0.412 (0.384–0.442)     | 0.442 (0.409–0.481)           | 0.674 (0.631–0.731) | 0.964 (0.891–1.07)  | 1.2 (1.09–1.36)  | 701         |
|                       | 2015–2016    | 0.440 (0.417–0.465)     | 0.465 (0.431–0.514)           | 0.718 (0.662–0.795) | 1.16 (0.991–1.34)   | 1.69 (1.34–2.03) | 982         |
|                       | 2017–2018    | 0.441 (0.420–0.463)     | 0.451 (0.427–0.478)           | 0.742 (0.696–0.829) | 1.20 (1.07–1.30)    | 1.41 (1.31–1.70) | 676         |

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**Table 5-18. Geometric Mean and Selected Percentiles of Urinary Cobalt (in µg/L) for the U.S. Population from NHANES**

|       | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) |                     |                    |                   | Sample size |
|-------|--------------|-------------------------|-------------------------------|---------------------|--------------------|-------------------|-------------|
|       |              |                         | 50 <sup>th</sup>              | 75 <sup>th</sup>    | 90 <sup>th</sup>   | 95 <sup>th</sup>  |             |
| Asian | 2011–2012    | 0.317 (0.282–0.357)     | 0.323 (0.300–0.355)           | 0.519 (0.445–0.634) | 0.968 (0.723–1.58) | 1.78 (0.980–2.31) | 353         |
|       | 2013–2014    | 0.362 (0.315–0.416)     | 0.354 (0.312–0.434)           | 0.653 (0.578–0.789) | 1.05 (0.854–1.25)  | 1.57 (1.09–2.26)  | 292         |
|       | 2015–2016    | 0.376 (0.334–0.424)     | 0.365 (0.342–0.438)           | 0.610 (0.533–0.698) | 0.990 (0.734–1.37) | 1.44 (0.990–2.31) | 332         |
|       | 2017–2018    | 0.416 (0.386–0.449)     | 0.462 (0.399–0.508)           | 0.759 (0.655–0.809) | 1.15 (0.966–1.37)  | 1.64 (1.12–2.18)  | 365         |

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey

Source: CDC (2022)

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**Table 5-19. Geometric Mean and Selected Percentiles of Urinary Cobalt (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from NHANES**

|             | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) |                     |                     |                    | Sample size |
|-------------|--------------|-------------------------|-------------------------------|---------------------|---------------------|--------------------|-------------|
|             |              |                         | 50 <sup>th</sup>              | 75 <sup>th</sup>    | 90 <sup>th</sup>    | 95 <sup>th</sup>   |             |
| Total       |              |                         |                               |                     |                     |                    |             |
|             | 2011–2012    | 0.370 (0.349–0.391)     | 0.347 (0.330–0.371)           | 0.557 (0.513–0.593) | 0.880 (0.768–1.03)  | 1.29 (1.12–1.46)   | 2,502       |
|             | 2013–2014    | 0.452 (0.437–0.466)     | 0.443 (0.427–0.454)           | 0.656 (0.625–0.688) | 0.969 (0.920–1.03)  | 1.31 (1.18–1.47)   | 2,663       |
|             | 2015–2016    | 0.465 (0.447–0.484)     | 0.444 (0.421–0.464)           | 0.682 (0.636–0.722) | 1.07 (0.999–1.16)   | 1.39 (1.24–1.52)   | 3,058       |
|             | 2017–2018    | 0.462 (0.437–0.490)     | 0.435 (0.410–0.463)           | 0.697 (0.644–0.733) | 1.12 (1.03–1.20)    | 1.55 (1.33–1.81)   | 2,806       |
| Age group   |              |                         |                               |                     |                     |                    |             |
| 3–5 years   | 2015–2016    | 0.980 (0.919–1.05)      | 0.952 (0.875–1.01)            | 1.35 (1.22–1.48)    | 1.94 (1.65–2.10)    | 2.45 (2.03–2.98)   | 485         |
|             | 2017–2018    | 0.974 (0.916–1.04)      | 0.978 (0.916–1.05)            | 1.31 (1.24–1.41)    | 1.91 (1.45–2.28)    | 2.29 (1.91–2.81)   | 403         |
| 6–11 years  | 2011–2012    | 0.567 (0.535–0.602)     | 0.571 (0.526–0.611)           | 0.778 (0.713–0.834) | 1.19 (0.974–1.30)   | 1.38 (1.10–1.67)   | 398         |
|             | 2013–2014    | 0.667 (0.614–0.725)     | 0.646 (0.593–0.704)           | 0.914 (0.853–0.986) | 1.26 (1.09–1.40)    | 1.57 (1.24–2.13)   | 402         |
|             | 2015–2016    | 0.757 (0.701–0.817)     | 0.732 (0.658–0.785)           | 1.03 (0.957–1.11)   | 1.37 (1.17–1.50)    | 1.7 (1.28–2.64)    | 379         |
|             | 2017–2018    | 0.724 (0.667–0.787)     | 0.708 (0.653–0.755)           | 0.966 (0.873–1.04)  | 1.42 (1.17–1.75)    | 1.82 (1.29–2.69)   | 332         |
| 12–19 years | 2011–2012    | 0.398 (0.349–0.455)     | 0.373 (0.316–0.441)           | 0.585 (0.454–0.700) | 0.832 (0.688–1.09)  | 1.26 (0.830–2.77)  | 390         |
|             | 2013–2014    | 0.497 (0.463–0.534)     | 0.480 (0.446–0.525)           | 0.692 (0.597–0.769) | 0.920 (0.819–1.10)  | 1.3 (1.09–1.61)    | 451         |
|             | 2015–2016    | 0.534 (0.504–0.565)     | 0.508 (0.455–0.552)           | 0.799 (0.697–0.939) | 1.16 (1.05–1.42)    | 1.5 (1.33–1.78)    | 402         |
|             | 2017–2018    | 0.465 (0.437–0.495)     | 0.423 (0.392–0.455)           | 0.723 (0.596–0.780) | 1.00 (0.848–1.13)   | 1.23 (1.05–1.38)   | 364         |
| ≥20 years   | 2011–2012    | 0.349 (0.330–0.369)     | 0.327 (0.300–0.341)           | 0.508 (0.467–0.552) | 0.803 (0.711–0.982) | 1.24 (1.10–1.50)   | 1,714       |
|             | 2013–2014    | 0.428 (0.412–0.444)     | 0.417 (0.390–0.441)           | 0.607 (0.580–0.643) | 0.929 (0.853–0.994) | 1.27 (1.10–1.46)   | 1,810       |
|             | 2015–2016    | 0.420 (0.402–0.439)     | 0.404 (0.384–0.426)           | 0.582 (0.551–0.616) | 0.900 (0.809–1.03)  | 1.2 (1.05–1.41)    | 1,792       |
|             | 2017–2018    | 0.425 (0.397–0.454)     | 0.397 (0.367–0.432)           | 0.591 (0.544–0.665) | 1.02 (0.892–1.16)   | 1.46 (1.20–1.81)   | 1,707       |
| Sex         |              |                         |                               |                     |                     |                    |             |
| Males       | 2011–2012    | 0.297 (0.280–0.315)     | 0.276 (0.254–0.294)           | 0.426 (0.397–0.456) | 0.637 (0.564–0.750) | 0.865 (0.748–1.17) | 1,261       |
|             | 2013–2014    | 0.379 (0.362–0.398)     | 0.368 (0.344–0.390)           | 0.529 (0.493–0.560) | 0.758 (0.689–0.852) | 1.02 (0.871–1.29)  | 1,317       |
|             | 2015–2016    | 0.377 (0.360–0.395)     | 0.348 (0.334–0.379)           | 0.526 (0.483–0.550) | 0.839 (0.746–0.913) | 1.08 (0.966–1.18)  | 1,524       |
|             | 2017–2018    | 0.390 (0.363–0.420)     | 0.360 (0.334–0.392)           | 0.563 (0.508–0.593) | 0.924 (0.799–1.08)  | 1.33 (1.11–1.59)   | 1,380       |

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-19. Geometric Mean and Selected Percentiles of Urinary Cobalt (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from NHANES**

|                       | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) |                     |                     |                  | Sample size |
|-----------------------|--------------|-------------------------|-------------------------------|---------------------|---------------------|------------------|-------------|
|                       |              |                         | 50 <sup>th</sup>              | 75 <sup>th</sup>    | 90 <sup>th</sup>    | 95 <sup>th</sup> |             |
| Females               | 2011–2012    | 0.455 (0.418–0.496)     | 0.433 (0.407–0.466)           | 0.660 (0.600–0.729) | 1.10 (0.900–1.36)   | 1.54 (1.28–1.84) | 1,241       |
|                       | 2013–2014    | 0.534 (0.515–0.553)     | 0.532 (0.502–0.549)           | 0.774 (0.733–0.816) | 1.12 (0.991–1.27)   | 1.48 (1.27–1.77) | 1,346       |
|                       | 2015–2016    | 0.568 (0.540–0.598)     | 0.533 (0.511–0.563)           | 0.799 (0.760–0.869) | 1.24 (1.16–1.40)    | 1.7 (1.48–1.98)  | 1,534       |
|                       | 2017–2018    | 0.544 (0.513–0.577)     | 0.498 (0.468–0.543)           | 0.815 (0.764–0.866) | 1.22 (1.14–1.36)    | 1.71 (1.45–1.98) | 1,426       |
| <b>Race/ethnicity</b> |              |                         |                               |                     |                     |                  |             |
| Mexican American      | 2011–2012    | 0.394 (0.357–0.435)     | 0.374 (0.322–0.400)           | 0.576 (0.531–0.637) | 1.02 (0.877–1.24)   | 1.5 (.988–2.02)  | 317         |
|                       | 2013–2014    | 0.474 (0.449–0.500)     | 0.448 (0.425–0.473)           | 0.669 (0.610–0.721) | 0.971 (0.888–1.03)  | 1.28 (1.03–1.51) | 453         |
|                       | 2015–2016    | 0.512 (0.479–0.548)     | 0.488 (0.464–0.533)           | 0.771 (0.690–0.850) | 1.18 (1.01–1.40)    | 1.5 (1.37–1.79)  | 584         |
|                       | 2017–2018    | 0.465 (0.432–0.500)     | 0.437 (0.378–0.497)           | 0.708 (0.662–0.786) | 1.14 (1.00–1.25)    | 1.45 (1.19–1.57) | 433         |
| Non-Hispanic Black    | 2011–2012    | 0.265 (0.248–0.282)     | 0.244 (0.222–0.267)           | 0.401 (0.342–0.457) | 0.645 (0.559–0.816) | 1.02 (.737–1.41) | 669         |
|                       | 2013–2014    | 0.356 (0.332–0.382)     | 0.337 (0.315–0.377)           | 0.545 (0.490–0.624) | 0.841 (0.754–0.952) | 1.08 (.930–1.22) | 581         |
|                       | 2015–2016    | 0.366 (0.347–0.386)     | 0.342 (0.328–0.377)           | 0.556 (0.504–0.595) | 0.799 (0.696–0.972) | 1.07 (.929–1.24) | 669         |
|                       | 2017–2018    | 0.355 (0.337–0.375)     | 0.330 (0.295–0.351)           | 0.576 (0.500–0.611) | 0.885 (0.798–1.02)  | 1.28 (.979–1.61) | 639         |
| Non-Hispanic White    | 2011–2012    | 0.387 (0.360–0.417)     | 0.365 (0.336–0.400)           | 0.574 (0.513–0.615) | 0.860 (0.749–1.09)  | 1.29 (1.04–1.57) | 818         |
|                       | 2013–2014    | 0.461 (0.442–0.480)     | 0.447 (0.430–0.469)           | 0.669 (0.613–0.703) | 0.987 (0.912–1.13)  | 1.32 (1.19–1.61) | 984         |
|                       | 2015–2016    | 0.475 (0.453–0.497)     | 0.457 (0.427–0.471)           | 0.686 (0.629–0.746) | 1.07 (0.972–1.20)   | 1.41 (1.19–1.63) | 924         |
|                       | 2017–2018    | 0.476 (0.439–0.517)     | 0.446 (0.415–0.473)           | 0.700 (0.605–0.760) | 1.14 (1.02–1.33)    | 1.64 (1.29–1.98) | 918         |
| All Hispanic          | 2011–2012    | 0.379 (0.351–0.409)     | 0.361 (0.322–0.384)           | 0.572 (0.520–0.626) | 0.944 (0.809–1.15)  | 1.33 (1.13–1.91) | 573         |
|                       | 2013–2014    | 0.460 (0.444–0.475)     | 0.448 (0.429–0.464)           | 0.663 (0.619–0.703) | 0.952 (0.888–1.00)  | 1.17 (1.03–1.35) | 701         |
|                       | 2015–2016    | 0.497 (0.468–0.527)     | 0.465 (0.436–0.503)           | 0.748 (0.669–0.837) | 1.16 (1.04–1.28)    | 1.46 (1.35–1.70) | 981         |
|                       | 2017–2018    | 0.475 (0.450–0.503)     | 0.454 (0.423–0.498)           | 0.719 (0.671–0.781) | 1.13 (1.02–1.24)    | 1.45 (1.25–1.57) | 674         |

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-19. Geometric Mean and Selected Percentiles of Urinary Cobalt (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from NHANES**

|       | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) |                     |                   |                  | Sample size |
|-------|--------------|-------------------------|-------------------------------|---------------------|-------------------|------------------|-------------|
|       |              |                         | 50 <sup>th</sup>              | 75 <sup>th</sup>    | 90 <sup>th</sup>  | 95 <sup>th</sup> |             |
| Asian | 2011–2012    | 0.424 (0.378–0.475)     | 0.386 (0.329–0.457)           | 0.659 (0.531–0.785) | 1.18 (0.907–1.51) | 1.61 (1.14–2.72) | 353         |
|       | 2013–2014    | 0.567 (0.516–0.624)     | 0.540 (0.482–0.567)           | 0.814 (0.670–0.931) | 1.38 (1.07–1.97)  | 2.09 (1.39–3.78) | 292         |
|       | 2015–2016    | 0.514 (0.473–0.559)     | 0.475 (0.421–0.548)           | 0.736 (0.624–0.885) | 1.30 (1.11–1.57)  | 1.66 (1.44–2.12) | 332         |
|       | 2017–2018    | 0.544 (0.504–0.588)     | 0.511 (0.450–0.569)           | 0.830 (0.768–0.882) | 1.39 (1.04–1.70)  | 1.86 (1.40–2.28) | 365         |

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey

Source: CDC (2022)



## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-20. Geometric Mean and Selected Percentiles of Blood Cobalt (in µg/L) for the U.S. Population from NHANES**

|                       | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) <sup>a</sup> |                     |                     |                     | Sample size |
|-----------------------|--------------|-------------------------|--------------------------------------------|---------------------|---------------------|---------------------|-------------|
|                       |              |                         | 50 <sup>th</sup>                           | 75 <sup>th</sup>    | 90 <sup>th</sup>    | 95 <sup>th</sup>    |             |
| Total                 | 2015–2016    | 0.151 (0.146–0.156)     | 0.130 (0.130–0.140)                        | 0.170 (0.170–0.180) | 0.280 (0.250–0.300) | 0.400 (0.370–0.450) | 3,454       |
|                       | 2017–2018    | 0.173 (0.167–0.180)     | 0.160 (0.150–0.160)                        | 0.200 (0.190–0.210) | 0.310 (0.280–0.330) | 0.430 (0.380–0.480) | 3,520       |
| <b>Age group</b>      |              |                         |                                            |                     |                     |                     |             |
| 40–59 years           | 2015–2016    | 0.144 (0.138–0.150)     | 0.130 (0.120–0.130)                        | 0.160 (0.150–0.170) | 0.260 (0.220–0.290) | 0.360 (0.300–0.440) | 1,726       |
|                       | 2017–2018    | 0.166 (0.158–0.175)     | 0.150 (0.150–0.160)                        | 0.180 (0.180–0.200) | 0.270 (0.250–0.320) | 0.420 (0.330–0.450) | 1,587       |
| ≥60 years             | 2015–2016    | 0.162 (0.155–0.168)     | 0.140 (0.140–0.150)                        | 0.190 (0.180–0.200) | 0.300 (0.270–0.370) | 0.450 (0.390–0.520) | 1,728       |
|                       | 2017–2018    | 0.183 (0.176–0.189)     | 0.160 (0.160–0.170)                        | 0.210 (0.200–0.230) | 0.340 (0.310–0.370) | 0.470 (0.380–0.570) | 1,933       |
| <b>Sex</b>            |              |                         |                                            |                     |                     |                     |             |
| Male                  | 2015–2016    | 0.135 (0.129–0.142)     | 0.120 (0.120–0.130)                        | 0.150 (0.140–0.160) | 0.210 (0.190–0.240) | 0.360 (0.250–0.400) | 1,661       |
|                       | 2017–2018    | 0.162 (0.154–0.170)     | 0.150 (0.140–0.150)                        | 0.180 (0.180–0.180) | 0.250 (0.230–0.280) | 0.380 (0.290–0.500) | 1,717       |
| Female                | 2015–2016    | 0.167 (0.161–0.173)     | 0.150 (0.140–0.150)                        | 0.200 (0.190–0.210) | 0.320 (0.280–0.360) | 0.460 (0.410–0.550) | 1,793       |
|                       | 2017–2018    | 0.185 (0.178–0.191)     | 0.170 (0.160–0.170)                        | 0.220 (0.200–0.240) | 0.340 (0.310–0.390) | 0.470 (0.410–0.560) | 1,803       |
| <b>Race/ethnicity</b> |              |                         |                                            |                     |                     |                     |             |
| Mexican American      | 2015–2016    | 0.151 (0.146–0.157)     | 0.130 (0.120–0.140)                        | 0.170 (0.160–0.190) | 0.300 (0.240–0.360) | 0.440 (0.350–0.610) | 592         |
|                       | 2017–2018    | 0.172 (0.162–0.183)     | 0.160 (0.150–0.160)                        | 0.180 (0.170–0.200) | 0.280 (0.240–0.340) | 0.400 (0.290–0.660) | 440         |
| Non-Hispanic Black    | 2015–2016    | 0.148 (0.138–0.159)     | 0.130 (0.120–0.140)                        | 0.180 (0.160–0.190) | 0.280 (0.250–0.340) | 0.440 (0.390–0.500) | 718         |
|                       | 2017–2018    | 0.163 (0.154–0.173)     | 0.150 (0.140–0.160)                        | 0.190 (0.180–0.200) | 0.270 (0.240–0.310) | 0.370 (0.310–0.430) | 816         |
| Non-Hispanic White    | 2015–2016    | 0.151 (0.145–0.157)     | 0.130 (0.130–0.140)                        | 0.170 (0.160–0.190) | 0.270 (0.240–0.290) | 0.390 (0.330–0.450) | 1,198       |
|                       | 2017–2018    | 0.176 (0.169–0.184)     | 0.160 (0.150–0.160)                        | 0.200 (0.190–0.220) | 0.320 (0.280–0.370) | 0.450 (0.380–0.590) | 1,272       |
| All Hispanic          | 2015–2016    | 0.150 (0.145–0.154)     | 0.130 (0.120–0.140)                        | 0.170 (0.160–0.180) | 0.300 (0.240–0.360) | 0.440 (0.350–0.560) | 1,067       |
|                       | 2017–2018    | 0.169 (0.161–0.177)     | 0.150 (0.150–0.160)                        | 0.180 (0.180–0.190) | 0.290 (0.260–0.320) | 0.410 (0.330–0.530) | 775         |

## 5. POTENTIAL FOR HUMAN EXPOSURE

**Table 5-20. Geometric Mean and Selected Percentiles of Blood Cobalt (in µg/L) for the U.S. Population from NHANES**

|       | Survey years | Geometric mean (95% CI) | Selected percentiles (95% CI) <sup>a</sup> |                     |                     |                     | Sample size |
|-------|--------------|-------------------------|--------------------------------------------|---------------------|---------------------|---------------------|-------------|
|       |              |                         | 50 <sup>th</sup>                           | 75 <sup>th</sup>    | 90 <sup>th</sup>    | 95 <sup>th</sup>    |             |
| Asian | 2015–2016    | 0.152 (0.145–0.160)     | 0.140 (0.130–0.150)                        | 0.170 (0.160–0.180) | 0.290 (0.210–0.370) | 0.380 (0.290–0.620) | 368         |
|       | 2017–2018    | 0.181 (0.173–0.189)     | 0.170 (0.160–0.170)                        | 0.200 (0.190–0.220) | 0.290 (0.270–0.330) | 0.420 (0.310–0.480) | 486         |

<sup>a</sup>The LOD for 2015–2016 and 2017–2018 is 0.06 µg/L.

CI = confidence interval; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC (2023)

## 5. POTENTIAL FOR HUMAN EXPOSURE

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, inhalation of traffic pollution, and iron deficiency anemia. Cao et al. (2014) found that children living near the largest coking plant in China had median blood cobalt levels of 1.12  $\mu\text{g/dL}$ . Mean cobalt concentrations were measured in the soil (12.0 mg/kg), dust (8.85 mg/kg), ambient air (0.03  $\mu\text{g/m}^3$ ), drinking water (0.14  $\mu\text{g/m}^3$ ), 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 years ranged from 7 to 14  $\mu\text{g/day}$ . 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 (IAEA 1982). The levels of cobalt in human breast milk from Nigeria, Zaire, Guatemala, Hungary, Philippines, and Sweden ranged from 150 ng/g (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 (1989) also estimated that infants 0–12 months old ingest an average of 0.52  $\mu\text{g Co/kg-day}$  (3.93  $\mu\text{g/day}$ ) from food and water and that the total dietary cobalt intake would range from 0.42  $\mu\text{g/kg-day}$  (3.39  $\mu\text{g/day}$ ) for a breastfed or milk-based formula-fed infant to 1.0  $\mu\text{g/kg-day}$  (7.33  $\mu\text{g/day}$ ) 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 years 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.); coal mining; metal mining, smelting, and refining; lithium-cobalt battery production or recycling (including electric vehicle batteries); cobalt dye painting industry; and cobalt chemical production can be exposed to higher levels of cobalt via airborne dust and direct contact. Of these industries, the largest group is the hard metal industry. Kennedy et al. (2017) estimates that through 2008, up to 14,348 individuals in the United States worked in the hard metal industry. Industrial foundry processes generate metal dust and fumes, and occupational

## 5. POTENTIAL FOR HUMAN EXPOSURE

exposure has been demonstrated in some metal workers (Freire et al. 2021; Linauskiene et al. 2021). 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). However, with increases in electric vehicle battery production and recycling in the early 2020s to meet the U.S. mandate to phase out fossil fueled activities from 2023 to 2050 (WH 2021a, 2021b), the population of workers with greatest risk of exposure may shift in future years.

The majority of occupational exposure data is from the hard metal industry. Historical concentrations of cobalt in the air of hard metal manufacturing, welding, and grinding factories may range from 1 to 300  $\mu\text{g}/\text{m}^3$ , compared to normal atmospheric levels of 0.4–2.0  $\text{ng}/\text{m}^3$  (Haddad and Zikovsky 1985; Koponen et al. 1982; Lichtenstein et al. 1975; Marsh et al. 2017a, 2017b; NIOSH 1989; Sauni et al. 2017; Svartengren et al. 2017). Data collected in hard metal factories since 2000 show a decrease in the uppermost reported concentrations, ranging from 0.9 to 190  $\mu\text{g}/\text{m}^3$  (Al-Abcha et al. 2021; Andersson et al. 2020, 2021; Hamzah et al. 2014; Hedbrant et al. 2022; Lantin et al. 2011, 2013). The maximum Occupational Safety and Health Administration (OSHA) permissible level is 100  $\mu\text{g}/\text{m}^3$ .

The concentration of cobalt in the dust of an electric welding factory was 4.2  $\mu\text{g}/\text{g}$  compared to its normal dust level of 0.1–1.0  $\mu\text{g}/\text{g}$  (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  $\text{mg}/\text{m}^3$ , the urinary excretion of cobalt exceeded normal values by orders of magnitude. When the cobalt concentration in the working atmosphere was  $\leq 0.01 \text{ mg}/\text{m}^3$ , 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).

In the hard metal industry in Japan, Kumagai et al. (1996) found that mean 8-hour TWAs of airborne cobalt were  $>50 \text{ }\mu\text{g}/\text{m}^3$  for workers involved in powder preparation (shift rotation that included varied work hours that were less than full time), powder preparation (full-time), rubber press, and shaping operations; mean atmospheric concentrations were 459, 147, 339, and 97  $\mu\text{g}/\text{m}^3$ , respectively. Workers involved in the manufacture and maintenance of hard metal and Stellite<sup>TM</sup> blades in Finland were exposed to breathing zone cobalt concentrations ranging from 2 to 240  $\mu\text{g}/\text{m}^3$ , with a geometric mean of 17  $\mu\text{g}/\text{m}^3$  (Linnainmaa et al. 1996). The average proportion of water-soluble cobalt in airborne cobalt was 68%

## 5. POTENTIAL FOR HUMAN EXPOSURE

(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 concentrations of cobalt in air were 21.2 and 137.7  $\mu\text{g}/\text{m}^3$  (PEL-TWA 100  $\mu\text{g}/\text{m}^3$ ) in workplaces with and without dust ventilation, respectively (Imbrogno and Alborghetti 1994).

In a metal finishing plant located in Turkey, aerosol samples were collected over an 8-hour period from the breathing zone at a dipping bath (Onat et al. 2020). Cobalt in total suspended particles was  $69.9 \times 10^{-6} \text{ mg}/\text{m}^3$ . In different fractions, cobalt was identified at concentrations of approximately  $2.9 \times 10^{-6} \text{ mg}/\text{m}^3$  in size fraction  $\text{PM}_{<0.25}$ ,  $14.6 \times 10^{-6} \text{ mg}/\text{m}^3$  in size fraction  $\text{PM}_{0.25-0.5}$ ,  $6.3 \times 10^{-6} \text{ mg}/\text{m}^3$  in size fraction  $\text{PM}_{0.5-1.0}$ ,  $23.8 \times 10^{-6} \text{ mg}/\text{m}^3$  in size fraction  $\text{PM}_{1.0}$ ,  $12.1 \times 10^{-6} \text{ mg}/\text{m}^3$  in size fraction  $\text{PM}_{1.0-2.5}$ ,  $35.9 \times 10^{-6} \text{ mg}/\text{m}^3$  in size fraction  $\text{PM}_{2.5}$ , and  $34.0 \times 10^{-6} \text{ mg}/\text{m}^3$  in size fraction  $\text{PM}_{>2.5}$ . Concentrations of cobalt detected in the air of an industrial foundry (Brazilian ferrous foundry industry producing automobile parts) ranged from 0.006 to 0.344  $\mu\text{g}/\text{m}^3$ , with an average concentration of  $0.047 \pm 0.062 \text{ }\mu\text{g}/\text{m}^3$ . In urine ( $n=194$ ) and blood ( $n=167$ ) samples collected from the foundry workers, cobalt concentrations ranged from 0.05 to 1.44  $\mu\text{g}/\text{L}$  (mean  $0.51 \pm 0.23 \text{ }\mu\text{g}/\text{L}$ , NHANES 75<sup>th</sup> percentile for men) and from 0.05 to 1.82  $\mu\text{g}/\text{L}$  (mean  $0.12 \pm 0.15 \text{ }\mu\text{g}/\text{L}$ , NHANES 50<sup>th</sup> percentile for men), respectively. Cobalt concentrations in urine increased with employment duration. Additionally, cobalt particulate concentrations correlated linearly with urine levels from workers performing pan operation and furnace activities (Freire et al. 2021).

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  $\mu\text{g}/\text{L}$ ). 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  $\mu\text{g}/\text{m}^3$  (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  $\mu\text{g}/\text{m}^3$  of cobalt, respectively (Stebbins et al. 1992). For the method collecting respirable particles, cobalt levels ranged from 2 to 28  $\mu\text{g}/\text{m}^3$ . 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  $\text{mg}/\text{mL}$ ) that can contribute to exposure during grinding (Stebbins et al. 1992).

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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 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 ( $8.18 \pm 2.73$   $\mu\text{g/L}$ ) and quality control workers ( $7.39 \pm 1.26$   $\mu\text{g/L}$ ) than in the control population ( $0.92 \pm 8.13$   $\mu\text{g/L}$ ). 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 ( $\mu\text{g/dL}$ ), including standard errors, were determined to be  $31 \pm 2$  (hospital workers),  $25 \pm 0.8$  (metal ore smelter workers),  $19 \pm 0.6$  (petroleum refinery workers), and  $22 \pm 1$  (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  $\mu\text{g/L}$  (range 1–51  $\mu\text{g/L}$ ) and 29 (range 3–159  $\mu\text{g/L}$ ), on Monday and Friday before the shift, respectively, and 85  $\mu\text{g/L}$  (range 6–505  $\mu\text{g/L}$ ) 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  $\mu\text{g/L}$  and the maximum was 86  $\mu\text{g/L}$ . The average urinary cobalt level among workers using wet/mixed sharpening methods was 4 times higher than those using dry sharpening methods (21.38  $\mu\text{g/L}$  as compared to 5  $\mu\text{g/L}$ , respectively).

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 to 1,328  $\mu\text{g}$  on hands and from 7.8 to 342  $\mu\text{g}$  on necks (Day et al. 2009). Kettelarij et al. (2018a) studied skin doses and exposure sources of workers in the hard metal

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industry, finding that the highest skin doses (median  $1.51 \mu\text{g}/\text{cm}^2$ , range  $0.25\text{--}28 \mu\text{g}/\text{cm}^2$ ) 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). 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 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  $4.5 \mu\text{g}/\text{cm}^2/\text{hour}$  on the thumb.

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).

Exposure information in other industries is limited. In a Japanese nickel-hydrogen battery plant, workers were exposed to a mixture of metallic cobalt, cobalt oxyhydroxide, and nickel hydroxide dust (Yokota et al. 2007). Measured breathing zone air levels of cobalt over 2 consecutive working days ranged from 4 to  $330 \mu\text{g}/\text{m}^3$  (mean of  $67 \mu\text{g}/\text{m}^3$ ). On day 1, urinary cobalt levels increased from  $10.7 \mu\text{g}$  pre-shift to  $38.6 \mu\text{g}$  post-shift. Day 2 levels were more stable, at  $25.7 \mu\text{g}$  pre-shift and  $28.2 \mu\text{g}$  post-shift. Urinary levels were not well correlated with air levels; the study authors attributed this to use of respirators by workers (Yokota et al. 2007). 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).

In addition to occupational exposure, the general population living near these industrial sites, hazardous waste sites, and agricultural areas that use sewage sludge, cobalt-containing fertilizers, or soil amendments may be exposed to high levels of cobalt in air and in 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.

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Exposure to stable cobalt in communities near current or historic mining and smelting facilities or metal shops where cobalt is used in grinding tools could be a public health concern. Concern is higher for infants and children due to closer proximity to the floor/ground, hand-to-mouth behavior, and intentional ingestion of soil that could contain cobalt contaminants (Hamel et al. 1998). In the case of children playing in and around unrestricted landfill sites, exposure via inhalation, oral, and dermal routes is possible. Cobalt-containing dust may be brought home in the clothing of parents working in cobalt-related industries and transferred to flooring on which children crawl and play. Data from communities near mining operations in the D.R. Congo confirm increased risk of exposure in children. Median measured urinary cobalt levels in children were nearly 3 times higher than values measured in adults from the same community; approximately 150 and 50  $\mu\text{g/g}$  creatinine, respectively, based on graphically presented data (Banza Lubaba Nkulu 2018). This is consistent with children ingesting up to 1,800 mg/day of soil from typical mouthing behavior as they play and lie on grass and soil (ATSDR 2001).

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 to 14.85  $\text{ng/m}^3$  (Han et al. 2020). Han et al. (2020) estimated that the cancer risks due to inhalation of cobalt were 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 D.R. Congo, mean urinary concentrations of cobalt were significantly higher in individuals living <3 km from the mining and refining operations (15.7  $\mu\text{g/g}$  creatinine) than in control subjects (1.34  $\mu\text{g/g}$  creatinine) (Banza et al. 2009). Mean urinary cobalt concentrations were 5.72  $\mu\text{g/g}$  creatinine in individuals living between 3 and 10 km from mining and refining (Banza et al. 2009). Urinary cobalt exceeded 15  $\mu\text{g/g}$  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. 2009). These levels are within or above the NHANES 95<sup>th</sup> percentile levels in Table 5-19. 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



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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 2-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  $\mu\text{g}/\text{cm}^3$  in exposed technicians and 0.0017  $\mu\text{g}/\text{cm}^3$  in non-exposed technicians (Kettelarij et al. 2016). After 2 hours of work without hand washing, concentrations had increased to 0.15  $\mu\text{g}/\text{cm}^3$  for exposed individuals and 0.0026  $\mu\text{g}/\text{cm}^3$  for non-exposed individuals (Kettelarij et al. 2016). At the end of the day, the median concentrations had increased overall to 0.014  $\mu\text{g}/\text{cm}^3$  in exposed individuals and 0.0057  $\mu\text{g}/\text{cm}^3$  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 to 155  $\mu\text{g}/\text{m}^3$  (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 as 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  $\mu\text{g}/\text{L}$ , one man who had undergone a hip replacement had a blood cobalt level of 14.3  $\mu\text{g}/\text{L}$  (Briani et al. 2015). Prosthetic

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devices that contain polyethylene components to avoid metal-to-metal contact do not appear to cause elevated levels of cobalt in tissues or 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 (Zywiell et al. 2013). Transient hearing loss was reported in individuals undergoing cobalt therapy attempting to increase hematocrit (Bowie and Hurley 1975). Using data from the NHANES database of U.S. individuals surveyed between 2015 and 2018, it was observed that people with metal implants tended to have higher blood concentrations of cobalt; however, the study indicted several shortcomings, including a lack of controlled parameters to demonstrate a clear relationship between metal implants and blood cobalt ion levels (He et al. 2023). Similar to joint implants, individuals with cobalt-chrome alloy dental implants may have elevated exposure to cobalt (Thyssen et al. 2010, 2011).

People who use cobalt supplements as a treatment for anemia and those who take large amounts of vitamin B<sub>12</sub> 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 1.8–5.1 µg/L (Tvermoes et al. 2013). Whole blood concentrations decreased to 1.1 µg/L 2 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 U.K. Expert Group on Vitamins and Minerals (600–1,400 µg/day) would result in mean whole blood concentrations of 5–12 µg/L and urinary concentrations of 57–130 µg/L after 30 days. After 1 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).

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

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

Exposures to acute-duration radiation doses of 0.09–1.91 Gy and chronic-duration doses of 0.13–15.16 Gy were estimated from mathematical models and cytogenic dosimetry of two scrapyards employees and eight individuals living near a truck carrying contaminated rebar. The contaminated rebar was a result of a release of  $^{60}\text{Co}$  from an incident in December 1983, in which steel foundries in Mexico and the United States processed contaminated material into construction materials that were shipped throughout North America (UNSCEAR 2011).

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Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of 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 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.

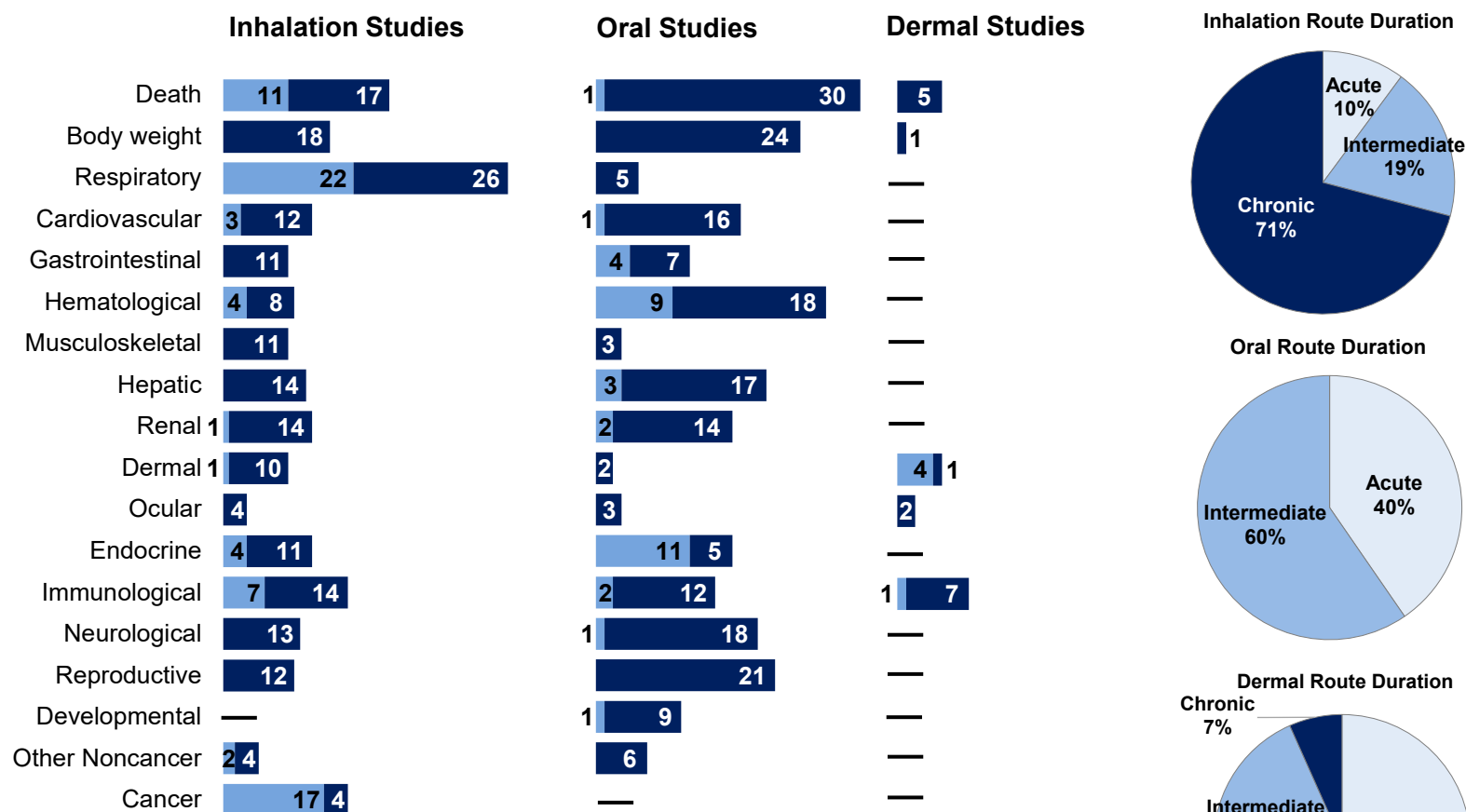
As shown in Figure 6-1, studies on the health effects in humans and animals exposed to cobalt primarily examine oral ingestion and inhalation. Many of these studies are case reports of individuals who intentionally or accidentally ingested cobalt or cobalt-containing substances. Controlled-exposure studies 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 assessed 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, evaluating only ocular, dermal, or immunological (skin sensitization) effects.

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

Potential lethal, body weight, respiratory, immunological, and hematological effects were the most studied endpoints

The majority of the studies evaluated inhalation exposure in **humans** and oral exposure in **rodents**



\*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; studies may have evaluated more than one endpoint.

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**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 was adequate for derivation of inhalation and oral MRLs based on respiratory and hematological effects, respectively. However, the database for both routes was limited, relying on supporting data from longer-duration studies to justify selection of critical effect. Additional studies to characterize dose-response data at low cobalt exposure levels could decrease uncertainty in the acute-duration MRLs

**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 identified respiratory effects (Johansson et al. 1987, 1991, 1992; Kerfoot 1974; NTP 1991, 2014; Palmes et al. 1959). The most sensitive effect in animals, laryngeal metaplasia, results in an MRL value lower than the chronic-duration inhalation MRL based on human data. Since there is higher confidence in an MRL based on human data, which precludes the need for interspecies extrapolation, an intermediate-duration inhalation MRL was not derived. The intermediate-duration oral database was adequate to derive an intermediate-duration oral MRL for cobalt.

**Chronic-Duration MRLs.** The inhalation database was adequate to derive a chronic-duration inhalation MRL. The oral database is inadequate to derive a chronic-duration MRL due to a lack of chronic-duration oral studies in humans or animals. Since the oral route is a relevant route for human exposure, chronic-duration oral exposure studies are needed to confirm targets of toxicity and establish dose-response following chronic-duration exposure.

**Health Effects.**

**Respiratory.** Signs and symptoms of respiratory effects of exposure to cobalt include decreased lung capacity, changes in lung weight, and 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

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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). Intermediate- and chronic-duration 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 study 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.

**Gastrointestinal.** Studies in humans suggest that the gastrointestinal system may be a target of cobalt toxicity (Duckham and Lee 1976; Holly 1955; Paley et al. 1958) and a limited number of animal studies reported delayed gastric emptying and damage to the small intestine (Akinrinde et al. 2016c; Salami et al. 2023). Additional studies at environmentally-relevant exposure levels would be useful to determine if the gastrointestinal system is a target of concern for oral exposure to cobalt.

**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 or 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<sup>3</sup>, but at a lower dose of 0.1 mg Co/m<sup>3</sup>, no changes were 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-duration 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-

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and intermediate-duration exposure in animals (rats, mice, dogs, and hamsters) have also shown hematological effects at doses ranging from 11 to 161 mg Co/kg/day (Bryan and Bright 1973; Corrier et al. 1985; Domingo and Llobet 1984; Domingo et al. 1985a; Holly 1955; Krasovskii and Fridlyand 1971; Shrivastava et al. 2008). While these doses do show a significant effect in animal models, they are much greater than likely human exposure; therefore, there is a 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.

**Endocrine.** A limited number of studies suggest that impaired thyroid function may occur with repeated exposure to cobalt (Paley et al. 1958; Roche and Layrisse 1956). These studies are supported by case reports of goiter or impaired thyroid function in some patients taking cobalt as a treatment for anemia associated with sickle-cell anemia, pregnancy, or chronic renal disease (Chamberlain 1961; Duckham and Lee 1976; Gross et al. 1955; Kriss et al. 1955; Little and Sunico 1958; Washburn and Kaplan 1964). Very few studies in animals have evaluated thyroid function or histology following oral exposure, but Shrivastava et al. (1996) reported severe histopathological changes in the thyroid of mice at high oral doses. Additional multi-dose studies in animals at environmentally relevant exposure levels would be useful to establish if there is a dose-response relationship for thyroid effects following oral exposure to cobalt.

**Neurological.** There is limited evidence from human and animal studies that indicate that 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 (Akinrinde and Adebisi 2019; Bourg et al. 1985; Garoui et al. 2013; Mohamed et al. 2019; Singh and Junnarkar 1991; 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.



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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 a risk for developmental toxicity after cobalt exposure at lower doses. There is a 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, 2004; Sauni et al. 2010; Shirakawa et al. 1988, 1989; Sprince et al. 1988) as well as three studies where the subjects were 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.** 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.

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

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amount is released slowly in urine. There are minimal data regarding the pharmacokinetics of cobalt after dermal exposure, but the few studies that examined 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 an apparent need for additional studies on the toxicokinetics of cobalt following dermal exposure, as addressed below under comparative toxicokinetics.

**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).

**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, 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* 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 United States. 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 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. Investigational uses of cobalt compounds and catalysts in plastic manufacturing and recycling are ongoing (e.g., Fuentes et al. 2019; Rogkotis et al. 2022).

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Continued monitoring of expanded uses for cobalt, particularly in products that have potential for human exposure (e.g., plastic food films), is needed.

**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 cobalt (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 United States (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.

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**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

Table 6-1 lists research studies identified in a search of the National Institutes of Health (NIH) Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER 2023) that are currently being conducted that may fill some of the data needs discussed in Section 6.2.

**Table 6-1. Ongoing Studies on Cobalt**

| Investigator          | Affiliation                         | Research description                                                   | Sponsor                                 |
|-----------------------|-------------------------------------|------------------------------------------------------------------------|-----------------------------------------|
| Dr. Elizabeth Oelsner | Columbia University Health Sciences | Metal exposure and subclinical lung disease in adult e-cigarette users | National Heart Lung and Blood Institute |

Source: RePORTER (2023)

## 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                 |
|-------------------------|------------------------------------------------|--------------------------------------------------------------------|---------------------------|
| <b>Air</b>              |                                                |                                                                    |                           |
| EPA                     | RfC                                            | No data                                                            | <a href="#">IRIS 2023</a> |
|                         | Provisional peer reviewed toxicity values      |                                                                    | <a href="#">EPA 2008</a>  |
|                         | Cobalt                                         |                                                                    |                           |
|                         | Provisional subchronic RfC                     | 0.00002 mg/m <sup>3</sup>                                          |                           |
|                         | Provisional chronic RfC                        | 0.000006 mg/m <sup>3</sup>                                         |                           |
| WHO                     | Air quality guidelines                         | No data                                                            | <a href="#">WHO 2010</a>  |
| USC                     | HAP                                            |                                                                    | USC 2011                  |
|                         | Cobalt compounds                               | Included in the Clean Air Acts list of HAPs to be regulated by EPA |                           |
| <b>Water &amp; Food</b> |                                                |                                                                    |                           |
| EPA                     | Drinking water standards and health advisories | Not listed                                                         | <a href="#">EPA 2018a</a> |
|                         | National primary drinking water regulations    | Not listed                                                         | <a href="#">EPA 2009</a>  |
|                         | RfD                                            | No data                                                            | <a href="#">IRIS 2023</a> |
|                         | Provisional peer reviewed toxicity values      |                                                                    | <a href="#">EPA 2008</a>  |
|                         | Cobalt                                         |                                                                    |                           |
|                         | Provisional subchronic RfD                     | 0.003 mg/kg/day                                                    |                           |
|                         | Provisional chronic RfD                        | 0.0003 mg/kg/day                                                   |                           |
| WHO                     | Drinking water quality guidelines              | No data                                                            | <a href="#">WHO 2022</a>  |

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**Table 7-1. Regulations and Guidelines Applicable to Cobalt**

| Agency              | Description                                                        | Information                                                                     | Reference                                                                  |
|---------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| FDA                 | Substances added to food (formerly EAFUS)                          |                                                                                 |                                                                            |
|                     | Cobalt sulfate (as catalyst)                                       | Permitted as boiler water additive in preparation of food for human consumption | <a href="#">FDA 2023b</a>                                                  |
|                     | Cobaltous salts and its derivatives                                | Prohibited from use in human food                                               | <a href="#">FDA 2023a</a>                                                  |
| <b>Cancer</b>       |                                                                    |                                                                                 |                                                                            |
| HHS                 | Carcinogenicity classification                                     |                                                                                 | <a href="#">NTP 2021</a>                                                   |
|                     | Cobalt and cobalt compounds that release cobalt ions in vivo       | Reasonably anticipated to be human carcinogens                                  |                                                                            |
| EPA                 | Carcinogenicity classification                                     | No data                                                                         | <a href="#">IRIS 2023</a>                                                  |
|                     | Provisional peer reviewed toxicity values                          |                                                                                 | <a href="#">EPA 2008</a>                                                   |
|                     | Cobalt                                                             |                                                                                 |                                                                            |
|                     | Provisional carcinogenicity classification                         | Likely to be carcinogenic to humans by the inhalation route                     |                                                                            |
|                     | Provisional IUR                                                    | 9 (mg/m <sup>3</sup> ) <sup>-1</sup>                                            |                                                                            |
| IARC                | Carcinogenicity classification                                     |                                                                                 |                                                                            |
|                     | Cobalt metal (without tungsten carbide or other metal alloys)      | Group 2A <sup>a</sup>                                                           | <a href="#">IARC 2023</a>                                                  |
|                     | Soluble cobalt (II) salts (cobalt chloride, cobalt sulfide)        | Group 2A <sup>a</sup>                                                           |                                                                            |
|                     | Cobalt (II) oxide                                                  | Group 2B <sup>b</sup>                                                           |                                                                            |
|                     | Cobalt (II, III) oxide                                             | Group 3 <sup>c</sup>                                                            |                                                                            |
|                     | Cobalt (II) sulfide                                                | Group 3 <sup>c</sup>                                                            |                                                                            |
|                     | Other cobalt (II) compounds                                        | Group 3 <sup>c</sup>                                                            |                                                                            |
|                     | Weapons-grade tungsten (with nickel and cobalt)                    | Group 2B <sup>b</sup>                                                           |                                                                            |
|                     | Cobalt metal with tungsten carbide                                 | Group 2A <sup>a</sup>                                                           | <a href="#">IARC 2006</a>                                                  |
| <b>Occupational</b> |                                                                    |                                                                                 |                                                                            |
| OSHA                | PEL (8-hour TWA) for general industry, shipyards, and construction |                                                                                 | OSHA <a href="#">2021a</a> , <a href="#">2021b</a> , <a href="#">2021c</a> |
|                     | Cobalt metal, dust, and fume (as Co)                               | 0.1 mg/m <sup>3</sup>                                                           |                                                                            |
| NIOSH               | REL (up to 10-hour TWA)                                            |                                                                                 |                                                                            |
|                     | Cobalt metal, dust, and fume (as Co)                               | 0.05 mg/m <sup>3</sup>                                                          | <a href="#">NIOSH 2019c</a>                                                |
|                     | Cobalt carbonyl (as Co)                                            | 0.1 mg/m <sup>3</sup>                                                           | <a href="#">NIOSH 2019a</a>                                                |
|                     | Cobalt hydrocarbonyl (as Co)                                       | 0.1 mg/m <sup>3</sup>                                                           | <a href="#">NIOSH 2019b</a>                                                |

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**Table 7-1. Regulations and Guidelines Applicable to Cobalt**

| Agency                    | Description                          | Information             | Reference                  |
|---------------------------|--------------------------------------|-------------------------|----------------------------|
| <b>Emergency Criteria</b> |                                      |                         |                            |
| AIHA                      | ERPGs                                |                         | AIHA 2016                  |
|                           | Cobalt hydrocarbonyl <sup>d</sup>    |                         |                            |
|                           | ERPG-1                               | Insufficient data       |                            |
|                           | ERPG-2                               | 0.9 mg/m <sup>3</sup>   |                            |
|                           | ERPG-3                               | 3 mg/m <sup>3</sup>     |                            |
| NIOSH                     | IDLH                                 |                         |                            |
|                           | Cobalt metal, dust, and fume (as Co) | 20 mg/m <sup>3</sup>    | <a href="#">NIOSH 1994</a> |
| EPA                       | AEGLs-air                            | Not listed              | <a href="#">EPA 2018b</a>  |
| DOE                       | PACs-air                             |                         | <a href="#">DOE 2018a</a>  |
|                           | Cobalt                               |                         |                            |
|                           | PAC-1 <sup>d</sup>                   | 0.18 mg/m <sup>3</sup>  |                            |
|                           | PAC-2 <sup>d</sup>                   | 2 mg/m <sup>3</sup>     |                            |
|                           | PAC-3 <sup>d</sup>                   | 20 mg/m <sup>3</sup>    |                            |
|                           | Cobalt acetate tetrahydrate          |                         |                            |
|                           | PAC-1 <sup>d</sup>                   | 2.1 mg/m <sup>3</sup>   |                            |
|                           | PAC-2 <sup>d</sup>                   | 23 mg/m <sup>3</sup>    |                            |
|                           | PAC-3 <sup>d</sup>                   | 140 mg/m <sup>3</sup>   |                            |
|                           | Cobalt carbonyl                      |                         |                            |
|                           | PAC-1 <sup>d</sup>                   | 0.3 mg/m <sup>3</sup>   |                            |
|                           | PAC-2 <sup>d</sup>                   | 3.3 mg/m <sup>3</sup>   |                            |
|                           | PAC-3 <sup>d</sup>                   | 20 mg/m <sup>3</sup>    |                            |
|                           | Cobalt chloride                      |                         |                            |
|                           | PAC-1 <sup>d</sup>                   | 0.13 mg/m <sup>3</sup>  |                            |
|                           | PAC-2 <sup>d</sup>                   | 18 mg/m <sup>3</sup>    |                            |
|                           | PAC-3 <sup>d</sup>                   | 83 mg/m <sup>3</sup>    |                            |
|                           | Cobalt (II) chloride hexahydrate     |                         |                            |
|                           | PAC-1 <sup>d</sup>                   | 0.24 mg/m <sup>3</sup>  |                            |
|                           | PAC-2 <sup>d</sup>                   | 25 mg/m <sup>3</sup>    |                            |
|                           | PAC-3 <sup>d</sup>                   | 150 mg/m <sup>3</sup>   |                            |
|                           | Cobalt hydrocarbonyl                 |                         |                            |
|                           | PAC-1 <sup>d</sup>                   | 0.3 mg/m <sup>3</sup>   |                            |
|                           | PAC-2 <sup>d</sup>                   | 0.9 mg/m <sup>3</sup>   |                            |
|                           | PAC-3 <sup>d</sup>                   | 3 mg/m <sup>3</sup>     |                            |
|                           | Cobalt hydroxide                     |                         |                            |
|                           | PAC-1 <sup>d</sup>                   | 0.095 mg/m <sup>3</sup> |                            |
|                           | PAC-2 <sup>d</sup>                   | 1.1 mg/m <sup>3</sup>   |                            |
|                           | PAC-3 <sup>d</sup>                   | 6.3 mg/m <sup>3</sup>   |                            |

## 7. REGULATIONS AND GUIDELINES

**Table 7-1. Regulations and Guidelines Applicable to Cobalt**

| Agency | Description                     | Information             | Reference |
|--------|---------------------------------|-------------------------|-----------|
|        | Cobalt nitrate                  |                         |           |
|        | PAC-1 <sup>d</sup>              | 0.19 mg/m <sup>3</sup>  |           |
|        | PAC-2 <sup>d</sup>              | 14 mg/m <sup>3</sup>    |           |
|        | PAC-3 <sup>d</sup>              | 86 mg/m <sup>3</sup>    |           |
|        | Cobalt nitrate hexahydrate      |                         |           |
|        | PAC-1 <sup>d</sup>              | 0.3 mg/m <sup>3</sup>   |           |
|        | PAC-2 <sup>d</sup>              | 23 mg/m <sup>3</sup>    |           |
|        | PAC-3 <sup>d</sup>              | 140 mg/m <sup>3</sup>   |           |
|        | Cobalt (II) oxide               |                         |           |
|        | PAC-1 <sup>d</sup>              | 0.076 mg/m <sup>3</sup> |           |
|        | PAC-2 <sup>d</sup>              | 4.2 mg/m <sup>3</sup>   |           |
|        | PAC-3 <sup>d</sup>              | 25 mg/m <sup>3</sup>    |           |
|        | Cobalt oxide [cobalt tetroxide] |                         |           |
|        | PAC-1 <sup>d</sup>              | 0.082 mg/m <sup>3</sup> |           |
|        | PAC-2 <sup>d</sup>              | 4.5 mg/m <sup>3</sup>   |           |
|        | PAC-3 <sup>d</sup>              | 27 mg/m <sup>3</sup>    |           |
|        | Cobalt sulfate                  |                         |           |
|        | PAC-1 <sup>d</sup>              | 0.16 mg/m <sup>3</sup>  |           |
|        | PAC-2 <sup>d</sup>              | 14 mg/m <sup>3</sup>    |           |
|        | PAC-3 <sup>d</sup>              | 84 mg/m <sup>3</sup>    |           |
|        | Cobalt sulfate heptahydrate     |                         |           |
|        | PAC-1 <sup>d</sup>              | 0.29 mg/m <sup>3</sup>  |           |
|        | PAC-2 <sup>d</sup>              | 19 mg/m <sup>3</sup>    |           |
|        | PAC-3 <sup>d</sup>              | 120 mg/m <sup>3</sup>   |           |
|        | Cobaltous carbonate             |                         |           |
|        | PAC-1 <sup>d</sup>              | 0.12 mg/m <sup>3</sup>  |           |
|        | PAC-2 <sup>d</sup>              | 210 mg/m <sup>3</sup>   |           |
|        | PAC-3 <sup>d</sup>              | 1,200 mg/m <sup>3</sup> |           |

<sup>a</sup>Group 2A: probably carcinogenic to humans.

<sup>b</sup>Group 2B: possibly carcinogenic to humans.

<sup>c</sup>Group 3: not classifiable as to its carcinogenicity to humans.

<sup>d</sup>Values are given as cobalt.

<sup>e</sup>Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline level; AIHA = American Industrial Hygiene Association; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = Emergency Response Planning Guideline; FDA = Food and Drug Administration; HAP = hazardous air pollutant; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; IUR = inhalation unit risk; 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; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization



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## APPENDIX A. ATSDR MINIMAL RISK LEVEL 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 ( $\geq 365$  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. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious 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.

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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 S106-5, Atlanta, Georgia 30329-4027.

This section only discusses the MRLs for cobalt. ATSDR 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).

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## MINIMAL RISK LEVEL (MRL) WORKSHEET

**Chemical Name:** Cobalt and compounds  
**CAS Numbers:** 7440-48-8  
**Date:** October 2024  
**Profile Status:** Final  
**Route:** Inhalation  
**Duration:** Acute  
**MRL:** 0.0003 mg Co/m<sup>3</sup> (3x10<sup>-4</sup> mg Co/m<sup>3</sup>)  
**Critical Effect:** Increased neutrophils in bronchoalveolar lavage fluid  
**Reference:** Viegas et al. 2022a, 2022b  
**Point of Departure:** NOAEL of 0.2 mg Co/m<sup>3</sup> (NOAEL<sub>HEC</sub> of 0.01 mg Co/m<sup>3</sup>)  
**Uncertainty Factor:** 30  
**LSE Graph Key:** 9  
**Species:** Rat

**MRL Summary:** An acute-duration inhalation MRL of 0.0003 mg Co/m<sup>3</sup> ppm was derived for cobalt based on an increased percent neutrophils in BALF in rats exposed to concentrations of 2.2 mg Co/m<sup>3</sup> as cobalt sulfate heptahydrate for 4 hours (Viegas et al. 2022a, 2022b). The MRL is based on a NOAEL of 0.2 mg Co/m<sup>3</sup>, which was converted to a human equivalent concentration NOAEL (NOAEL<sub>HEC</sub>) of 0.01 mg Co/m<sup>3</sup> and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

**Selection of the Critical Effect:** Endpoints evaluated in the available acute-duration inhalation studies were limited to acute lethality and respiratory endpoints. Available NOAELs and LOAELs for respiratory effects are shown in Table A-1. The lowest concentration associated with lethality was 32 mg Co/m<sup>3</sup> (Viegas et al. 2022a). Although the acute-duration inhalation database is limited, systematic review (Appendix C) determined that respiratory effects are a known target of cobalt toxicity in humans following inhalation exposure. Therefore, respiratory toxicity was selected as the critical effect for the acute-duration inhalation MRL.

**Table A-1. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Acute-Duration Inhalation Exposure to Cobalt and Compounds**

| Species (strain)/ number | Duration/ frequency | NOAEL (mg Co/m <sup>3</sup> ) | LOAEL (mg Co/m <sup>3</sup> ) | Effect                                                                       | Compound                                 | Reference                  |
|--------------------------|---------------------|-------------------------------|-------------------------------|------------------------------------------------------------------------------|------------------------------------------|----------------------------|
| Human 15 M               | 6 hours             | ND                            | 0.038                         | Subjective complaints of respiratory irritation; unspecified decrease in FVC | Hard metal dust                          | Kusaka et al. 1986a        |
| Rat (SD) 5 F             | 4 hours             | 0.2                           | 2.2                           | Increased BALF neutrophils, decreased BALF cell viability                    | Cobalt sulfate heptahydrate <sup>a</sup> | Viegas et al. 2022a, 2022b |
| Rat (Albino) 1–33 M      | 30 minutes          | 7                             | 26                            | Gross lung lesions, pulmonary edema                                          | Cobalt hydrocarbonyl <sup>b</sup>        | Palmer et al. 1959         |

**Table A-1. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Acute-Duration Inhalation Exposure to Cobalt and Compounds**

| Species (strain)/ number | Duration/ frequency | NOAEL (mg Co/m <sup>3</sup> ) | LOAEL (mg Co/m <sup>3</sup> ) | Effect                                                         | Compound          | Reference              |
|--------------------------|---------------------|-------------------------------|-------------------------------|----------------------------------------------------------------|-------------------|------------------------|
| Rat (Wistar) 5 M, 5 F    | 14 days 6 hours/day | 9.86                          | 33.87                         | Increased BALF levels of LDH and polymorphonuclear neutrophils | Cobalt tetraoxide | Burzlauff et al. 2022a |

<sup>a</sup>Test substance was likely converted to cobalt sulfate hexahydrate in the inhalation chamber due to relative humidity <70% (Redhammer et al. 2007; Viegas 2024).

<sup>b</sup>Exposure to cobalt hydrocarbonyl plus oxide/carbonate decomposition products due to instability of test substance in oxygen.

Selected study for the acute-duration inhalation MRL derivation.

BALF = bronchoalveolar lavage fluid; F = females; FVC = forced vital capacity; LDH = lactate dehydrogenase; M = males; ND = not determined; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

**Selection of the Principal Study:** One human study and three animal studies were identified that evaluated respiratory effects following acute-duration inhalation exposure to cobalt and cobalt compounds. In the human study, a group of 15 young men were exposed to hard metal dust containing mean cobalt concentrations of 0.038 mg Co/m<sup>3</sup> (range 0.004–0.076 mg Co/m<sup>3</sup> (Kusaka et al. 1986a). While all subjects reported respiratory irritation, including coughing, expectoration, or a sore throat, and the study authors reported a significant decrease in FVC after the 6-hour exposure, quantitative data were not provided. Additionally, the study authors did indicate that “no dose-effect relation” could be discerned; however, this claim is unsubstantiated by the available data, and it is unclear how this would be ascertained based on the exposure paradigm. While previous case studies by Harding (1950) and Davison et al. (1983) indicated that cobalt is a potentially toxic substance in hard metal exposure, hard metal is composed of a combination of cobalt, tungsten, and/or tungsten carbide. Due to these study limitations, this study is not considered adequate to serve as the basis for an MRL.

Three studies in rats reported respiratory effects characterized by inflammatory changes in the lungs following acute-duration inhalation exposure to cobalt compounds (Burzlauff et al. 2022a; Palmes et al. 1959; Viegas et al. 2022a, 2022b). Of these, the most sensitive is the study exposing rats to cobalt sulfate heptahydrate, which reported elevated neutrophils in BALF at  $\geq 2.2$  mg Co/m<sup>3</sup> (Viegas et al. 2022a, 2022b). The study by Burzlauff et al. (2022a) also reported BALF alterations following exposure to cobalt tetraoxide at a higher concentration. The differences in adverse effect level between Viegas et al. (2022a) and Burzlauff et al. (2022a) is attributable to differences in bioaccessibility of cobalt in the administered compound. A series of studies by this group of researchers suggests two groupings of compounds based on high acute toxicity (cobalt metal powder, cobalt dihydroxide, cobalt monoxide, and cobalt sulfate heptahydrate) and low acute toxicity (cobalt tetraoxide, cobalt sulfide) (Danzeisen et al. 2022a, 2022b; Derr et al. 2022; van den Brule et al. 2022; Verougstraete et al. 2022; Viegas et al. 2022a). Toxicity findings in these studies are correlated with bioaccessibility of cobalt in the various compounds.

Regarding the LOAEL endpoint of elevated neutrophils in BALF identified in the study by Viegas et al. (2022a, 2022b), neutrophil-mediated inflammation is considered a key event in particle-induced lung inflammation and toxicity (Lam et al. 2023). In support, Viegas et al. (2022a, 2022b) reported that inflammatory changes at the LOAEL (2.2 mg Co/m<sup>3</sup>) progressed to histopathological changes at the next

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tested concentration (6.7 mg Co/m<sup>3</sup>). Furthermore, data from several other inhalation studies with particulates support that increased neutrophils in BALF correlated well with histological changes in the alveoli in 90-day studies in rats (Weber et al. 2023). Weber et al. (2023) proposed that progressive inflammatory changes were associated with macrophage destruction, which decreased particle clearance from the lungs.

Based on these findings, the study by Viegas et al. (2022a, 2022b), which identified an early key event for respiratory toxicity following exposure to a cobalt compound belonging to the “high acute toxicity” group (cobalt sulfate heptahydrate), appears to be an appropriate, health-protective study on which to base the acute-duration inhalation MRL. While the administered NOAEL is higher than the LOAEL identified by Kusaka et al. (1986a), the NOAEL<sub>HEC</sub> of 0.03 mg Co/m<sup>3</sup> is below the human LOAEL (see **Human Equivalent Concentration** section for calculations below).

***Summary of the Principal Study:***

Viegas V, Burzlaff A, Brock TO, et al. 2022a. A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 3: Inflammatory response following acute inhalation exposure correlates with lower tier data. Regul Toxicol Pharmacol 130:105127. <http://doi.org/10.1016/j.yrtph.2022.105127>.

Viegas V, Burzlaff A, Brock TO, et al. 2022b. Supplementary data: A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 3: Inflammatory response following acute inhalation exposure correlates with lower tier data. Regul Toxicol Pharmacol 130. <http://doi.org/10.1016/j.yrtph.2022.105127>.

Groups of female Crl:CD (SD) rats were exposed to cobalt sulfate heptahydrate at 0, 0.1, 0.3, 1, 10, or 30 mg/m<sup>3</sup> via whole-body inhalation for 4 hours and sacrificed at the following timepoints (five per timepoint): 4, 8, and 16 hours postexposure and 1, 7, 16, and 32 days postexposure. While the initial test compound was cobalt sulfate heptahydrate, this compound is unstable at room temperature at humidity levels <70%; at lower humidity levels, the compound is converted into cobalt sulfate hexahydrate (Redhammer et al. 2007). Based on personal communication with study authors (Viegas 2024), it is likely that the analytically verified concentrations were cobalt sulfate hexahydrate based on the temperature (20–23°C) and humidity (25–31% at lower concentrations, 46–51% at the highest concentration) of the inhalation chambers. Using the ratio of molecular weights for cobalt (58.933 g/mol) and cobalt sulfate hexahydrate (263.11 g/mol), cobalt concentrations were calculated to be 0, 0.02, 0.07, 0.2, 2.2, and 6.7 mg Co/m<sup>3</sup>.

BALF was collected for biochemical analysis. Histopathology was conducted on the lungs and upper respiratory system at 1 and 16 days postexposure only. Histopathology data were not reported as incidence data. Rather, the data were reported based on severity score (1–4) for four histopathological markers for inflammation (perivascular inflammatory edema, alveolar pulmonary edema, pneumonia) and upper respiratory tract reactivity (hyperplasia, metaplasia), adjusted by the number of animals affected as well as the spread of the effect (focal, multifocal, locally extensive, no modifier), and then normalized to 1,000 mg/m<sup>3</sup> exposure (to be comparable across various concentrations utilized for eight cobalt compounds tested in this study). The normalized score was reported on a scale of 0–100.

The mass median aerodynamic diameter (MMAD) was 1.87 µm. No deaths occurred. The percentages of neutrophils in BALF were significantly increased by approximately 3.3- and 4.5-fold at 2.2 and 6.7 mg Co/m<sup>3</sup>, respectively, at 1-day postexposure. Increases were also observed at 6.7 mg Co/m<sup>3</sup> at 8 hours postexposure and at 2.1 mg Co/m<sup>3</sup> at 16 hours postexposure. Values returned to control levels at 7 days and beyond (data presented graphically). The study authors also noted decreased BALF cell viability at ≥2.2 mg Co/m<sup>3</sup> at 4–16 hours postexposure. Particle-laden macrophages were occasionally noted at

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6.7 mg Co/m<sup>3</sup>. No histopathological changes were observed the day after exposure; however, by 16 days postexposure, squamous cell metaplasia of the epiglottis in the larynx was observed in almost all rats tested at 6.7 mg Co/m<sup>3</sup>. The normalized severity score was approximately 20 based on this upper respiratory tract reactivity. The study authors stated that the 1 mg/m<sup>3</sup> (0.2 mg Co/m<sup>3</sup>) level is a NOAEL for inhalation toxicity for this compound based on study results.

**Selection of the Point of Departure for the MRL:** The NOAEL of 0.2 mg Co/m<sup>3</sup> for elevated neutrophils in BALF was selected as the point of departure (POD) for the acute-duration inhalation MRL.

Effects observed at the LOAEL include increased percentage of neutrophils in BALF and decreased BALF cell viability. Data were reported graphically for BALF neutrophils in the supplemental files (Viegas et al. 2022b); quantitative data were obtained via personal communication with study authors (Viegas 2024). Data for 1-day postexposure were selected for benchmark dose (BMD) modeling because it showed the best dose-response data (Table A-2). Data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS) (version 3.3.2) using a benchmark response (BMR) of 1 standard deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, benchmark concentration lower confidence limit (BMCL) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Based on these criteria, none of the models tested adequately fit the data. Therefore, the NOAEL of 0.2 mg Co/m<sup>3</sup> was selected as the POD for the acute-duration inhalation MRL.

**Table A-2. Neutrophils in Bronchoalveolar Lavage Fluid in Female Rats 1 Day After a 4-Hour Inhalation Exposure to Cobalt Sulfate Heptahydrate**

|                 | Concentration in mg Co/m <sup>3</sup> |               |                 |                |                               |                                |
|-----------------|---------------------------------------|---------------|-----------------|----------------|-------------------------------|--------------------------------|
|                 | 0                                     | 0.02          | 0.07            | 0.2            | 2.2                           | 6.7                            |
| Neutrophils (%) | 4.6±3.31 <sup>a</sup><br>(5)          | 1±0.61<br>(5) | 8.1±4.74<br>(5) | 3.9±2.3<br>(5) | 15.1±2.48 <sup>b</sup><br>(5) | 20.8±11.56 <sup>b</sup><br>(5) |

<sup>a</sup>Mean±standard deviation (number of animals).

<sup>b</sup>p<0.01.

Source: Viegas 2024; Viegas et al. 2022b

**Adjustment for Intermittent Exposure:** The NOAEL of 0.2 mg Co/m<sup>3</sup> was adjusted from intermittent exposure to continuous exposure using the following equation:

$$NOAEL_{ADJ} = 0.2 \text{ mg Co/m}^3 \times \frac{4 \text{ hours}}{24 \text{ hours}} = 0.03 \text{ mg Co/m}^3$$

**Human Equivalent Concentration:** While an inhalation PBPK model for cobalt is available (Unice et al. 2020a), this model was inadequate for interspecies extrapolation because model assumptions are based on human data for insoluble cobalt dust. There are no rat PBPK models to allow for interspecies extrapolation, and there are no models based on kinetics for soluble cobalt compounds. Therefore, a HEC was calculated using the following equation from Lee et al. (2019), adopted from NIOSH (2013):

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$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{VR_R}{VR_H} \times \frac{DF_R}{DF_H} \times \frac{\frac{1 - k_R^n}{1 - k_R}}{\frac{1 - k_H^n}{1 - k_H}} \times \frac{RH_R}{RH_H} \times \frac{SA_H}{SA_R}$$

where VR = ventilation rate, DF = deposition fraction,  $k = 1 - \text{clearance rate}$ , RH = particle retention half-time, SA = alveolar surface area, n = exposure days, R = rat, and H = human.

For this equation, deposition fractions for rats and humans must be calculated. The regional deposited dose ratio (RDDR) for the pulmonary region is used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using the Multiple-Path Particle Dosimetry Model (MPPD version 3.04) developed by Applied Research Associates, Inc. (ARA) to first calculate the deposition fraction (DF) for rats and humans. The MPPD model parameters and results for the rat and human deposition fractions are presented in Table A-3. For breathing frequency and tidal volume parameter values in humans, a TWA of default values in males (ICRP 1994) was calculated based on the following activity pattern over a 24-hour exposure period: 8 hours sleeping (nasal breathing) + 8 hours at rest/sitting (nasal breathing) + 8 hours of light activity (oronasal-mouth breather). Default values in males were selected to be health protective, as males are predicted to have higher deposition fractions than females. The TWA values were then used in the calculation of the deposition fraction (to represent TWA deposition over a 24-hour period).

**Table A-3. MPPD Model (Version 3.04) Inputs and Results for Rat and Human Models**

| Parameters                                    | Rats                         | Humans                                            |
|-----------------------------------------------|------------------------------|---------------------------------------------------|
| Deposition/clearance                          | Deposition only              | Deposition only                                   |
| Airway morphometry                            |                              |                                                   |
| Model                                         | Asymmetric Multiple Path     | Yem/Schum 5-Lobe                                  |
| Functional residual capacity                  | 4 mL (default)               | 3,300 mL (default)                                |
| Upper respiratory tract                       | 0.42 mL (default)            | 50 mL (default)                                   |
| Inhalant properties                           |                              |                                                   |
| Density <sup>a</sup>                          | 1.95 g/cm <sup>3</sup>       | 1.95 g/cm <sup>3</sup>                            |
| Aspect ratio                                  | 1                            | 1                                                 |
| Diameter, MMAD <sup>a</sup>                   | 1.87 µm                      | 1.87 µm                                           |
| GSD <sup>a</sup>                              | 2.49                         | 2.49                                              |
| Inhalability adjustment                       | On                           | On                                                |
| Exposure conditions                           |                              |                                                   |
| Aerosol concentration (NOAEL <sub>ADJ</sub> ) | 0.03 mg Co/m <sup>3</sup>    | 0.03 mg Co/m <sup>3</sup>                         |
| Breathing frequency                           | 102 breaths/minute (default) | 14.7 breaths/minute (calculated TWA) <sup>b</sup> |
| Tidal volume                                  | 2.1 mL (default)             | 875 mL (calculated TWA) <sup>c</sup>              |
| Breathing scenario                            | Nose only                    | Nasal/oronasal-mouth breather <sup>d</sup>        |



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**Table A-3. MPPD Model (Version 3.04) Inputs and Results for Rat and Human Models**

| Parameters                                                                   | Rats            | Humans          |
|------------------------------------------------------------------------------|-----------------|-----------------|
| Deposition/clearance                                                         | Deposition only | Deposition only |
| Results                                                                      |                 |                 |
| Alveolar region deposition fraction<br>(Total pulmonary deposition fraction) | 0.0363          | 0.1462          |

<sup>a</sup>Viegas et al. (2022b).

<sup>b</sup>Breathing frequency is 12 breaths/minute at sleep/rest and 20 breaths/minute with light activity (ICRP 1994).

<sup>c</sup>Tidal volumes are 625 mL at sleep, 750 mL at rest, and 1,250 mL with light activity (ICRP 1994).

<sup>d</sup>Breathing scenario is assumed nasal with sleep and at rest and oronasal-mouth with light activity.

ADJ = adjusted; GSD = geometric standard deviation; NOAEL = no-observed-adverse-effect level; MMAD = mass median aerodynamic diameter; MPPD = Multiple-Path Particle Dosimetry; TWA = time-weighted average

The deposition fractions calculated by the MPPD model and the daily ventilation rates were then used to calculate the  $NOAEL_{HEC}$ . Table A-4 lists the values used within the equation and the source of these values. The exposure days (n) are 1 day to represent 24 hours of continuous exposure since the exposure concentration was adjusted from an intermittent to continuous exposure. Since clearance data are not available for cobalt sulfate heptahydrate, clearance data for nickel sulfate were used to approximate clearance in humans and rats (Oller et al. 2014).

$$NOAEL_{HEC} = 0.03 \text{ mg/m}^3 \times \frac{0.22 \frac{\text{m}^3}{\text{day}}}{20 \frac{\text{m}^3}{\text{day}}} \times \frac{0.0363}{0.1462} \times \frac{1 - (1 - 0.289 \text{ day}^{-1})^1}{1 - (1 - 0.289 \text{ day}^{-1})} \times \frac{1}{1.04} \times \frac{54 \text{ m}^2}{0.34 \text{ m}^2}$$

$$NOAEL_{HEC} = 0.01 \text{ mg Co/m}^3$$

**Table A-4. Values Used to Calculate the  $NOAEL_{HEC}$  for Cobalt**

| Variable                                             | Rats value (R)           | Human value (H)         | Source                                                                   |
|------------------------------------------------------|--------------------------|-------------------------|--------------------------------------------------------------------------|
| Ventilation rate (VR)                                | 0.22 m <sup>3</sup> /day | 20 m <sup>3</sup> /day  | EPA (1994)                                                               |
| Deposition fraction (DF)                             | 0.0363                   | 0.1462                  | Calculated using MPPD software                                           |
| Clearance rate                                       | 0.289 day <sup>-1</sup>  | 0.277 day <sup>-1</sup> | Calculated from retention half-times in Oller et al. (2014) <sup>a</sup> |
| Retention half-time                                  | 2.4 days                 | 2.5 days                | Oller et al. (2014)                                                      |
| Ratio of retention half-time (RH) (to rat half-time) | 1                        | 1.04                    | Calculated                                                               |
| Alveolar surface area (SA)                           | 0.34 m <sup>2</sup>      | 54 m <sup>2</sup>       | EPA (1994)                                                               |
| Exposure days (n)                                    | 1 day                    | 1 day                   | Viegas et al. (2022a)                                                    |

<sup>a</sup>Total clearance rate =  $\ln 2$ /retention half-time; example:  $0.693/2.4 \text{ days} = 0.289 \text{ day}^{-1}$ .

HEC = human equivalent concentration;  $\ln$  = natural logarithm; MPPD = Multiple-Path Particle Dosimetry; NOAEL = no-observed-adverse-effect level

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**Uncertainty Factor:** The following uncertainty factors were applied to the  $NOAEL_{HEC}$  to derive the MRL:

- Uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustments
- Uncertainty factor of 10 for human variability

Subsequently, the MRL for acute-duration exposure to cobalt via inhalation is:

$$MRL = \frac{NOAEL_{HEC}}{(UF)} = \frac{0.01 \text{ mg Co}/m^3}{3 \times 10}$$

$$MRL = 0.0003 \text{ mg Co}/m^3$$

**Other Additional Studies or Pertinent Information that Lend Support to this MRL:** Systematic review concluded that the respiratory tract is a known target of cobalt toxicity in humans following inhalation exposure based on a high level of evidence in humans and laboratory animals (Appendix C).

Findings in occupational cohorts of workers exposed to cobalt include reports of adverse respiratory symptoms (e.g., cough, phlegm, wheezing), impaired lung function, and asthma (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a, 1986b; Linna et al. 2003; Nemery et al. 1992; Swennen et al. 1993; Walters et al. 2012). In laboratory animals, acute-duration exposure is associated with inflammatory responses at low concentrations (Burzlaff et al. 2022a; Viegas et al. 2022a) and severe lung damage at lethal concentrations (Palmer et al. 1959; Viegas et al. 2022a). Dose- and duration-dependent damage throughout the respiratory tract is consistently observed in rodents following intermediate- or chronic-duration inhalation exposure (Burzlaff et al. 2022a; NTP 1991, 1998, 2014). Specifically, the critical effect of elevated neutrophils in BALF has also been observed in Wistar rats exposed to cobalt sulfate heptahydrate at concentrations  $\geq 0.46 \text{ mg Co}/m^3$  for 28 days (Burzlaff et al. 2022a, 2022b). Respiratory effects have also been noted in rabbits and pigs following intermediate-duration inhalation exposure (Johansson et al. 1987; Kerfoot 1974).

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

**Chemical Name:** Cobalt and compounds  
**CAS Numbers:** 7440-48-8  
**Date:** October 2024  
**Profile Status:** Final  
**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. No human exposure studies for this duration were identified. While numerous laboratory animal studies are available, an MRL based on the available studies would result in an intermediate-duration inhalation MRL value lower than the chronic-duration inhalation MRL value based on human data. Due to the higher confidence in an MRL based on human data, no intermediate-duration inhalation MRL is proposed for cobalt.

**Rationale for Not Deriving an MRL:** No studies evaluating cobalt toxicity in humans following intermediate-duration inhalation exposure were identified. However, animal toxicity studies evaluating a comprehensive set of endpoints were available (Burzlaff et al. 2022a; NTP 1991, 2014). These studies consistently identify the respiratory system as the most sensitive target of toxicity for various cobalt compounds in both rats and mice. Additional studies confirm that the respiratory tract is a target of toxicity in rabbits and pigs following intermediate-duration inhalation exposure (Johansson et al. 1992; Kerfoot 1974).

The NOAELs and LOAELs for respiratory effects from intermediate-duration inhalation studies are presented in Table A-5. The lowest LOAEL identified for intermediate-duration inhalation exposure (0.114 mg Co/m<sup>3</sup>; NTP 1991) was identified as a potential POD for the intermediate-duration inhalation MRL. BMD modeling was attempted for all respiratory lesions in female rats and male and female mice reported at 0.114 mg Co/m<sup>3</sup> by NTP (1991); male rat squamous metaplasia data were not amenable to modeling (incidence was 100% at all administered concentrations). Incidence data for these lesions are presented in Table A-6. The data amenable to modeling were fit to all available dichotomous models in EPA's BMDS (version 3.3.2) using the extra risk option with a BMR of 10%. Adequate model fit was judged as described in the acute-duration section above. Model fits were obtained for squamous metaplasia in female rats only, resulting in benchmark concentration (BMC) and BMCL values of 0.029 and 0.021 mg Co/m<sup>3</sup>, respectively. That BMCL value of 0.021 mg Co/m<sup>3</sup> provided the lowest candidate POD (Table A-7).

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**Table A-5. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Intermediate-Duration Inhalation Exposure to Cobalt and Compounds**

| Species (strain)/ number                     | Duration/ frequency                                                  | NOAEL (mg Co/m <sup>3</sup> ) | LOAEL (mg Co/m <sup>3</sup> ) | Effect                                                                                                                               | Compound                                 | Reference                    |
|----------------------------------------------|----------------------------------------------------------------------|-------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|------------------------------|
| Rat (F344/N)<br>Mouse (B6C3F1)<br>10 M, 10 F | 13 weeks<br>5 days/week<br>6 hours +<br>12 minutes <sup>a</sup> /day | ND                            | 0.114                         | Squamous metaplasia of the larynx in both sexes in rats and mice; histiocytic infiltrates in the lungs in male mice                  | Cobalt sulfate heptahydrate <sup>b</sup> | NTP 1991                     |
| Pig<br>5 NS                                  | 3 months<br>5 days/week<br>6 hour/day                                | ND                            | 0.115                         | Decreased lung compliance                                                                                                            | Cobalt metal                             | Kerfoot 1974                 |
| Rabbit (NS) 8 M                              | 17 weeks<br>5 days/week 6 hours/day                                  | ND                            | 0.4                           | Moderate lung inflammation and accumulation of macrophages                                                                           | Cobalt metal                             | Johansson et al. 1987        |
| Rat (Wistar)<br>10 M, 10 F                   | 28 days<br>6 hours/day                                               | ND                            | 0.43                          | Slight focal squamous metaplasia and inflammatory changes; increased BALF LDH levels and neutrophils in males                        | Cobalt sulfate heptahydrate <sup>c</sup> | Burzlaff et al. 2022a, 2022b |
| Rabbit (NS) 8 M                              | 4 months<br>5 days/week<br>6 hours/day                               | 0.5                           | ND                            |                                                                                                                                      | Cobalt chloride                          | Johansson et al. 1991        |
| Rabbit (NS) 8 M                              | 4 months<br>5 days/week<br>6 hours/day                               | ND                            | 0.6                           | Inflammatory lesions in the lung; increased cellularity of BALF                                                                      | Cobalt chloride                          | Johansson et al. 1992        |
| Rat (F344/N)<br>10 M, 10 F                   | 14 weeks<br>5 days/week<br>6 hours +<br>12 minutes <sup>a</sup> /day | ND                            | 0.625                         | Chronic active inflammation in lung, pulmonary alveolar proteinosis; increased relative lung weight                                  | Cobalt metal                             | NTP 2014                     |
| Mouse (B6C3F1)<br>10 M, 9–<br>10 F           | 14 weeks<br>5 days/week<br>6 hours +<br>12 minutes <sup>a</sup> /day | ND                            | 0.625                         | Squamous metaplasia of the larynx; cytoplasmic vacuolization of bronchiole epithelium and alveolar histiocytic cellular infiltration | Cobalt metal                             | NTP 2014                     |

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**Table A-5. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Intermediate-Duration Inhalation Exposure to Cobalt and Compounds**

| Species (strain)/ number | Duration/ frequency                                                 | NOAEL (mg Co/m <sup>3</sup> ) | LOAEL (mg Co/m <sup>3</sup> ) | Effect                                                                                                                                     | Compound                                 | Reference              |
|--------------------------|---------------------------------------------------------------------|-------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|------------------------|
| Mouse (B6C3F1) 5 M, 5 F  | 16 days<br>5 days/week<br>6 hours +<br>12 minutes <sup>a</sup> /day | 0.19                          | 1.8 (SLOAEL)                  | Inflammation and necrosis of respiratory epithelium (larynx, trachea, bronchioles, nasal turbinates); degeneration of olfactory epithelium | Cobalt sulfate heptahydrate <sup>b</sup> | NTP 1991               |
| Rat (F344/N) 5 M, 5 F    | 16 days<br>5 days/week<br>6 hours +<br>12 minutes <sup>a</sup> /day | ND                            | 2.5                           | Minimal cytoplasmic vacuolization of bronchiolar epithelium; minimal-to-mild atrophy and necrosis of olfactory epithelium                  | Cobalt metal                             | NTP 2014               |
| Mouse (B6C3F1) 5 M, 5 F  | 17 days<br>5 days/week<br>6 hours +<br>12 minutes <sup>a</sup> /day | ND                            | 2.5                           | Minimal-to-mild nasal lesions; minimal cytoplasmic vacuolization of bronchiolar epithelium with histiocytic infiltrates in males           | Cobalt metal                             | NTP 2014               |
| Rat (Wistar) 10 M, 10 F  | 28 days<br>6 hours/day                                              | 3.76                          | 15.05                         | Alveolar lipoproteinosis, increased LDH and polymorphonuclear neutrophils in BALF                                                          | Cobalt tetraoxide                        | Burzlauff et al. 2022a |

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**Table A-5. Summary of NOAEL and LOAEL Values for Respiratory Effects Following Intermediate-Duration Inhalation Exposure to Cobalt and Compounds**

| Species (strain)/ number | Duration/ frequency                                              | NOAEL (mg Co/m <sup>3</sup> ) | LOAEL (mg Co/m <sup>3</sup> ) | Effect                                                                                                                      | Compound                                 | Reference |
|--------------------------|------------------------------------------------------------------|-------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------|-----------|
| Rat (F344/N) 5 M, 5 F    | 16 days<br>5 days/week<br>6 hours + 12 minutes <sup>a</sup> /day | 1.8                           | 19 (SLOAEL)                   | Respiratory tract lesions (inflammation, necrosis, hyperplasia, metaplasia, acanthosis, fibrosis, histiocytic infiltration) | Cobalt sulfate heptahydrate <sup>b</sup> | NTP 1991  |

<sup>a</sup>Exposure was for 6 hours plus T<sub>90</sub> time (12 minutes); T<sub>90</sub> time = the time to reach 90% of the target chamber concentration.

<sup>b</sup>Exposure chamber analysis showed that aerosolization of the test substance (cobalt sulfate heptahydrate) resulted in exposure to cobalt sulfate hexahydrate (Behl et al. 2015).

<sup>c</sup>Cobalt sulfate heptahydrate is unstable at room temperature and humidity levels <70% (Redhammer et al. 2007), converting into cobalt sulfate hexahydrate. It is likely that the analytically determined concentrations were in terms of cobalt sulfate hexahydrate, consistent with Behl et al. (2015). While temperature and humidity were not reported for this study, humidity was <70% in the inhalation chamber in other studies by this laboratory (Viegas 2024).

BALF = bronchoalveolar lavage fluid; F = females; FVC = forced vital capacity; LDH = lactate dehydrogenase; M = males; ND = not determined; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

**Table A-6. Sensitive Respiratory Lesions Rats and Mice Following Intermittent Exposure to Cobalt Sulfate Heptahydrate for 13 Weeks**

|                                             | Concentration (mg Co/m <sup>3</sup> ) |                    |                    |                    |                    |                    |
|---------------------------------------------|---------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
|                                             | 0                                     | 0.114              | 0.346              | 1.11               | 3.78               | 11.4               |
| <b>Squamous metaplasia of the larynx</b>    |                                       |                    |                    |                    |                    |                    |
| Male rats                                   | 0/10 <sup>a</sup>                     | 9/9 <sup>b</sup>   | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> |
| Female rats                                 | 1/10                                  | 7/8 <sup>b</sup>   | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> |
| Male mice                                   | 0/10                                  | 7/10 <sup>b</sup>  | 10/10 <sup>b</sup> | 5/9 <sup>c</sup>   | 9/10 <sup>b</sup>  | 10/10 <sup>b</sup> |
| Female mice                                 | 0/10                                  | 8/10 <sup>b</sup>  | 8/10 <sup>b</sup>  | 8/9 <sup>b</sup>   | 9/10 <sup>b</sup>  | 9/9 <sup>b</sup>   |
| <b>Histiocytic infiltrates in the lungs</b> |                                       |                    |                    |                    |                    |                    |
| Male mice                                   | 0/10                                  | 10/10 <sup>b</sup> | 9/10 <sup>b</sup>  | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> | 10/10 <sup>b</sup> |

<sup>a</sup>Affected animals/total animals.

<sup>b</sup>p<0.01.

<sup>c</sup>p<0.05.

Source: NTP 1991

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**Table A-7. Candidate PODs for Intermediate-Duration Inhalation MRL based on Respiratory Effects in Rodents Exposed to Cobalt Sulfate Heptahydrate for 13 Weeks**

| Effect (species, sex)                              | Effect level (mg Co/m <sup>3</sup> ) |       |       |       |
|----------------------------------------------------|--------------------------------------|-------|-------|-------|
|                                                    | NOAEL                                | LOAEL | BMCL  | BMC   |
| Squamous metaplasia of the larynx (rat, male)      | ND                                   | 0.114 | ND    | ND    |
| Squamous metaplasia of the larynx (rat, female)    | ND                                   | 0.114 | 0.021 | 0.029 |
| Squamous metaplasia of the larynx (mouse, male)    | ND                                   | 0.114 | NA    | NA    |
| Squamous metaplasia of the larynx (mouse, female)  | ND                                   | 0.114 | NA    | NA    |
| Histiocytic infiltrates in the lungs (mouse, male) | ND                                   | 0.114 | NA    | NA    |

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the benchmark concentration; LOAEL = lowest-observed-adverse-effect level; NA = not applicable (modeling attempted; no adequate models); ND = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure

Source: NTP 1991

The BMCL of 0.021 mg Co/m<sup>3</sup> was adjusted for continuous exposure (6.2 hours/24 hours; 5 days/7 days) to a BMCL<sub>ADJ</sub> of 0.0039 mg Co/m<sup>3</sup> and converted into a BMCL<sub>HEC</sub> of 0.0023 mg Co/m<sup>3</sup> using the methodology and equations shown in the acute-duration MRL section above and the values shown in Table A-8. Using the BMCL<sub>HEC</sub> of 0.0023 mg Co/m<sup>3</sup> as the final POD and a total uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability) would result in an intermediate-duration inhalation MRL of 0.00008 mg Co/m<sup>3</sup> (8x10<sup>-5</sup> mg Co/m<sup>3</sup>). However, this value is not proposed for the intermediate-duration inhalation MRL because the value would be lower than the chronic-duration inhalation MRL based on respiratory effects in humans. The confidence in the chronic-duration MRL is much higher due to study population (human), which precludes the need for interspecies extrapolation and associated uncertainties.

**Table A-8. Values Used to Calculate the BMCL<sub>HEC</sub> for Cobalt**

| Variable                                             | Rats value (R)           | Human value (H)         | Source                                                                   |
|------------------------------------------------------|--------------------------|-------------------------|--------------------------------------------------------------------------|
| Ventilation rate (VR)                                | 0.17 m <sup>3</sup> /day | 20 m <sup>3</sup> /day  | EPA (1994) <sup>a</sup>                                                  |
| Deposition fraction (DF)                             | 0.0653                   | 0.1370                  | Calculated using MPPD software                                           |
| Clearance rate                                       | 0.289 day <sup>-1</sup>  | 0.277 day <sup>-1</sup> | Calculated from retention half-times in Oller et al. (2014) <sup>b</sup> |
| Retention half-time                                  | 2.4 days                 | 2.5 days                | Oller et al. (2014)                                                      |
| Ratio of retention half-time (RH) (to rat half-time) | 1                        | 1.04                    | Calculated                                                               |
| Alveolar surface area (SA)                           | 0.34 m <sup>2</sup>      | 54 m <sup>2</sup>       | EPA (1994)                                                               |
| Exposure days (n)                                    | 91 days                  | 91 days                 | NTP (1991)                                                               |

<sup>a</sup>The average of the starting and final body weights from the dose groups above and below the BMCL (0.144 kg) from NTP (1991) was used to calculate the VR (instead of the default body weight of 0.124 kg provided in EPA 1994).

<sup>b</sup>Total clearance rate = ln2/retention half-time; example: 0.693/2.4 days = 0.289 day<sup>-1</sup>.

HEC = human equivalent concentration; ln = natural logarithm; MPPD = Multiple-Path Particle Dosimetry; NOAEL = no-observed-adverse-effect level

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



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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

**Chemical Name:** Cobalt and compounds  
**CAS Numbers:** 7440-48-8  
**Date:** October 2024  
**Profile Status:** Final  
**Route:** Inhalation  
**Duration:** Chronic  
**MRL:** 0.0001 mg Co/m<sup>3</sup> (1x10<sup>-4</sup> mg Co/m<sup>3</sup>)  
**Critical Effect:** Respiratory reduced spirometry parameter values  
**Reference:** Nemery et al. 1992  
**Point of Departure:** NOAEL of 0.0053 mg/m<sup>3</sup> (NOAEL<sub>ADJ</sub> of 0.0013 mg/m<sup>3</sup>)  
**Uncertainty Factor:** 10  
**LSE Graph Key:** 28  
**Species:** Human

**MRL Summary:** A chronic-duration inhalation MRL of 0.0001 mg Co/m<sup>3</sup> was derived for cobalt based on reduced 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 Co/m<sup>3</sup>, which was adjusted for intermittent exposure to a continuous exposure concentration of 0.0013 mg Co/m<sup>3</sup> and divided by a total uncertainty factor of 10 for human variability.

**Selection of the Critical Effect:** Several occupational studies examining chronic-duration inhalation exposure to cobalt support respiratory toxicity as the critical effect (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a; Linna et al. 2003; Nemery et al. 1992; Swennen et al. 1993). Chronic-duration inhalation studies in animals support that the respiratory system is the most sensitive target of cobalt toxicity in rodents (NTP 1998, 2014; Wehner et al. 1977). The lowest LOAEL for respiratory effects is 0.0151 mg Co/m<sup>3</sup> for reduced spirometry parameters, coughing, wheezing, and upper airway irritation; this finding is associated with a NOAEL of 0.0053 mg Co/m<sup>3</sup> (Nemery et al. 1992). Case studies show that the sensitization of lymphocytes by cobalt potentially plays a crucial role in some of the respiratory effects (e.g., wheezing, asthma) that are observed in the exposed workers (Krakowiak et al. 2005; Shirakawa et al. 1988, 1989). Limitations of Kusaka et al. (1986a) and Swennen et al. (1993) is the workers' co-exposure to tungsten, carbide, and cobalt. A study by Gennart and Lauwerys (1990) measured the cobalt air concentrations from two rooms where the workers were moving between freely and no stay times were provided. The absence of this information did not allow estimation of the average exposure for the workers; therefore, a reliable exposure estimate cannot be determined and 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 to 2003 where the mean air concentrations of cobalt in different departments ranged from 0.03 to 0.15 mg/m<sup>3</sup>. Until 1987, cobalt was being produced from pyrite ore concentrate, which resulted in occupational co-exposures to sulphur dioxide (SO<sub>2</sub>) and ammonia (NH<sub>3</sub>). These gases are both known respiratory irritants (Andersson et al. 2006; ATSDR 1998; Huber and Loving 1991). After 1987, cobalt was produced using byproducts of metallurgic industry as raw material, which eliminated the co-exposure to the irritant gases, and the incidence of asthma reduced to only one case. Therefore, it is likely that the health effects observed in this study were due to the co-exposure to sulphur dioxide and ammonia 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 effects, and cancer effects after chronic-duration inhalation exposure to cobalt at concentrations higher than those in the human studies (NTP 1998, 2014; Wehner et al. 1977). Wehner et al. (1977) used a high concentration of 7.9 mg Co/m<sup>3</sup> for a lifetime exposure in hamsters, resulting in lung inflammation and emphysema. In the NTP (1998) study, mice

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showed respiratory effects at the lowest exposure concentration in the chronic-duration inhalation database (0.06 mg Co/m<sup>3</sup>) in addition to cancer effects, which included hyperplasia of the squamous epithelium in the larynx. Although rats did not show serious respiratory health effects, the lowest concentration caused cancer effects in rats (alveolar/bronchiolar neoplasms along with metaplasia of the nose and epiglottis) (NTP 1998). In the NTP (2014) study, the concentration of 1.25 mg Co/m<sup>3</sup> produced serious respiratory and cancer effects in both rats and mice; cancer effects 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 studies are presented below in Table A-9.

**Table A-9. Summary of Respiratory NOAEL and LOAEL Values of Chronic-Duration Inhalation Exposure to Cobalt**

| Species (sex) | Frequency/duration                                                    | NOAEL (NOAEL <sub>ADJ</sub> ) (mg/m <sup>3</sup> ) | LOAEL (LOAEL <sub>ADJ</sub> ) (mg/m <sup>3</sup> ) | Effect                                                                                                                                 | Compound                                 | Reference           |
|---------------|-----------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|---------------------|
| Human (M, F)  | Current employees; duration of employment not reported (occupational) | 0.0053 (0.0013)                                    | 0.0151 (0.0027)                                    | Decreased FEV <sub>1</sub> (5%) and FVC (5%); increased cough (11/91), wheezing (4/91), and upper airway irritation (40/91) in workers | Cobalt metal                             | Nemery et al. 1992  |
| Human (M, F)  | 21 years (occupational)                                               | 0.0175 (0.004)                                     | ND                                                 |                                                                                                                                        | Cobalt metal                             | Deng et al. 1991    |
| Human (M,F)   | 8 years (occupational)                                                | ND                                                 | 0.125 (0.03)                                       | Dyspnea and wheezing                                                                                                                   | Hard metal                               | Swennen et al. 1993 |
| Human (M, F)  | 3 years (occupational)                                                | ND                                                 | 0.126 (0.03)                                       | 2.7% decrease in FEV <sub>1</sub> in exposed workers                                                                                   | Hard metal                               | Kusaka et al. 1986b |
| Rat (M, F)    | 105 weeks 5 days/week 6 hours/day                                     | ND                                                 | 0.12 (0.02) (SLOAEL)                               | Hyperplasia and metaplasia of upper and lower respiratory tract tissues; pulmonary fibrosis; inflammatory changes in lungs             | Cobalt sulfate heptahydrate <sup>a</sup> | NTP 1998            |
| Mice (M, F)   | 105 weeks 5 days/week 6 hours/day                                     | ND                                                 | 0.11 (0.02) (SLOAEL)                               | Squamous metaplasia of the larynx                                                                                                      | Cobalt sulfate heptahydrate <sup>a</sup> | NTP 1998            |
| Rats (M, F)   | 105 weeks 5 days/week 6 hours/day                                     | ND                                                 | 1.25 (0.223) (SLOAEL)                              | Hyperplastic and metaplastic pulmonary and nasal lesions                                                                               | Cobalt metal                             | NTP 2014            |
| Mice (M, F)   | 105 weeks 5 days/week 6 hours/day                                     | ND                                                 | 1.25 (0.223) (SLOAEL)                              | Hyperplastic and metaplastic pulmonary and nasal lesions                                                                               | Cobalt metal                             | NTP 2014            |

**Table A-9. Summary of Respiratory NOAEL and LOAEL Values of Chronic-Duration Inhalation Exposure to Cobalt**

| Species (sex) | Frequency/duration                     | NOAEL (NOAEL <sub>ADJ</sub> ) (mg/m <sup>3</sup> ) | LOAEL (LOAEL <sub>ADJ</sub> ) (mg/m <sup>3</sup> ) | Effect                          | Compound     | Reference          |
|---------------|----------------------------------------|----------------------------------------------------|----------------------------------------------------|---------------------------------|--------------|--------------------|
| Hamster       | Lifetime<br>5 days/week<br>7 hours/day | ND                                                 | 7.9<br>(1.4)<br>(SLOAEL)                           | Lung Inflammation and emphysema | Cobalt oxide | Wehner et al. 1977 |

<sup>a</sup>Exposure chamber analysis showed that aerosolization of the test substance (cobalt sulfate heptahydrate) resulted in exposure to cobalt sulfate hexahydrate (Behl et al. 2015).

Selected study for the chronic-duration inhalation MRL derivation.

ADJ = adjusted; F = females; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

**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.

While this study has limitations (discussed below in the *Summary of the Principal Study*), available data based on findings from the group analysis showing impaired lung function and increased subjective complaints of respiratory symptoms in the high-exposure group support identification of the low-exposure group mean (0.0053 mg Co/m<sup>3</sup>) as a NOAEL for respiratory effects. While causality cannot be determined in studies with cross-sectional design, findings from the systematic review presented in Appendix C (*Respiratory effects are a known health effect for humans following inhalation exposure to cobalt*) support that observed exposure-related effects are likely attributable to occupational exposure to cobalt.

### **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. <http://doi.org/10.1164/ajrccm/145.3.610>.

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 almost 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.

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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 was significant ( $R=0.85-0.88$ ) when one workshop with poor hygienic conditions was excluded. The study authors noted 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  $\text{mg}/\text{m}^3$  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 study authors to produce a functional impairment. The study authors noted that cobalt appears to be the only relevant exposure; however, details on the exposure duration were not provided.

Characteristics of the three groups were similar, with the exception that men in the referent group were slightly younger and taller than men in the exposed groups. The average respective ages in the control, low-, and high-exposure groups were 28.2, 32.1, and 32.8 years for men and 21.1, 25.9, and 25.4 years for women. The average respective heights in the control, low-, and high-exposure groups were 177.6, 175.9, and 174.2 cm for men and 163.6, 164.1, and 164.2 cm for women. For smoking status, 47, 41, and 37% of subjects had never smoked, 32, 41, and 50% were smokers, and 20, 18, and 13% were ex-smokers in the control, low-, and high-exposure groups, respectively.

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 FVC and  $\text{FEV}_1$ , even after consideration of smoking status. Additionally, maximal mid-expiratory flow and mean PEF rates 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. 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, and control. However, the higher rate of smokers in exposed workers, compared to control, confounds interpretation of the incidence of work-related cough; no group analyses with adjustment for smoking status were performed. 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 the 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  $\text{FEV}_1$  are presented in Table A-10.

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**Table A-10. FVC and FEV<sub>1</sub> Values in Humans Exposed to Inhaled Cobalt in an Occupational Setting<sup>a</sup>**

| Dose (mg Co/m <sup>3</sup> ) |                  | 0.0004<br>(control) |         | 0.0053<br>(low exposure) |        | 0.0151<br>(high exposure) |        |
|------------------------------|------------------|---------------------|---------|--------------------------|--------|---------------------------|--------|
| Number (total/men/women)     |                  | 59/46/13            |         | 102/93/9                 |        | 92/73/19                  |        |
| Parameter                    |                  | Mean                | SD      | Mean                     | SD     | Mean                      | SD     |
| FVC (mL)                     | Men              | 5,648               | 936     | 5,445                    | 754    | 5,184                     | 799    |
|                              | Women            | 4,033               | 688     | 4,018                    | 627    | 3,733                     | 592    |
|                              | Total (weighted) | 5,292               | 1,110.6 | 5,319                    | 845.2  | 4,884                     | 960.85 |
| FEV <sub>1</sub> (mL)        | Men              | 4,644               | 803     | 4,451                    | 679    | 4,191                     | 712    |
|                              | Women            | 3,416               | 634     | 3,468                    | 384    | 3,123                     | 599    |
|                              | Total (weighted) | 4,373               | 920.31  | 4,364                    | 714.24 | 3,970                     | 813.04 |

<sup>a</sup>Means and standard deviations for men and women are raw data from Table 4 in Nemery et al. (1992). Total (weighted) combines data for men and women to calculate the weighted means and standard deviations of the data.

FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; SD = standard deviation

Source: Nemery et al. (1992)

In addition to limitations described above (e.g., lack of control for other potential exposures, use of proxy exposure data), there are additional study limitations to consider. As with all cross-sectional studies, causality between cobalt exposure and observed outcomes cannot be definitively determined. Also, the statistical analysis for spirometry data did not adjust for known characteristics that can affect lung function in addition to smoking status, such as age and height. Lastly, the exposure duration for workers was not reported.

***Selection of the Point of Departure for the MRL:*** The NOAEL of 0.0053 mg/m<sup>3</sup> for 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-10) were amenable to BMD modeling. The weighted data for FVC and FEV<sub>1</sub> were each modeled separately, and each dataset was fit to all available continuous models in EPA's BMDS (version 3.3.2). Adequate model fit was judged as described in the acute-duration section above. A BMR of 1 standard deviation from the control mean was selected in the absence of a biologically based BMR.

Results of the BMD modeling for FVC and FEV<sub>1</sub> are presented in Tables A-11 and A-12, respectively. Using the criteria listed above, only the Linear model provides an adequate fit to the FVC and the FEV<sub>1</sub> data. However, for both endpoints, both the BMC and BMCL values were higher than the maximum concentration in the dataset, lending considerable uncertainty to the model. These results are due, in part, to the large variance in the control groups, which directly impacts the outcome of the default BMR of 1 standard deviation. Based on BMC and BMCL values outside the range of concentrations in the dataset, the extrapolated BMCL values were not considered suitable as the basis for the POD for the MRL. In the absence of a suitable BMD model, the NOAEL of 0.0053 mg/m<sup>3</sup> for reduced respiratory function in male and female workers was selected as the POD for the chronic-duration inhalation MRL.

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**Table A-11. Model Predictions (Constant Variance) for FVC in Workers Exposed to Cobalt Chronically via Inhalation (Nemery et al. 1992)**

| Model                            | BMD <sub>1SD</sub> <sup>a</sup><br>(mg/m <sup>3</sup> ) | BMDL <sub>1SD</sub> <sup>a</sup><br>(mg/m <sup>3</sup> ) | Test 4<br>p-value <sup>b</sup> | AIC      | Scaled residuals <sup>c</sup> |                   |
|----------------------------------|---------------------------------------------------------|----------------------------------------------------------|--------------------------------|----------|-------------------------------|-------------------|
|                                  |                                                         |                                                          |                                |          | Dose below<br>BMD             | Dose above<br>BMD |
| Exponential 3 <sup>d</sup>       |                                                         |                                                          | NA                             | 4,194.69 | -9.07x10 <sup>-7</sup>        | NA                |
| Exponential 5 <sup>d</sup>       |                                                         |                                                          | NA                             | 4,194.69 | -1.99x10 <sup>-7</sup>        | NA                |
| Hill <sup>d</sup>                |                                                         |                                                          | NA                             | 4,194.69 | -1.04x10 <sup>-6</sup>        | NA                |
| Polynomial Degree 2 <sup>d</sup> |                                                         |                                                          | 0.01                           | 4,192.95 | 1.74                          | NA                |
| Power <sup>d</sup>               |                                                         |                                                          | NA                             | 4,194.69 | 4.16x10 <sup>-8</sup>         | NA                |
| Linear                           | 0.0294                                                  | 0.0193                                                   | 0.21                           | 4,194.24 | -0.3210                       | NA                |

<sup>a</sup>BMD and BMDL values for models that do not provide adequate fit are not included in this table.

<sup>b</sup>Values <0.1 fail to meet adequate fit.

<sup>c</sup>Scaled residuals at doses immediately below and above the BMD.

<sup>d</sup>Restricted model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., <sub>1SD</sub> = exposure dose associated with a 1 standard deviation change from the control); FVC = forced vital capacity; NA = not applicable, goodness-of-fit test could not be performed

**Table A-12. Model Predictions (Constant Variance) for FEV<sub>1</sub> in Workers Exposed to Cobalt Chronically via Inhalation (Nemery et al. 1992)**

| Model                            | BMD <sub>1SD</sub> <sup>a</sup><br>(mg/m <sup>3</sup> ) | BMDL <sub>1SD</sub> <sup>a</sup><br>(mg/m <sup>3</sup> ) | Test 4<br>p-value <sup>b</sup> | AIC      | Scaled residuals <sup>c</sup> |                   |
|----------------------------------|---------------------------------------------------------|----------------------------------------------------------|--------------------------------|----------|-------------------------------|-------------------|
|                                  |                                                         |                                                          |                                |          | Dose below<br>BMD             | Dose above<br>BMD |
| Exponential 3 <sup>d</sup>       |                                                         |                                                          | NA                             | 4,106.64 | -6.99x10 <sup>-7</sup>        | NA                |
| Exponential 5 <sup>c,d</sup>     |                                                         |                                                          | NA                             | 4,108.64 | -4.67x10 <sup>-7</sup>        | NA                |
| Hill <sup>d</sup>                |                                                         |                                                          | NA                             | 4,108.64 | 5.73x10 <sup>-7</sup>         | NA                |
| Polynomial Degree 2 <sup>d</sup> |                                                         |                                                          | <0.0001                        | 4,120.19 | -0.157                        | 2.541             |
| Power <sup>d</sup>               |                                                         |                                                          | NA                             | 4,106.64 | -6.60x10 <sup>-7</sup>        | NA                |
| Linear                           | 0.0258                                                  | 0.0177                                                   | 0.25                           | 4,105.97 | -0.294                        | NA                |

<sup>a</sup>BMD and BMDL values for models that do not provide adequate fit are not included in this table.

<sup>b</sup>Values <0.1 fail to meet adequate fit.

<sup>c</sup>Scaled residuals at doses immediately below and above the BMD.

<sup>d</sup>Restricted model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., <sub>1SD</sub> = exposure dose associated with a 1 standard deviation change from the control); FEV<sub>1</sub> = forced expiratory volume in 1 second; NA = not applicable, goodness-of-fit test could not be performed

**Adjustment for Intermittent Exposure:** Assuming 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<sup>3</sup>, Table A-9). A typical workweek of 8 hours/day, 5 days/week was assumed:

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

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

- 10 for human variability

Subsequently, the MRL for chronic-duration exposure to cobalt via inhalation is:

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

$$MRL = 0.00013 \text{ mg Co/m}^3 \text{ (rounded to } 0.0001 \text{ mg Co/m}^3\text{)}$$

**Other Additional Studies or Pertinent Information that Lend Support to this MRL:** Systematic review concluded that the respiratory tract is a known target of cobalt toxicity in humans following inhalation exposure based on a high level of evidence in humans and laboratory animals (Appendix C).

Findings in occupational cohorts of workers exposed to cobalt include reports of adverse respiratory symptoms (e.g., cough, phlegm, wheezing), impaired lung function, and asthma (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a, 1986b; Linna et al. 2003; Nemery et al. 1992; Swennen et al. 1993; Walters et al. 2012). In laboratory animals, acute-duration exposure is associated with inflammatory responses at low concentrations (Burzlaff et al. 2022a; Viegas et al. 2022a) and severe lung damage at lethal concentrations (Viegas et al. 2022a; Palmes et al. 1959). Dose- and duration-dependent damage throughout the respiratory tract is consistently observed in rodents following intermediate- or chronic-duration inhalation exposure (Burzlaff et al. 2022a; NTP 1991, 1998, 2014). Respiratory effects have also been noted in rabbits and pigs following intermediate-duration inhalation exposure (Johansson et al. 1987; Kerfoot 1974).

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

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

**Chemical Name:** Cobalt and compounds  
**CAS Numbers:** 7440-48-8  
**Date:** October 2024  
**Profile Status:** Final  
**Route:** Oral  
**Duration:** Acute  
**MRL:** 0.03 mg Co/kg/day  
**Critical Effect:** Transient polycythemia (clinically elevated red blood cell levels)  
**Reference:** Davis and Fields 1958  
**Point of Departure:** Minimal LOAEL of 1 mg Co/kg/day  
**Uncertainty Factor:** 30  
**LSE Graph Key:** 1  
**Species:** Human

**MRL Summary:** An acute-duration oral MRL of 0.03 mg Co/kg/day was derived for cobalt based on a hematological endpoint of transient production of polycythemia (clinically elevated red blood cell levels) in humans orally exposed to cobalt chloride for 7–14 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 and 3 for use of a minimal LOAEL).

**Selection of the Critical Effect:** The most sensitive effects in humans following acute-duration oral exposure to cobalt are gastrointestinal upset, impaired thyroid function, and hematological effects. However, based on systematic review (Appendix C), gastrointestinal effects are not classifiable as to their toxicity to humans following oral exposure to cobalt; therefore, they were not considered as a potential critical effect. The NOAELs and LOAELs for hematological and thyroid effects in humans and animals are shown in Table A-13. The lowest LOAELs for hematological and thyroid effects ranged from 0.54 to 1 mg Co/kg/day in humans (Davis and Fields 1958; Paley et al. 1958; Roche and Layrisse 1956). However, the study by Paley et al. (1958) was determined to be a third-tier study based on risk of bias evaluation (Appendix C). Due to high risk of bias associated with this study, it was not considered further for MRL development. Therefore, remaining candidate MRLs for thyroid and hematological effects had equivalent LOAELs of 1 mg Co/kg/day based on LOAELs. Based on systematic review of the entire oral database (Appendix C), evidence is stronger for hematological effects (presumed health effect based on a moderate level of evidence in humans and high level of evidence in animals) than thyroid effects (suspected health effect based on a low level of evidence in humans and a moderate level of evidence in animals). Since effects occur at the same exposure level, the health effect with a stronger weight-of-evidence (hematological effects) was selected as the critical effect.



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**Table A-13. Select NOAEL and LOAEL Values Following Acute-Duration Oral Exposure to Cobalt and Compounds**

| Species                      | Duration       | NOAEL<br>(mg<br>Co/kg/day) | LOAEL<br>(mg<br>Co/kg/day) | Effect                                                                                                   | Compound                    | Reference                  |
|------------------------------|----------------|----------------------------|----------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------|----------------------------|
| <b>Hematological effects</b> |                |                            |                            |                                                                                                          |                             |                            |
| Human<br>8–16 M              | 7–<br>14 days  | 0.03                       | ND                         |                                                                                                          | Cobalt (II)                 | Hoffmeister et al. 2018    |
| Human<br>5 M                 | 7–<br>14 days  | ND                         | 1                          | Polycythemia (14% increase in erythrocyte levels, compared to pre-exposure values)                       | Cobalt chloride             | Davis and Fields 1958      |
| Rat<br>6 M                   | 7 days         | ND                         | 12.5                       | Increased hematocrit and hemoglobin levels                                                               | Cobalt chloride hexahydrate | Shrivastava et al. 2008    |
| Rat<br>8 M                   | 7 days         | ND                         | 12.5                       | Increased red blood cell count, hematocrit, and hemoglobin; increased percent granulocytes and monocytes | Cobalt chloride hexahydrate | Shrivastava et al. 2010    |
| Rat<br>8 M                   | 8 days         | 12.4                       | 24.8                       | Increased hematocrit, hemoglobin, and reticulocytes                                                      | Cobalt chloride hexahydrate | Paternian and Domingo 1988 |
| Rat<br>20 M                  | Once           | ND                         | 161                        | Increased hematocrit                                                                                     | Cobalt chloride hexahydrate | Domingo and Llobet 1984    |
| <b>Thyroid effects</b>       |                |                            |                            |                                                                                                          |                             |                            |
| Human<br>3 M                 | 10–<br>14-days | ND                         | 0.54                       | Impaired thyroid uptake of radioactive iodine-131                                                        | Cobalt chloride             | Paley et al. 1958          |
| Human<br>12 NS               | 14 days        | ND                         | 1                          | Impaired thyroid uptake of radioactive iodine-131                                                        | Cobalt chloride             | Roche and Layrisse 1956    |

Selected study for the acute-duration oral MRL derivation.

M = males; ND = not determined; NS = not specified

**Selection of the Principal Study:** Davis and Fields (1958) was selected as the principal study because it identifies the lowest LOAEL for the critical effect (hematological effects).

**Summary of the Principal Study:**

Davis JE, Fields JP. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc Soc Exp Biol Med 99:493-495. <http://doi.org/10.3181/00379727-99-24395>.

Five apparently healthy men, ages 20–47 years, 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. It is noted that one of these subjects (subject 4) continued treatment past 14 days; these data are not included in this acute-duration analysis. In this study, each subject served as their own control, and blood samples were collected from each



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**Table A-15. Data Extracted from Figure 1 in Davis and Fields (1958): Erythrocyte Levels During Acute-Duration Cobalt Exposure for 7–14 days (Red Blood Cells in Millions/mm<sup>3</sup>)**

| Person #                                                                                                                        | Symbol | Days of acute cobalt exposure |     |     |     |     |     |     |            |     |     |            |     |     |            | Average Days 7–14 |     |
|---------------------------------------------------------------------------------------------------------------------------------|--------|-------------------------------|-----|-----|-----|-----|-----|-----|------------|-----|-----|------------|-----|-----|------------|-------------------|-----|
|                                                                                                                                 |        | 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 | <b>6.7</b> |     |     |            |                   | 6.8 |
| 3                                                                                                                               | •      | 5.6                           | 5.8 | 5.9 | 6.1 | 6.4 | 6.5 | 6.5 | <b>6.3</b> |     |     |            |     |     |            |                   | 6.3 |
| 4                                                                                                                               | □      | 5.6                           | 5.6 | 5.7 |     | 5.7 | 6.0 | 6.0 | 6.2        |     | 6.4 | 6.5        | 6.5 | 6.4 | 6.3        |                   | 6.4 |
| 5                                                                                                                               | ○      | 5.5                           | 5.7 | 5.9 |     | 5.8 | 6.0 |     | 6.1        |     | 6.3 | 6.5        |     | 6.4 | <b>6.4</b> |                   | 6.3 |
| 6                                                                                                                               | Δ      | 5.4                           | 5.5 | 5.5 |     | 5.6 | 5.9 | 6.0 |            | 6.2 |     | 6.2        |     | 6.2 | 6.4        | <b>6.4</b>        | 6.3 |
| Average erythrocytes after exposure for 7–14 days (in millions/mm <sup>3</sup> ): <b>6.4</b>                                    |        |                               |     |     |     |     |     |     |            |     |     |            |     |     |            |                   |     |
| Average erythrocytes on the final day of exposure (in millions/mm <sup>3</sup> ): <b>6.4</b>                                    |        |                               |     |     |     |     |     |     |            |     |     |            |     |     |            |                   |     |
| Percent increase in erythrocyte levels after acute-duration exposure for 7–14 days, compared to pretreatment levels: <b>14%</b> |        |                               |     |     |     |     |     |     |            |     |     |            |     |     |            |                   |     |

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No conclusions can be made regarding other hematological findings from this study due to inadequate data reporting. All subjects in this study (including the four exposed for  $\leq 14$  days, the one exposed  $>14$  days at 1 mg Co/kg/day, a sixth subject exposed for  $>14$  days to a different exposure paradigm) showed increased reticulocyte counts ranging from 1.9 to 2.7% (normal range 0.5–2.5%; NLM 2022b), with all but one showing an increase of at least 2-fold. Based on data-reporting, it cannot be determined which subjects had values above the normal range of 0.5–2.5% (NLM 2022b), or which individual showed a mild change  $<2$ -fold. Similarly, increases in hemoglobin percentages were reported to a “lesser extent” in subjects, compared to observed increases in red blood cell levels. Increases in all subjects were reportedly 6–11%, compared to pre-exposure values; hemoglobin values per subject were not reported. No exposure-related changes in total leukocyte or thrombocyte counts were observed, compared to pre-exposure values.

***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/day, which was converted to a daily dose of cobalt using a reference body weight of 70 kg for adult humans:

$$150 \text{ mg CoCl}_2/\text{day} = 150 \times \frac{58.9 \frac{\text{g}}{\text{mol}} \text{ Co}}{128.8 \frac{\text{g}}{\text{mol}} \text{ CoCl}_2} = 68.1 \text{ mg Co/day}$$

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

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

The available data in Davis and Fields (1958) are not amenable to BMD 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; the finding was considered a minimal LOAEL based on transient nature of effect (hematological levels returned to baseline for all individuals 4–9 days after cessation of cobalt administration) as well as mild nature of the effect (average erythrocyte levels were just above the clinically normal range of 4.7–6.1 million cells/mm<sup>3</sup> for adult male men)

Subsequently, the MRL for acute-duration exposure to cobalt via oral exposure is:

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

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

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Systematic review concluded that the hematological system is a presumed target of cobalt toxicity in humans following oral exposure based on a moderate level of evidence in humans and a high level of evidence laboratory animals (Appendix C).

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Available animal studies corroborate the effects seen in the limited human database. Increased erythrocytes, hematocrit, and/or hemoglobin were observed in rats following acute-duration exposure (Domingo and Llobet 1984; Paternain and Domingo 1988; Shrivastava et al. 2008, 2010) and intermediate-duration oral exposure (Corrier et al. 1985; Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955; Murdock 1959; Stanley et al. 1947).

Based on limited available human data, the acute-duration oral MRL of 0.03 mg Co/kg/day should be protective of other side effects reported in controlled trials and/or case reports of cobalt supplementation (e.g., gastrointestinal distress, thyroid effects), reported at doses  $\geq 0.54$  mg Co/kg/day (Paley et al. 1958; Roche and Layrisse 1956).

***Agency Contact (Chemical Managers):*** Sam Keith, MS, CHP

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## MINIMAL RISK LEVEL (MRL) WORKSHEET

**Chemical Name:** Cobalt and compounds  
**CAS Numbers:** 7440-48-8  
**Date:** October 2024  
**Profile Status:** Final  
**Route:** Oral  
**Duration:** Intermediate  
**MRL:** 0.02 mg Co/kg/day  
**Critical Effect:** Elevated red blood cells  
**Reference:** Danzeisen et al. 2020a  
**Point of Departure:** BMDL<sub>1SD</sub> of 1.95 mg Co/kg/day  
**Uncertainty Factor:** 100  
**LSE Graph Key:** 53  
**Species:** Rat

**MRL Summary:** An intermediate-duration oral MRL of 0.02 mg Co/kg/day was derived for cobalt based on elevated red blood cell counts in male rats exposed to cobalt chloride hexahydrate at concentrations  $\geq 2.48$  mg Co/kg/day for 90 days (Danzeisen et al. 2020a). The MRL is based on a BMDL<sub>1SD</sub> of 1.9 mg Co/kg/day divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

**Selection of the Critical Effect:** Endpoints identified as presumed (hematological) or suspected (thyroid) human health effects following oral exposure based on systematic review (Appendix C) were considered as candidate critical effects for the intermediate-duration inhalation MRL. The NOAELs and LOAELs identified for these endpoints in humans and animals are presented in Table A-16. Review of the available data indicate that hematological effects are the most sensitive effects; therefore, they are selected as the critical effect for derivation of the intermediate-duration oral MRL.

**Table A-16. Select NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to Cobalt and Compounds**

| Species               | Duration | NOAEL<br>(mg<br>Co/kg/day) | LOAEL<br>(mg<br>Co/kg/day) | Effect                                                                    | Compound                          | Reference                  |
|-----------------------|----------|----------------------------|----------------------------|---------------------------------------------------------------------------|-----------------------------------|----------------------------|
| Hematological effects |          |                            |                            |                                                                           |                                   |                            |
| Human<br>5 M, 5 F     | 31 days  | 0.013                      | ND                         |                                                                           | Cobalt<br>chloride                | Finley et al.<br>2013      |
| Human<br>5 M, 5 F     | 91 days  | 0.013                      | ND                         |                                                                           | Cobalt<br>chloride                | Tvermoes et<br>al. 2014    |
| Human<br>8–16 M       | 21 days  | 0.03                       | ND                         |                                                                           | Cobalt (II)                       | Hoffmeister et<br>al. 2018 |
| Rat<br>10 M,<br>10 F  | 90 days  | 0.74                       | 2.48                       | Increased red blood cell<br>count, hemoglobin, and<br>hematocrit in males | Cobalt<br>chloride<br>hexahydrate | Danzeisen et<br>al. 2020a  |
| Rat<br>4–6 M          | 8 weeks  | 0.62                       | 2.5                        | Increased red blood cell<br>count and hemoglobin                          | Cobalt<br>chloride<br>hexahydrate | Stanley et al.<br>1947     |

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**Table A-16. Select NOAEL and LOAEL Values Following Intermediate-Duration Oral Exposure to Cobalt and Compounds**

| Species              | Duration                | NOAEL<br>(mg<br>Co/kg/day) | LOAEL<br>(mg<br>Co/kg/day) | Effect                                                                                  | Compound                    | Reference               |
|----------------------|-------------------------|----------------------------|----------------------------|-----------------------------------------------------------------------------------------|-----------------------------|-------------------------|
| Rat<br>6–30 M        | 150 days<br>5 days/week | ND                         | 10                         | Increased red blood cell count, hemoglobin, and hematocrit                              | Cobalt chloride             | Murdock 1959            |
| Rat<br>8–15 M        | 30 days                 | 8.99                       | 13.8                       | Decreased hemoglobin                                                                    | Cobalt chloride             | Chetty et al. 1979      |
| Rat<br>20 M          | 13 weeks                | ND                         | 16.5                       | Increased hematocrit and hemoglobin                                                     | Cobalt chloride             | Domingo et al. 1984     |
| Rat<br>3–8 M         | 4 months                | ND                         | 18                         | Increased red blood cell count and hemoglobin levels                                    | Cobalt chloride             | Holly 1955              |
| Rat<br>3 M           | 98 days                 | ND                         | 20                         | Increased red blood cell count, hemoglobin level, and packed cell volume                | Cobalt chloride hexahydrate | Corrier et al. 1985     |
| Rat<br>10 M,<br>10 F | 90 days                 | 73.4                       | 220                        | Increased red blood cell count, hemoglobin, and hematocrit in males                     | Cobalt tetroxide            | Danzeisen et al. 2020a  |
| Thyroid effects      |                         |                            |                            |                                                                                         |                             |                         |
| Human<br>5 M, 5 F    | 31 days                 | 0.013                      | ND                         |                                                                                         | Cobalt chloride             | Finley et al. 2013      |
| Human<br>5 M, 5 F    | 91 days                 | 0.013                      | ND                         |                                                                                         | Cobalt chloride             | Tvermoes et al. 2014    |
| Human<br>20–55 F     | 13 weeks                | 0.57                       | ND                         |                                                                                         | Cobalt chloride             | Holly 1955              |
| Rat<br>10 M,<br>10 F | 90 days                 | 7.44                       | ND                         |                                                                                         | Cobalt chloride hexahydrate | Danzeisen et al. 2020a  |
| Rat<br>3–8 M         | 4 months                | 18                         | ND                         |                                                                                         | Cobalt chloride             | Holly 1955              |
| Mouse<br>6 F         | 45 days                 | ND                         | 45<br>(SLOAEL)             | Degeneration and necrotic changes in thyroid epithelial cells; lymphocytic infiltration | Cobalt chloride             | Shrivastava et al. 1996 |
| Rat<br>10 M,<br>10 F | 90 days                 | 734                        |                            |                                                                                         | Cobalt tetroxide            | Danzeisen et al. 2020a  |

Selected study for the intermediate-duration oral MRL derivation.

F = females; LOAEL = lowest-observed-adverse-effect level; M = males; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

**Selection of the Principal Study:** The Danzeisen et al. (2020a) in rats was selected as the principal study because it identifies the lowest LOAEL for the critical effect (hematological effects).

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Available human studies do not identify adverse hematological effects following intermediate-duration oral exposure to cobalt supplements at doses up to 0.03 mg Co/kg/day (Finley et al. 2013; Hoffmeister et al. 2018; Tvermoes et al. 2014). The principal study for the acute-duration MRL (Davis and Fields 1958) also evaluated hematological effects in two subjects following intermediate-duration exposure. As described in the acute-duration MRL worksheet, graphically-presented data were digitized using an open-source software, Curve Snap, to estimate changes in red blood cell counts. One subject was exposed to 1.0 mg Co/kg/day for a total of 15 days, showing an approximate 18% increase in red blood cell count at the end of exposure, compared to pre-exposure levels. The second subject was exposed to 0.8 mg Co/kg/day for 15 days, at which point, no alterations in red blood cell counts were observed compared to pre-exposure values. The dose for the subject was increased to 1 mg Co/kg/day for an additional 7 days, at which point, red blood cell levels were increased by approximately 5%. These data suggest that the no adverse effect level may be around 0.8 mg Co/kg/day for intermediate-duration oral studies; however, with only a single subject per dose group, this study is of insufficient study design to make that determination. However, the comparability of that value (0.8 mg Co/kg/day) to the NOAEL value of 0.74 mg Co/kg/day from the rat study by Danzeisen et al. (2020a) lends support to the selection of the rat study as the principal study for derivation of the intermediate-duration oral MRL.

***Summary of the Principal Study:***

Danzeisen R, Williams DL, Viegas V, et al. 2020a. Bioelution, bioavailability, and toxicity of cobalt compounds correlate. *Toxicol Sci* 174(2): 311-325. <http://doi.org/10.1093/toxsci/kfz249>.

In an OECD 408 guideline repeat-dose toxicity study, groups of male and female Crl:CD(SD) rats (10/sex/group) were exposed to 0, 3, 10, or 30 mg cobalt chloride hexahydrate/kg/day (0, 0.74, 2.48, and 7.44 mg Co/kg/day, as per the study authors) for 90 days via gavage in 0.5% hydroxypropyl methylcellulose. Animals were sacrificed immediately after exposure. Additional animals (5/sex/group) served as the recovery group; were similarly exposed to 0 or 30 mg cobalt chloride hexahydrate/kg/day, and were sacrificed 28 days after the end of exposure. Parameters monitored included clinical observations, body weight, food and water consumption, neurological and observational screening, functional tests, hematology and clinical biochemistry, ophthalmology, and reproductive endpoints (serum hormone levels, estrous cyclicity). At sacrifice, gross necropsy was conducted and selected organs were weighed and examined for a complete histopathological examination conducted as per OECD 408 guidelines.

All rats survived. No exposure-related clinical signs or alterations in neurobehavioral screening or functional testing were observed. No changes in food or water consumption were seen. Body weight effects were noted throughout exposure at the highest dose ranging from 5 to 14% decrease from day 8 onward; at necropsy, final body weights were reduced by 11% in males and 9% in females. Body weights remained reduced by 17% in males and 14% in females at the end of the recovery period, compared to controls. Adverse hematological effects were noted in male rats at  $\geq 2.48$  mg Co/kg/day and female rats at 7.44 mg Co/kg/day. In males, findings at 2.48 and 7.44 mg Co/kg/day included elevations in red blood cell counts (9.2 and 18.9%, respectively), hemoglobin levels (10.7 and 25.6%, respectively), and hematocrit (10.3 and 24.2%, respectively). In females, red blood cell counts, hemoglobin levels, and hematocrit were elevated by 9.8, 13.4, and 13.7%, respectively, at 7.44 mg Co/kg/day. Red blood cell parameters were comparable to control in both sexes at the end of the 28-day recovery period. No changes in urinalysis or ophthalmology were observed. No changes in hormone levels or estrous cyclicity were observed. At sacrifice, no gross pathological changes were noted and no exposure-related changes in organ weight were observed. The only organs specifically mentioned as having “no effect” were testes and prostate. Dose-dependent increases in erythroid hyperplasia were observed in the bone marrow at 2.48 mg Co/kg/day (4/10 males, 7/10 females) and 7.44 mg Co/kg/day (7/10 males, 7/10 females), compared to control and 0.74 mg Co/kg/day (0/10 incidence for both sexes). This lesion was not



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observed at the end of the recovery period. The study authors specifically noted that there were no macroscopic or histopathological findings in the heart or thyroid at any dose. No other measured endpoints were explicitly discussed. In the methods section, the study authors stated: "Due to the wealth of parameters measured in these studies, only those endpoints that were affected by the treatment are reported." Based on this statement, it is assumed that all parameters set forth in the OECD 408 guidelines that are not discussed in the results section represented no adverse effect levels.

The study authors determined a systemic NOAEL of 0.74 mg Co/kg/day and LOAEL of 2.48 mg Co/kg/day based on hematological effects. The study authors determined a reproductive NOAEL of >7.44 mg Co/kg/day based on the complete absence of findings on any reproductive parameter.

***Selection of the Point of Departure for the MRL:*** The BMDL<sub>1SD</sub> of 1.95 mg Co/kg/day for elevated red blood cell counts in male rats was selected as the POD for the intermediate-duration oral MRL.

In order to identify the POD, BMD modeling was attempted for red blood cell parameters in male rats reported by Danzeisen et al. (2020a), with standard deviation data obtained via personal communication with the study author (Viegas 2023). The red blood cell parameters modeled are shown in Table A-17. Data were fit to all available continuous models in EPA's BMDS (version 3.3.2) using a BMR of 1 standard deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within  $\pm 2$  units at the data point (except the control) closest to the predefined BMR. Based on these criteria, none of the models tested adequately fit the data for hemoglobin levels. Model outputs for red blood cell data are shown in Table A-18. Model fit for elevated red blood cells in male rats is shown in Figure A-1 (Linear model).

**Table A-17. Red Blood Cell Parameters in Male Rats Exposed to Cobalt Chloride Hexahydrate for 90 Days via Gavage**

|                                                  | Concentration in mg/kg/day (mg Co/kg/day) |                           |                                         |                                         |
|--------------------------------------------------|-------------------------------------------|---------------------------|-----------------------------------------|-----------------------------------------|
|                                                  | 0                                         | 3 (0.74)                  | 10 (2.48)                               | 30 (7.44)                               |
| Red blood cells<br>( $\times 10^6/\mu\text{L}$ ) | 9.455 $\pm$ 0.461 <sup>a</sup><br>(10)    | 9.325 $\pm$ 0.580<br>(10) | 10.325 $\pm$ 0.756 <sup>b</sup><br>(10) | 11.245 $\pm$ 0.746 <sup>c</sup><br>(10) |
| Hemoglobin<br>(mmol/L)                           | 10.35 $\pm$ 0.34<br>(10)                  | 10.50 $\pm$ 0.46<br>(10)  | 11.46 $\pm$ 0.89 <sup>b</sup><br>(10)   | 13.00 $\pm$ 0.61 <sup>c</sup><br>(10)   |

<sup>a</sup>Mean $\pm$ SD (number of animals).

<sup>b</sup>p<0.01.

<sup>c</sup><0.001.

Sources: Danzeisen et al. 2020a; Viegas 2023

**Table A-18. Model Predictions (Constant Variance) for Red Blood Cell Count in Male Rats Exposed to Cobalt Chloride Hexahydrate for 90 Days Via Gavage (Danzeisen et al. 2020a; Viegas 2023)**

| Model                            | BMD <sub>1SD</sub> <sup>a</sup><br>(mg Co/kg/day) | BMDL <sub>1SD</sub> <sup>a</sup><br>(mg Co/kg/day) | Test 4<br>p-value <sup>b</sup> | AIC          | Scaled residuals <sup>c</sup> |                       |
|----------------------------------|---------------------------------------------------|----------------------------------------------------|--------------------------------|--------------|-------------------------------|-----------------------|
|                                  |                                                   |                                                    |                                |              | Dose below<br>BMD             | Dose above<br>BMD     |
| Exponential 3 <sup>d</sup>       | 2.71                                              | 2.13                                               | 0.11                           | 84.92        | 1.51                          | -0.33                 |
| Exponential 5 <sup>d</sup>       |                                                   |                                                    | NA                             | 84.75        | -0.33                         | 2.56x10 <sup>-8</sup> |
| Hill <sup>d</sup>                | 2.38                                              | 1.24                                               | 0.64                           | 82.75        | -0.33                         | 1.85x10 <sup>-7</sup> |
| Polynomial Degree 2 <sup>d</sup> | 2.52                                              | 1.95                                               | 0.13                           | 84.57        | 1.39                          | -0.32                 |
| Polynomial Degree 3 <sup>d</sup> | 2.52                                              | 1.95                                               | 0.13                           | 84.57        | 1.39                          | -0.34                 |
| Power <sup>d</sup>               | 2.52                                              | 1.95                                               | 0.13                           | 84.57        | 1.39                          | -0.33                 |
| <b>Linear<sup>e</sup></b>        | <b>2.52</b>                                       | <b>1.95</b>                                        | <b>0.13</b>                    | <b>84.57</b> | <b>1.39</b>                   | <b>-0.33</b>          |

<sup>a</sup>BMD and BMDL values for models that do not provide adequate fit are not included in this table.

<sup>b</sup>Values <0.1 fail to meet adequate fit.

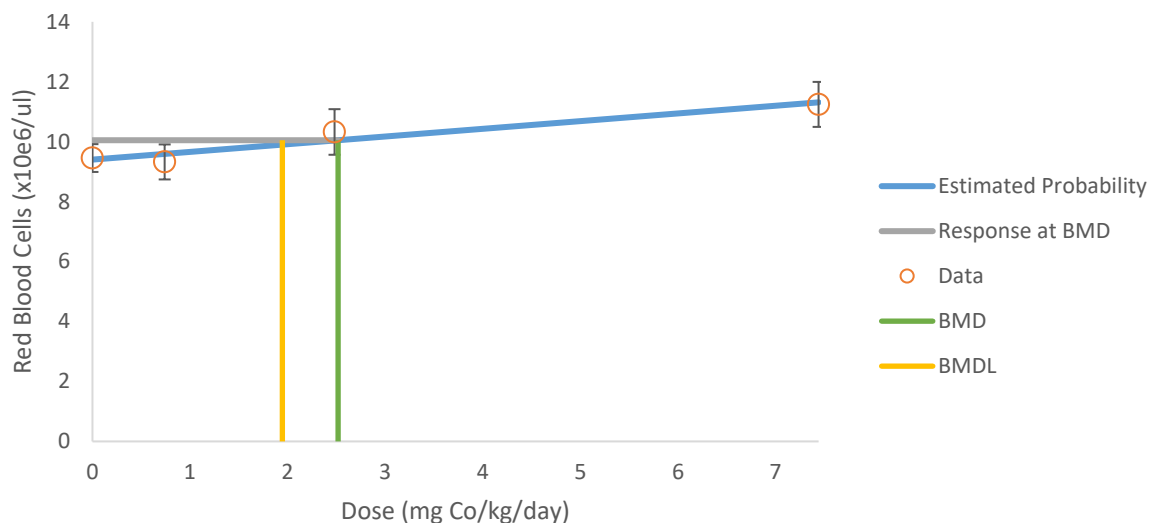
<sup>c</sup>Scaled residuals at doses immediately below and above the BMD.

<sup>d</sup>Restricted model.

<sup>e</sup>Selected model. All models except Exponential 5 provided adequate fit to the data. BMDLs were sufficiently close (differed by <3-fold). While the model with the lowest AIC is the Hill model, this model is overparameterized for the dataset (n=4 dose groups); therefore, the model with the next lowest AIC was selected (Linear; the polynomial 2-degree and power models converged on the linear model).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., <sub>1SD</sub> = exposure dose associated with a 1 standard deviation change from the control); NA = not applicable, goodness-of-fit test could not be performed

**Figure A-1. Fit of Linear Model to Red Blood Cell Count in Male Rats Following Oral Exposure to Cobalt Chloride Hexahydrate for 90 Days (Danzeisen et al. 2020a; Viegas 2023)**



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**Adjustment for Intermittent Exposure:** Not applicable.

**Human Equivalent Concentration:** While PBPK models are available for cobalt oral dosimetry (ICRP 1995; Legget 2008; Unice et al. 2014a), these models are inadequate for interspecies extrapolation because they are specific to humans.

**Uncertainty Factor:** The  $BMDL_{1SD}$  is divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

Subsequently, the MRL for intermediate-duration exposure to cobalt via oral exposure is:

$$MRL = \frac{BMDL_{1SD}}{UFs} = \frac{1.95 \text{ mg/kg/day}}{10 \times 10}$$

$$MRL = 0.0195 \text{ mg Co/kg/day (Rounded to 0.02 mg Co/kg/day)}$$

**Other Additional Studies or Pertinent Information that Lend Support to this MRL:** Systematic review concluded that the hematological system is a presumed target of cobalt toxicity in humans following oral exposure based on a moderate level of evidence in humans and a high level of evidence laboratory animals (Appendix C).

Polycythemia has been reported in healthy human volunteers orally exposed to cobalt chloride at a dose of 1 mg Co/kg/day for 7–15 days (Davis and Fields 1958). However, no changes in hematological parameters were observed in humans exposed to low-dose cobalt supplements at mean doses of 0.03 mg Co/kg/day for 7–21 days (Hoffmeister et al. 2018) or 0.013 mg Co/kg/day for up to 91 days (Finley et al. 2013; Tvermoes et al. 2014). These findings in humans are consistent with the oral intermediate-duration MRL of 0.02 mg Co/kg/day based on hematological findings in rats in the 90-day study by Danzeisen et al. (2020a).

Available animal studies corroborated the effects seen in the limited human database. Increased erythrocytes, hematocrit, and/or hemoglobin were observed in rats following acute-duration exposure (Domingo and Llobet 1984; Paternain and Domingo 1988; Shrivastava et al. 2008, 2010) and intermediate-duration oral exposure (Corrier et al. 1985; Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955; Murdock 1959; Stanley et al. 1947).

Based on limited available human data, the intermediate-duration oral MRL of 0.02 mg Co/kg/day should be protective of gastrointestinal intolerance reported in some patients following intermediate-duration oral exposure to cobalt supplements at doses at or above doses 0.36 mg Co/kg/day (Duckham and Lee 1976; Holly 1955).

**Agency Contact (Chemical Managers):** Sam Keith, MS, CHP

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

***Chemical Name:*** Cobalt and compounds  
***CAS Numbers:*** 7440-48-8  
***Date:*** October 2024  
***Profile Status:*** Final  
***Route:*** Oral  
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration oral MRL as no studies were identified that examined chronic-duration oral exposure to cobalt in either humans or animals.

***Rationale for Not Deriving an MRL:*** No adequately conducted chronic-duration oral studies in humans or laboratory animals were identified that adhered to ATSDR guidelines and investigated health effects resulting from chronic-duration 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. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. 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<sup>a</sup>**

#### Health Effects

##### Species

Human

Laboratory mammals

##### Route of exposure

Inhalation

Oral

Dermal (or ocular)

Parenteral (these studies will be considered supporting data)

In vitro (these studies will be considered supporting data)

##### Health outcome

Death

Systemic effects

Body weight effects

Respiratory effects

Cardiovascular effects

Gastrointestinal effects

Hematological effects

Musculoskeletal effects

Hepatic effects

Renal effects

Dermal effects

Ocular effects

Endocrine effects

Immunological effects

Neurological effects

**Table B-1. Inclusion Criteria for the Literature Search and Screen<sup>a</sup>**


---

|                                   |
|-----------------------------------|
| Reproductive effects              |
| Developmental effects             |
| Other noncancer effects           |
| Cancer                            |
| Toxicokinetics                    |
| Absorption                        |
| Distribution                      |
| Metabolism                        |
| Excretion                         |
| PBPK models                       |
| Biomarkers                        |
| Biomarkers of exposure            |
| Biomarkers of effect              |
| Interactions with other chemicals |
| Potential for human exposure      |
| Releases to the environment       |
| Air                               |
| Water                             |
| Soil                              |
| Environmental fate                |
| Transport and partitioning        |
| Transformation and degradation    |
| Environmental monitoring          |
| Air                               |
| Water                             |
| Sediment and soil                 |
| Other media                       |
| Biomonitoring                     |
| General populations               |
| Occupation populations            |

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<sup>a</sup>Physical-chemical properties are not generally obtained from literature searches, but rather from curated governmental databases such as PubChem.

### **B.1.1 Literature Search**

The current literature search was intended to update the Draft Toxicological Profile for Cobalt released for public comment in 2023. All literature cited in the previous (2023) toxicological profile were considered for inclusion in the updated profile; thus, the literature search was restricted to studies published between September 2020 and June 2023. The following main databases were searched in June 2023:

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- PubMed
- National Technical Reports Library (NTRL)
- 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-3. 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      | search date | Query string                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PubMed</b> |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 06/2023       |             | (((Cobalt[mh] OR 7440-48-4[rn] OR 10026-22-9[rn] OR 10124-43-3[rn] OR 10141-05-6[rn] OR 10210-68-1[rn] OR 1307-96-6[rn] OR 1308-04-9[rn] OR 1308-06-1[rn] OR 1317-42-6[rn] OR 21041-93-0[rn] OR 27016-73-5[rn] OR 513-79-1[rn] OR 61789-51-3[rn] OR 71-48-7[rn] OR 7646-79-9[rn] OR 917-69-1[rn] OR "cobalt tetraoxide"[nm] OR "cobalt(II) acetate"[nm] OR 10026-17-2[rn] OR 10026-18-3[rn] OR 13817-37-3[rn] OR 33485-99-3[rn]) AND ((("Cobalt/toxicity"[mh] OR "Cobalt/adverse effects"[mh] OR "Cobalt/poisoning"[mh] OR "Cobalt/pharmacokinetics"[mh]) OR ("Cobalt"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Cobalt"[mh] AND toxicokinetics[mh:noexp]) OR ("Cobalt/blood"[mh] OR "Cobalt/cerebrospinal fluid"[mh] OR "Cobalt/urine"[mh]) OR ("Cobalt"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Cobalt"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Cobalt/antagonists and inhibitors"[mh]) OR ("Cobalt/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Cobalt/pharmacology"[majr]) OR ("Cobalt"[mh] AND ((("Neoplasms"[mh] OR "Carcinogens"[mh] OR "Lymphoproliferative disorders"[mh] OR "Myeloproliferative disorders"[mh] OR "Toxicity Tests"[mh] OR ((cancer*[tiab] OR carcinogen*[tiab]) AND (risk*[tiab] OR health[tiab]) AND assessment*[tiab]) OR "Mutagens"[mh] OR "Mutagenicity |

**Table B-2. Database Query Strings**

| Database search date | Query string                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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|                      | <p>Tests"[mh] OR "Chromosome Aberrations"[mh] OR "DNA Damage"[mh] OR "DNA Repair"[mh] OR "DNA Replication/drug effects"[mh] OR "DNA/drug effects"[mh] OR "DNA/metabolism"[mh] OR "Genomic Instability"[mh] OR "Salmonella typhimurium/drug effects"[mh] OR "Salmonella typhimurium/genetics"[mh] OR "Sister Chromatid Exchange"[mh] OR strand-break*[tiab]))) OR 21158-51-0[rn] ) AND (2020/09/01:3000[mhda] OR 2020/09/01:3000[crdt] OR 2020/09/01:3000[edat] OR 2020:3000[dp])</p> <p>((((Cobalt[mh] AND 2022/04/01:3000[mhda]) OR ((("Sulfido)cobalt"[tw] OR "Acetic acid, cobalt(2+) salt"[tw] OR "Acetic acid, cobalt(3+) salt"[tw] OR "Aquacat"[tw] OR "Arsanylidynecobalt"[tw] OR "C.I. Pigment Black 13"[tw] OR "Carbonic acid, cobalt(2+) salt"[tw] OR "CI Pigment Black 13"[tw] OR "Co mesoporphyrin"[tw] OR "Cobalt (2+) sulfate"[tw] OR "cobalt (II) acetate"[tw] OR "cobalt (II) carbonate"[tw] OR "cobalt (II) chloride"[tw] OR "cobalt (II) hydroxide"[tw] OR "cobalt (II) meso-porphyrin"[tw] OR "cobalt (II) naphthenate"[tw] OR "cobalt (II) naphthenate"[tw] OR "cobalt (II) nitrate"[tw] OR "cobalt (II) oxide"[tw] OR "cobalt (II) sulfate"[tw] OR "cobalt (II,III) oxide"[tw] OR "cobalt (III) acetate"[tw] OR "cobalt (III) oxide"[tw] OR "Cobalt 59"[tw] OR "Cobalt acetate"[tw] OR "Cobalt arsenide"[tw] OR "Cobalt bis(nitrate)"[tw] OR "Cobalt Black"[tw] OR "Cobalt Brown"[tw] OR "Cobalt carbonate"[tw] OR "cobalt carbonyl"[tw] OR "Cobalt chloride"[tw] OR "Cobalt di(acetate)"[tw] OR "Cobalt diacetate"[tw] OR "Cobalt dichloride"[tw] OR "Cobalt dihydride"[tw] OR "Cobalt dihydroxide"[tw] OR "Cobalt dinitrate"[tw] OR "Cobalt dinitrate hexahydrate"[tw] OR "Cobalt fume"[tw] OR "Cobalt hydroxide"[tw] OR "Cobalt I, (dihydrogen 7,12-diethyl-3,8,13,17-tetramethyl-2,18-porphinedipropionato(2-))-"[tw] OR "Cobalt mesoporphyrin"[tw] OR "Cobalt mesoporphyrin IX"[tw] OR "Cobalt Metal"[tw] OR "Cobalt metal powder"[tw] OR "Cobalt metal, dust and fume"[tw] OR "Cobalt monoarsenide"[tw] OR "Cobalt monocarbonate"[tw] OR "Cobalt monooxide"[tw] OR "Cobalt monosulfate"[tw] OR "Cobalt monosulfide"[tw] OR "Cobalt monoxide"[tw] OR "Cobalt muriate"[tw] OR "Cobalt naphthenate"[tw] OR "Cobalt naphthenates"[tw] OR "Cobalt nitrate"[tw] OR "Cobalt octacarbonyl"[tw] OR "Cobalt oxide"[tw] OR "Cobalt peroxide"[tw] OR "Cobalt sesquioxide"[tw] OR "Cobalt sesquioxide"[tw] OR "Cobalt spar"[tw] OR "Cobalt sulfate"[tw] OR "Cobalt sulfide"[tw] OR "Cobalt sulphate"[tw] OR "cobalt sulphide"[tw] OR "Cobalt tetracarbonyl dimer"[tw] OR "Cobalt tetraoxide"[tw] OR "Cobalt triacetate"[tw] OR "Cobalt trioxide"[tw] OR "Cobalt(2+) acetate"[tw] OR "Cobalt(2+) carbonate"[tw] OR "Cobalt(2+) diacetate"[tw] OR "Cobalt(2+) dichloride"[tw] OR "Cobalt(2+) dihydroxide"[tw] OR "Cobalt(2+) dinitrate"[tw] OR "Cobalt(2+) hydroxide"[tw] OR "Cobalt(2+) nitrate"[tw] OR "Cobalt(2+) oxide"[tw] OR "Cobalt(2+) sulfate"[tw] OR "Cobalt(2+) sulfide"[tw] OR "Cobalt(3+) acetate"[tw] OR "Cobalt(3+) oxide"[tw] OR "Cobalt(3+) triacetate"[tw] OR "Cobalt(II) acetate"[tw] OR "Cobalt(II) carbonate"[tw] OR "Cobalt(II) chloride"[tw] OR "Cobalt(II) hydroxide"[tw] OR "Cobalt(II) mesoporphyrin"[tw] OR "Cobalt(II) naphthenate"[tw] OR "Cobalt(II) nitrate"[tw] OR "Cobalt(II) oxide"[tw] OR "Cobalt(II) sulfate"[tw] OR "Cobalt(II) sulfide"[tw] OR "Cobalt(II) sulphate"[tw] OR "Cobalt(II,III) oxide"[tw] OR "Cobalt(III) acetate"[tw] OR "Cobalt(III) oxide"[tw] OR "Cobalt, (sulfido)-"[tw] OR "Cobalt, [dihydrogen 7,12-diethyl-3,8,13,17-tetramethyl-2,18-porphinedipropionato(2-))-"[tw] OR "Cobalt, [dihydrogen mesoporphyrin IX-ato(2-))-"[tw] OR "Cobalt, arsinidyne-"[tw] OR "Cobalt, di-mu-carbonylhexacarbonyldi-"[tw] OR "Cobalt, elemental"[tw] OR "Cobalt-59"[tw] OR "Cobaltate(2-), [7,12-diethyl-3,8,13,17-tetramethyl-21H,23H-porphine-2,18-dipropanoato(4-)-kN21,kN22,kN23,kN24]-, hydrogen (1:2), (SP-4-2)-"[tw] OR "Cobalti protoporphyrin"[tw] OR "Cobaltic acetate"[tw] OR "Cobaltic oxide"[tw] OR "Cobaltic-cobaltous oxide"[tw] OR "Cobalto-cobaltic oxide"[tw] OR "Cobalto-cobaltic tetroxide"[tw] OR "Cobaltosic oxide"[tw] OR "Cobaltous acetate"[tw] OR "Cobaltous</p> |



**Table B-2. Database Query Strings**

| Database    | Query string                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| search date | <p>carbonate"[tw] OR "Cobaltous chloride"[tw] OR "Cobaltous diacetate"[tw] OR "Cobaltous dichloride"[tw] OR "Cobaltous hydroxide"[tw] OR "Cobaltous naphthenate"[tw] OR "Cobaltous nitrate"[tw] OR "Cobaltous oxide"[tw] OR "Cobaltous sulfate"[tw] OR "Cobaltous sulfide"[tw] OR "Di-mu-carbonylhexacarbonyldicobalt"[tw] OR "Dichlorocobalt"[tw] OR "Dicobalt carbonyl"[tw] OR "Dicobalt octacarbonyl"[tw] OR "Dicobalt oxide"[tw] OR "dicobalt trioxide"[tw] OR "Monocobalt oxide"[tw] OR "Naftolite"[tw] OR "Naphthenic acid, cobalt salt"[tw] OR "Naphthenic acids, cobalt salt"[tw] OR "Naphthenic acids, cobalt salts"[tw] OR "Nitric acid, cobalt(2+) salt"[tw] OR "Octacarbonyldicobalt"[tw] OR "Sphaerocobaltite"[tw] OR "Sulfuric acid, cobalt(2+) salt"[tw] OR "Super cobalt"[tw] OR "Sycoporite"[tw] OR "Tricobalt tetraoxide"[tw] OR "Tricobalt tetroxide"[tw] OR "Zaffre"[tw] OR "cobalt hydride"[tw] OR "cobalt(II) hydride"[tw] OR "cobalt(2+) hydride"[tw] OR "cobalt dihydride"[tw] OR "cobaltous hydride"[tw] OR "cobalt nitride"[tw] OR "glucosaminic acid cobalt"[tw] OR "cobalt fluoride"[tw] OR "cobalt difluoride"[tw] OR "cobalt trifluoride"[tw] OR "cobalt(2+) difluoride"[tw] OR "cobalt(3+) trifluoride"[tw] OR "cobalt(II) fluoride"[tw] OR "cobalt(III) fluoride"[tw] OR "cobaltic fluoride"[tw] OR "cobaltous fluoride"[tw]) NOT medline[sb])) AND (toxicity[ti] OR death OR lethal OR fatal OR fatality OR necrosis OR LC50* OR LD50* OR "body weight" OR "weight loss" OR "weight gain" OR weight-change* OR overweight OR obesity OR inhal* OR respiratory 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 OR lungs OR nose OR nasal OR nasopharyngeal OR larynx OR laryngeal OR pharynx OR bronchial OR bronchi OR bronchioles OR bronchitis OR hemothorax OR alveolar OR alveoli OR irritation OR irritant OR sensitization OR sensitizer OR cilia OR mucocilliary OR cvd OR cardio OR vascular OR cardiovascular 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 "myocardial-infarction" OR "chest pain" OR artery OR arteries OR veins OR venules OR cardiotox* OR "gastro-intestinal" OR gastrointestinal 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 hemato OR haemato OR blood OR anemia OR cyanosis OR erythrocytopenia OR leukopenia OR thrombocytopenia OR hemoglobin OR erythrocyte OR hematocrit OR "bone marrow" OR reticulocyte OR methemoglobin OR red-blood-cell OR musculoskeletal OR skeletal OR muscle OR muscular OR arthritis OR "altered bone" OR "joint pain" OR "joint-ache" OR "limb pain" OR "limb ache" OR hepatic 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 hepatocytes OR gallbladder OR cirrhosis OR jaundice OR "hepatocellular degeneration" OR "hepatocellular hypertrophy" OR hepatomegaly OR hepatotox* OR renal 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 nephrotox* OR dermal OR "skin rash" OR "skin itch" OR "skin irritation" OR "skin redness" OR "skin effect" OR "skin necrosis" OR "skin exposure" OR "skin contact" OR acanthosis OR dermatitis OR psoriasis OR edema OR ulceration OR acne</p> |

## APPENDIX B

**Table B-2. Database Query Strings**

| Database search date | Query string                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | OR ocular OR "eye function" OR "eye effect" OR "eye irritation" OR "eye drainage" OR "eye tearing" OR blindness OR myopia OR cataracts OR endocrine OR "hormone changes" OR "hormone excess" OR "hormone deficiency" OR "hormone gland" OR "hormone secretion" OR "hormone toxicity" OR "sella turcica" OR thyroid OR adrenal OR pituitary OR immunological OR immunologic OR immune OR lymphoreticular OR lymph-node OR spleen OR thymus OR macrophage OR leukocyte* OR white-blood-cell OR immunotox* OR neurological OR neurologic OR neurotoxic OR neurotoxicity OR neurodegenerat* OR "nervous system" OR brain OR neurotoxicant OR neurochemistry OR neurophysiology OR neuropathology OR "motor activity" OR motor change* OR behavior-change* OR behavioral-change* OR sensory-change* 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 "in utero" OR terata* OR terato* OR embryo* OR fetus* OR foetus* OR fetal* OR foetal* OR prenatal* OR "pre-natal" OR perinatal* OR "post-natal" OR postnatal* OR neonat* OR newborn* OR zygote* OR child OR children OR infant* OR offspring OR elderly OR "altered food consumption" OR "altered water consumption" OR "metabolic effect" OR "metabolic toxicity" OR fever OR cancer OR cancerous OR neoplas* OR tumor OR tumors OR tumour* OR malignan* OR carcinoma OR carcinogen OR carcinogen* OR angiosarcoma OR blastoma OR fibrosarcoma OR glioma OR leukemia OR leukaemia OR lymphoma OR melanoma OR meningioma OR mesothelioma OR myeloma OR neuroblastoma OR osteosarcoma OR sarcoma OR mutation OR mutations OR genotoxicity OR genotoxic OR mutagenicity OR mutagenic OR "mechanism of action"[tiab:~0] OR "mechanism of absorption"[tiab:~0] OR "mechanism of distribution"[tiab:~0] OR "mechanism of excretion"[tiab:~0] OR "mechanism of metabolism"[tiab:~0] OR "mechanism of toxic effect"[tiab:~0] OR "mechanism of toxicity" OR "adverse effect" OR "adverse effects" OR "health effects" OR noncancer OR poisoning OR morbidity OR inflammation OR antagonist OR inhibitor OR metabolism OR "environmental exposure" OR toxicokinetics OR pharmacokinetics OR "gene expression" OR "population health" OR epidemiology OR epidemiological OR case-control* OR case-referent OR case-report OR case-series OR cohort* OR correlation-stud* OR cross-sectional-stud* OR ecological-studies OR ecological-study OR follow-up-stud* OR longitudinal-stud* OR metaanalyses OR metaanalysis OR meta-analysis OR prospective-stud* OR record-link* OR retrospective-stud* OR seroepidemiologic-stud* OR occupation* OR worker* OR workmen* OR workplace* OR "human health" OR "oral intake" OR "oral feed" OR "oral ingestion" OR "oral exposure" OR "oral administration" OR ingest* OR gavage* OR "drinking-water" OR NHANES OR "National Health and Nutrition Examination Survey" OR (human AND (risk OR toxic* OR safety)) OR mammal* OR ape OR apes OR baboon* OR balb OR beagle* OR boar OR boars OR bonobo* OR bovine OR C57 OR C57bl OR callithrix OR canine OR canis OR capra OR capuchin* OR cats OR cattle OR cavia OR chicken OR chickens OR chimpanzee* OR chinchilla* OR cow OR cows OR cricetinae OR dog OR dogs OR equus OR feline OR felis OR ferret OR ferrets OR flying-fox OR Fruit-bat OR gerbil* OR gibbon* OR goat OR goats OR guinea-pig* OR guppy OR hamster OR hamsters OR horse OR horses OR jird OR jirds OR lagomorph* OR leontopithecus OR longevans OR macaque* OR marmoset* OR marmoset OR merione OR meriones OR mice OR monkey OR monkeys OR mouse OR muridae OR murinae OR murine OR mustela-putorius OR nomascus OR non-human-primate* OR orangutan* OR pan-paniscus OR pan-troglodytes OR pig OR piglet* OR pigs OR polecat* OR pongopygmaeus OR quail OR rabbit OR rabbits OR rat OR rats OR rhesus OR rodent OR rodentia OR rodents OR saguinus OR sheep OR sheeps OR siamang* OR sow OR sows OR Sprague-Dawley OR swine OR swines OR symphalangus OR tamarin* OR vervet* OR |

## APPENDIX B

**Table B-2. Database Query Strings**

| Database         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| search date      | Query string                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                  | wistar OR wood-mouse OR zebra-fish OR zebrafish)) AND (2020/09/01:3000[mhda] OR 2020/09/01:3000[crdt] OR 2020/09/01:3000[edat] OR 2020:3000[dp])                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>NTRL</b>      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 06/2023          | Date limit 2020-2023<br>Search Titles OR Keywords;<br>"cobalt" OR "cobaltic" OR "cobalto" OR "cobaltosic" OR "cobaltous" OR "dicobalt" OR "monocobalt" OR "tricobalt" OR "dichlorocobalt"                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Toxcenter</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 06/2023          | FILE 'TOXCENTER' ENTERED AT 13:13:40 ON 02 JUN 2023<br>L1 102164 SEA FILE=TOXCENTER 7440-48-4 OR 10026-17-2 OR 10026-18-3 OR<br>10026-22-9 OR 10124-43-3 OR 10141-05-6 OR 10210-68-1 OR<br>1307-96-6 OR 1308-04-9 OR 1308-06-1 OR 1317-42-6 OR 13817-37-3<br>OR 21041-93-0 OR 21158-51-0 OR 27016-73-5 OR 513-79-1 OR<br>61789-51-3 OR 71-48-7 OR 7646-79-9 OR 917-69-1<br>L2 102098 SEA FILE=TOXCENTER L1 NOT TSCATS/FS<br>L3 83010 SEA FILE=TOXCENTER L2 NOT PATENT/DT<br>L4 15967 SEA FILE=TOXCENTER L3 AND PY>2019<br>ACT TOXQUERY/Q<br>-----<br>L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR<br>BIOMARKER? OR NEUROLOG?)<br>L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR<br>EPIDEMIOLOGY/ST,CT,<br>IT)<br>L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR<br>LC(W)50)<br>L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT<br>L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)<br>L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)<br>L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS<br>OR<br>DIETARY OR DRINKING(W)WATER?)<br>L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR<br>PERMISSIBLE))<br>L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)<br>L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM?<br>OR<br>OVUM?)<br>L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)<br>L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR<br>TERATOGEN?)<br>L17 QUE (SPERM OR SPERMATOC? OR SPERMAG? OR SPERMATOC? OR<br>SPERMATOC? OR<br>SPERMATOC? OR SPERMATOC? OR SPERMATOC?)<br>L18 QUE (SPERMATOC? OR SPERMATOC? OR SPERMATOC? OR<br>SPERMATOC? OR<br>SPERMATOC? OR SPERMATOC? OR SPERMATOC?) |

## APPENDIX B

**Table B-2. Database Query Strings**

| Database<br>search date | Query string                                                                                                                                                               |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| L19                     | QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)                                                                                                                 |
| L20                     | QUE (ENDOCRIN? AND DISRUPT?)                                                                                                                                               |
| L21                     | QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)                                                                                                                |
| L22                     | QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)                                                                                                                                  |
| L23                     | QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)                                                                                                                  |
| L24                     | QUE (CARCINO? OR COCARCINO? OR CANCER? OR PRECANCER? OR                                                                                                                    |
|                         | NEOPLAS?)                                                                                                                                                                  |
| L25                     | QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)                                                                                                              |
| L26                     | QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)                                                                                                                 |
| L27                     | QUE (NEPHROTOX? OR HEPATOTOX?)                                                                                                                                             |
| L28                     | QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)                                                                                                                       |
| L29                     | QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)                                                                                                                      |
| L30                     | QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 |
| L31                     | QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE                                                                                                              |
|                         | OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE                                                                                                              |
|                         | OR PORCINE OR MONKEY? OR MACAQUE?)                                                                                                                                         |
| L32                     | QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA                                                                                                              |
|                         | OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)                                                                                                                   |
| L33                     | QUE L30 OR L31 OR L32                                                                                                                                                      |
| L34                     | QUE (NONHUMAN MAMMALS)/ORGN                                                                                                                                                |
| L35                     | QUE L33 OR L34                                                                                                                                                             |
| L36                     | QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR                                                                                                                 |
|                         | PRIMATES OR PRIMATE?)                                                                                                                                                      |
| L37                     | QUE L35 OR L36                                                                                                                                                             |
|                         | -----                                                                                                                                                                      |
| L38                     | 7202 SEA FILE=TOXCENTER L4 AND L37                                                                                                                                         |
| L39                     | 545 SEA FILE=TOXCENTER L38 AND MEDLINE/FS                                                                                                                                  |
| L40                     | 1156 SEA FILE=TOXCENTER L38 AND BIOSIS/FS                                                                                                                                  |
| L41                     | 1628 DUP REM L39 L40 (73 DUPLICATES REMOVED)                                                                                                                               |
| L*** DEL                | 545 S L38 AND MEDLINE/FS                                                                                                                                                   |
| L*** DEL                | 545 S L38 AND MEDLINE/FS                                                                                                                                                   |
| L42                     | 545 SEA FILE=TOXCENTER L41                                                                                                                                                 |
| L*** DEL                | 1156 S L38 AND BIOSIS/FS                                                                                                                                                   |
| L*** DEL                | 1156 S L38 AND BIOSIS/FS                                                                                                                                                   |
| L43                     | 1083 SEA FILE=TOXCENTER L41                                                                                                                                                |
| L44                     | 1083 SEA FILE=TOXCENTER (L42 OR L43) AND BIOSIS/FS                                                                                                                         |
|                         | D SCAN L44                                                                                                                                                                 |

## APPENDIX B

**Table B-3. Strategies to Augment the Literature Search**

| Source                     | Query and number screened when available                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>TSCATS via ChemView</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>06/2023</b>             | 7440-48-4; 10026-22-9; 10124-43-3; 10141-05-6; 10210-68-1; 1307-96-6; 1308-04-9; 1308-06-1; 1317-42-6; 21041-93-0; 21158-51-0; 27016-73-5; 513-79-1; 61789-51-3; 71-48-7; 7646-79-9; 917-69-1; 33485-99-3; 10026-17-2; 10026-18-3; 13817-37-3                                                                                                                                                                                                                                                                                                    |
| <b>NTP</b>                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>06/2023</b>             | Date limit: 2020-2023 or not dated; Content types Reports & Publications; Systematic Reviews; ROC Profiles, Reviews, or Candidates<br>"7440-48-4" "cobalt" "10124-43-3" "7646-79-9"<br>"cobaltous" "dicobalt" "tricobalt" "dichlorocobalt"<br>"10026-22-9" "10141-05-6" "10210-68-1" "1307-96-6"<br>"1308-04-9" "1308-06-1" "1317-42-6" "21041-93-0"<br>"21158-51-0" "27016-73-5" "513-79-1" "61789-51-3"<br>"71-48-7" "917-69-1" "33485-99-3" "10026-17-2"<br>"10026-18-3" "13817-37-3"                                                         |
| <b>Regulations.gov</b>     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>06/2023</b>             | Dockets, no date limit<br>Document, limited to notices, limited to EPA or FDA), and limited to posted date 2020-01-01 to 2023-05-31<br>cobalt<br>"cobaltous"<br>"dicobalt"<br>"tricobalt"<br>"dichlorocobalt"<br>"7440-48-4"<br>"10026-22-9"<br>"10124-43-3"<br>"10141-05-6"<br>"10210-68-1"<br>"1307-96-6"<br>"1308-04-9"<br>"1308-06-1"<br>"1317-42-6"<br>"21041-93-0"<br>"21158-51-0"<br>"27016-73-5"<br>"513-79-1"<br>"61789-51-3"<br>"71-48-7"<br>"7646-79-9"<br>"917-69-1"<br>"33485-99-3"<br>"10026-17-2"<br>"10026-18-3"<br>"13817-37-3" |
| <b>NPIRS</b>               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>06/2023</b>             | Active Ingredient: Cobalt naphthenate (CAS #: 61789-51-3) (PC Code: 25101),<br>Naphthenic acids, cobalt salts (CAS #: 61789-51-3) (PC Code: 25101)                                                                                                                                                                                                                                                                                                                                                                                               |

**Table B-3. Strategies to Augment the Literature Search**

| Source              | Query and number screened when available                                                                                                                                                                                                                              |
|---------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>NIH RePORTER</b> |                                                                                                                                                                                                                                                                       |
| 11/2023             | Search Criteria<br>Fiscal Year: Active Projects Text Search: "cobalt" OR "cobaltic" OR "cobalto" OR "cobaltosic" OR "cobaltous" OR "dicobalt" OR "monocobalt" OR "tricobalt" OR "dichlorocobalt" (advanced) Limit to: Project Title, Project Terms, Project Abstracts |
| <b>Other</b>        | Identified throughout the assessment process                                                                                                                                                                                                                          |

The 2023 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 2,098
- Number of records identified from other strategies: 223
- Total number of records to undergo literature screening: 2,321

### B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on cobalt:

- 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.

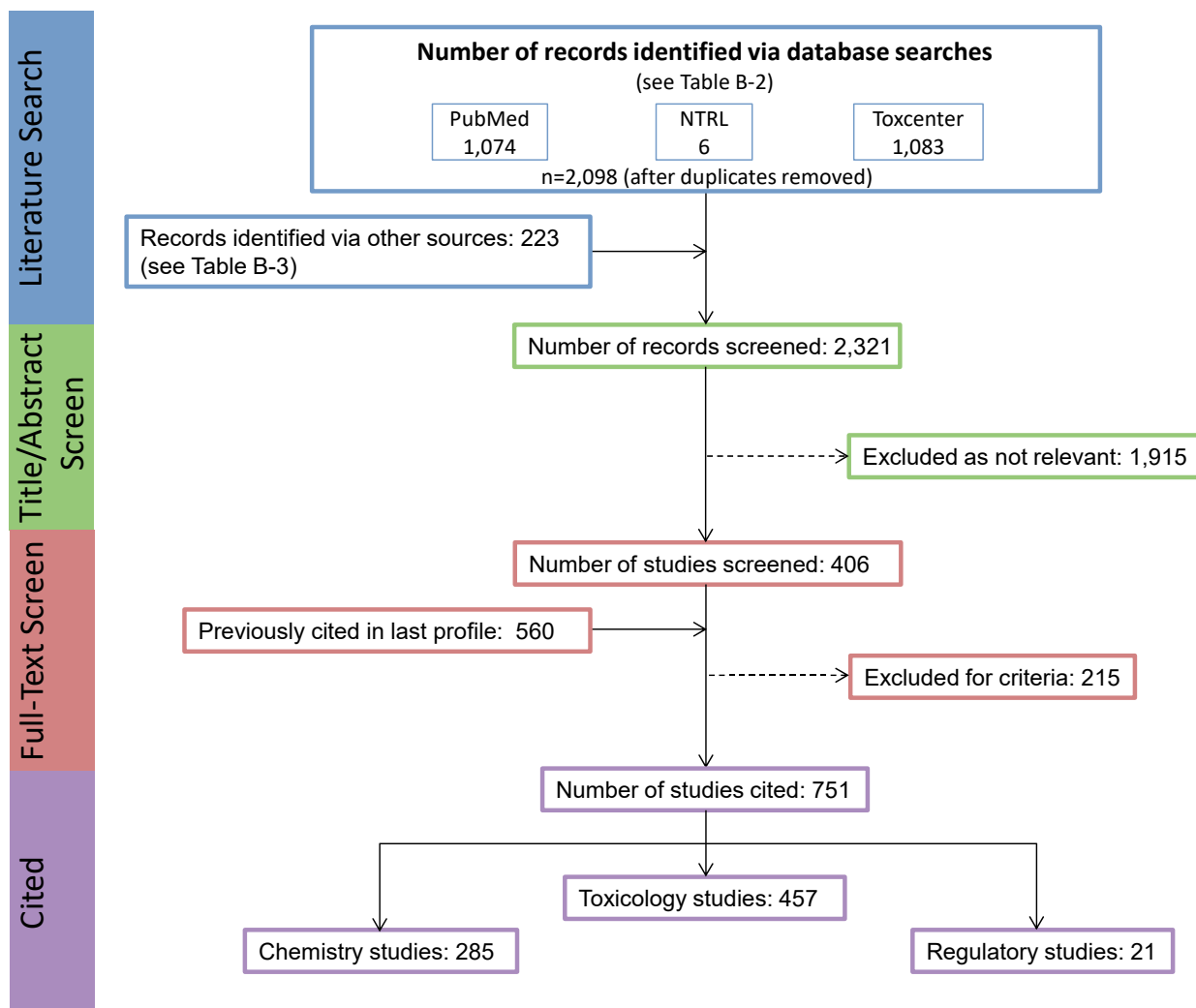
- Number of titles and abstracts screened: 2,321
- Number of studies considered relevant and moved to the next step: 406

**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: 406
- Number of studies cited in the pre-public draft of the toxicological profile: 560
- Total number of studies cited in the profile: 751

A summary of the results of the literature search and screening is presented in Figure B-1.

## APPENDIX B

**Figure B-1. June 2023 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. Inclusion Criteria for Identifying Health Effects Studies**

|                                                               |
|---------------------------------------------------------------|
| Species                                                       |
| Human                                                         |
| Laboratory mammals                                            |
| Route of exposure                                             |
| Inhalation                                                    |
| Oral                                                          |
| Dermal (or ocular)                                            |
| Parenteral (these studies will be considered supporting data) |
| Health outcome                                                |
| Death                                                         |
| Systemic effects                                              |
| Body weight effects                                           |
| Respiratory effects                                           |
| Cardiovascular effects                                        |



**Table C-1. Inclusion Criteria for Identifying Health Effects Studies**


---

|                          |
|--------------------------|
| Gastrointestinal effects |
| Hematological effects    |
| Musculoskeletal effects  |
| Hepatic effects          |
| Renal effects            |
| Dermal effects           |
| Ocular effects           |
| Endocrine effects        |
| Immunological effects    |
| Neurological effects     |
| Reproductive effects     |
| Developmental effects    |
| Other noncancer effects  |
| Cancer                   |

---

**Prioritization of Human Data.** Numerous general population studies evaluated potential associations cobalt levels in the blood or urine and adverse health outcomes without assessment of potential sources of exposure. Since cobalt is a trace essential element (part of the vitamin B12 complex), these studies are of limited usefulness because cobalt levels are often detected at background levels. Therefore, epidemiology studies included in this profile were restricted to those with known exposure above background levels (e.g., occupational exposure). Additionally, individuals with durable medical implants containing cobalt, such as total joint replacement, may be exposed to cobalt from these devices. Since this profile is focused on environmental exposures via inhalation, oral, and dermal exposure routes, studies focused on the kinetics and/or toxicity associated with medical implants were not included.

## **C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES**

A literature search and screen were 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 current literature search was intended to update the Draft Toxicological Profile for Cobalt released for public comment in 2023. See Appendix B for the databases searched and the search strategy.

A total of 2,321 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.

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**Title and Abstract Screen.** In the Title and Abstract Screen step, 2,321 records were reviewed; 26 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

**Full Text Screen.** In the second step in the literature screening process for the systematic review, a full text review of 147 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 147 documents (194 studies), 64 documents (86 studies) were included in the qualitative 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-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

**Table C-2. 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                              |

---

A summary of the extracted data for each study is presented in the Supplemental Document for Cobalt and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.20 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1, 2-2, and 2-3, respectively).

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**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 Tables C-3 and C-4, respectively. Available human studies evaluating noncancer effects include numerous occupational exposure studies and a limited number of controlled exposure and case reports of healthy subjects and patients taking cobalt supplements. Occupational studies identify the respiratory tract as the primary target of cobalt toxicity following inhalation exposure. Controlled exposure and case report studies indicate that hematological, gastrointestinal, and endocrine (thyroid) effects are the most sensitive targets of oral toxicity. Based on effects noted in human and animal studies, studies examining respiratory endpoints following inhalation exposure and hematological, gastrointestinal, or thyroid endpoints following oral exposure were carried through to Steps 4–8 of the systematic review. There were 86 studies (published in 64 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

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**Table C-3. 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                               | 8           | 3           |                |                  | 2             |                 |         | 1     | 1      |        | 2         | 4             |              |              |               | 1               | 14     |
|                                      | 5           | 1           |                |                  | 1             |                 |         | 1     | 1      |        | 0         | 0             |              |              |               | 0               | 4      |
| Case control                         | 1           |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
|                                      | 1           |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
| Population                           | 7           |             |                |                  | 2             |                 |         |       |        |        | 2         | 1             |              |              |               | 1               |        |
|                                      | 5           |             |                |                  | 1             |                 |         |       |        |        | 1         | 0             |              |              |               | 0               |        |
| Case series                          | 5           |             |                |                  |               |                 |         |       |        |        |           | 2             |              |              |               |                 |        |
|                                      | 4           |             |                |                  |               |                 |         |       |        |        |           | 2             |              |              |               |                 |        |
| Meta-analysis                        |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 | 2      |
|                                      |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 | 0      |
| Oral studies                         |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
| Cohort                               |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
| Case control                         |             |             | 1              | 4                | 9             |                 | 3       | 2     |        |        | 7         | 2             | 1            |              | 1             |                 |        |
|                                      |             |             | 0              | 4                | 4             |                 | 0       | 0     |        |        | 4         | 0             | 0            |              | 0             |                 |        |
| Population                           |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
| Case series                          |             |             |                |                  |               |                 |         |       |        |        | 4         |               |              |              |               |                 |        |
|                                      |             |             |                |                  |               |                 |         |       |        |        | 4         |               |              |              |               |                 |        |
| Dermal studies                       |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
| Cohort                               |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
| Case control                         |             |             |                |                  |               |                 |         |       |        |        |           |               |              |              |               |                 |        |
| Population                           |             |             |                |                  |               |                 |         |       | 1      |        |           |               |              |              |               |                 |        |
|                                      |             |             |                |                  |               |                 |         |       | 1      |        |           |               |              |              |               |                 |        |
| Case series                          |             |             |                |                  |               |                 |         |       | 3      |        |           |               |              |              |               |                 |        |
|                                      |             |             |                |                  |               |                 |         |       | 3      |        |           |               |              |              |               |                 |        |
| Meta-analysis                        |             |             |                |                  |               |                 |         |       |        |        |           | 1             |              |              |               |                 |        |
|                                      |             |             |                |                  |               |                 |         |       |        |        |           | 1             |              |              |               |                 |        |
| 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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**Table C-4. 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 <sup>a</sup> | Neurological <sup>a</sup> | Reproductive <sup>a</sup> | Developmental | Other Noncancer | Cancer |
|--------------------------------------|-------------|-------------|----------------|------------------|---------------|-----------------|---------|---------|--------|--------|-----------|----------------------------|---------------------------|---------------------------|---------------|-----------------|--------|
| Inhalation studies                   |             |             |                |                  |               |                 |         |         |        |        |           |                            |                           |                           |               |                 |        |
| Acute-duration                       | 1<br>0      | 6<br>6      |                |                  |               |                 |         |         |        |        |           |                            |                           |                           |               |                 |        |
| Intermediate-duration                | 12<br>9     | 15<br>14    | 8<br>1         | 7<br>0           | 8<br>6        | 7<br>0          | 10<br>5 | 10<br>3 | 6<br>0 | 2<br>0 | 7<br>1    | 10<br>4                    | 9<br>4                    | 8<br>8                    |               | 4<br>1          |        |
| Chronic-duration                     | 5<br>4      | 5<br>5      | 4<br>0         | 4<br>0           |               | 4<br>0          | 4<br>1  | 4<br>0  | 4<br>0 | 2<br>0 | 4<br>0    | 4<br>0                     | 4<br>0                    | 4<br>2                    |               |                 | 4<br>4 |
| Oral studies                         |             |             |                |                  |               |                 |         |         |        |        |           |                            |                           |                           |               |                 |        |
| Acute-duration                       | 4<br>3      | 1<br>0      | 7<br>6         | 3<br>2           | 4<br>4        |                 | 6<br>4  | 7<br>6  |        | 1<br>0 |           | 4<br>3                     | 8<br>7                    | 2<br>1                    | 2<br>0        | 3<br>3          |        |
| Intermediate-duration                | 20<br>7     | 4<br>0      | 9<br>4         | 4<br>0           | 14<br>9       | 3<br>0          | 11<br>3 | 7<br>2  | 2<br>0 | 2<br>0 | 5<br>1    | 8<br>3                     | 10<br>4                   | 19<br>13                  | 7<br>6        | 7<br>6          |        |
| Chronic-duration                     |             |             |                |                  |               |                 |         |         |        |        |           |                            |                           |                           |               |                 |        |
| Dermal studies                       |             |             |                |                  |               |                 |         |         |        |        |           |                            |                           |                           |               |                 |        |
| Acute-duration                       |             |             |                |                  |               |                 |         |         |        |        |           | 6<br>6                     |                           |                           |               |                 |        |
| Intermediate-duration                | 1<br>0      |             |                |                  |               |                 |         |         | 1<br>1 | 2<br>2 |           |                            |                           |                           |               |                 |        |
| 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    |           |                            |                           |                           |               |                 |        |

<sup>a</sup>Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

## 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 Tables C-5, C-6, and C-7, 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 C-5. 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-6. 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-7. 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.

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***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 Tables C-8, C-9, and C-10, respectively.



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**Table C-8. Summary of Risk of Bias Assessment for Cobalt—Observational Epidemiology Studies**

| Reference | Risk of bias criteria and ratings       |                                                                                              |                                                                          |                                                        |                                                 |                                      | Risk of bias tier |
|-----------|-----------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|           | Selection bias                          | Confounding bias                                                                             | Attrition / exclusion bias                                               | Detection bias                                         |                                                 | Selective reporting bias             |                   |
|           | Were the comparison groups appropriate? | Did the study design or analysis account for important confounding and modifying variables?* | 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 only)***Cohort studies*

|                           |   |   |   |   |   |   |        |
|---------------------------|---|---|---|---|---|---|--------|
| Al-Abcha et al. 2021      | + | – | – | + | – | + | Second |
| Andersson et al. 2020     | + | – | + | + | + | + | Second |
| Linna et al. 2003         | + | + | + | + | + | + | First  |
| Gennart and Lauwerys 1990 | + | – | – | – | + | – | Second |
| Kusaka et al. 1986a       | + | – | + | + | + | + | Second |
| Kusaka et al. 1986b       | + | – | + | + | + | + | Second |
| Rehfishch et al. 2012     | + | – | + | – | – | + | Second |
| Verougstraete et al. 2004 | + | – | + | + | + | + | Second |

*Case-control*

|           |   |   |   |   |   |   |        |
|-----------|---|---|---|---|---|---|--------|
| Roto 1980 | – | – | + | + | + | + | Second |
|-----------|---|---|---|---|---|---|--------|

*Case-series*

|                      |     |   |   |     |    |    |        |
|----------------------|-----|---|---|-----|----|----|--------|
| Al-Abcha et al. 2021 | – – | – | + | –   | +  | +  | Second |
| Demedts et al. 1984  | – – | – | + | – – | ++ | ++ | Second |
| Sauni et al. 2010    | – – | – | + | –   | +  | +  | Second |
| Walters et al. 2014  | – – | + | + | –   | +  | +  | Second |

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**Table C-8. Summary of Risk of Bias Assessment for Cobalt—Observational Epidemiology Studies**

| Reference                                          | Risk of bias criteria and ratings       |                                                                                              |                                                                          |                                                        |                                                 |                                      | Risk of bias tier |
|----------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|                                                    | Selection bias                          | Confounding bias                                                                             | Attrition / exclusion bias                                               | Detection bias                                         |                                                 | Selective reporting bias             |                   |
|                                                    | Were the comparison groups appropriate? | Did the study design or analysis account for important confounding and modifying variables?* | 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? |                   |
|                                                    |                                         |                                                                                              |                                                                          |                                                        |                                                 |                                      |                   |
| <i>Cross-sectional</i>                             |                                         |                                                                                              |                                                                          |                                                        |                                                 |                                      |                   |
| Walters et al. 2012                                | +                                       | -                                                                                            | +                                                                        | -                                                      | +                                               | +                                    | Second            |
| Hamzah et al. 2014                                 | +                                       | -                                                                                            | +                                                                        | +                                                      | +                                               | +                                    | Second            |
| Meyer-Bisch et al. 1989                            | +                                       | -                                                                                            | +                                                                        | +                                                      | +                                               | +                                    | Second            |
| Roto 1980                                          | +                                       | -                                                                                            | +                                                                        | +                                                      | +                                               | +                                    | Second            |
| Swennen et al. 1993                                | +                                       | +                                                                                            | +                                                                        | +                                                      | +                                               | +                                    | First             |
| Nemery et al. 1992                                 | +                                       | -                                                                                            | +                                                                        | +                                                      | +                                               | +                                    | Second            |
| Deng et al. 1991                                   | -                                       | -                                                                                            | +                                                                        | -                                                      | +                                               | +                                    | Second            |
| <b><i>Outcome: thyroid effects (oral only)</i></b> |                                         |                                                                                              |                                                                          |                                                        |                                                 |                                      |                   |
| <i>Case series</i>                                 |                                         |                                                                                              |                                                                          |                                                        |                                                 |                                      |                   |
| Chamberlain 1961                                   | -                                       | -                                                                                            | -                                                                        | +                                                      | +                                               | -                                    | Third             |
| Little and Sunico 1958                             | -                                       | -                                                                                            | -                                                                        | -                                                      | +                                               | -                                    | Third             |
| Washburn and Kaplan 1964                           | -                                       | -                                                                                            | -                                                                        | +                                                      | -                                               | -                                    | Third             |

++ = definitely low risk of bias; + = probably low risk of bias; - = probably high risk of bias; -- = definitely high risk of bias

\*Key question used to assign risk of bias tier

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**Table C-9. Summary of Risk of Bias Assessment for Cobalt—Human-Controlled Exposure Studies**

| Reference                                            | Risk of bias criteria and ratings                              |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      | Risk of bias tier |
|------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|                                                      | Selection bias                                                 |                                                          | Performance bias                                                         | Attrition/<br>exclusion bias                                             | Detection bias                                        |                                                 | Selective reporting bias             |                   |
|                                                      | Was administered dose or exposure level adequately randomized? | Was the allocation to study groups adequately concealed? | 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? |                   |
| <b>Outcome: respiratory effects (inhalation)</b>     |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| <i>Inhalation acute-duration exposure</i>            |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Kusaka et al. 1986a                                  | –                                                              | –                                                        | –                                                                        | +                                                                        | –                                                     | +                                               | +                                    | Second            |
| <b>Outcome: gastrointestinal effects (oral only)</b> |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| <i>Oral acute-duration exposure</i>                  |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Paley et al. 1958                                    | –                                                              | –                                                        | –                                                                        | +                                                                        | +                                                     | –                                               | –                                    | Third             |
| <i>Oral intermediate-duration exposure</i>           |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Duckham and Lee 1976                                 | –                                                              | –                                                        | –                                                                        | –                                                                        | +                                                     | –                                               | –                                    | Third             |
| Holly 1955                                           | –                                                              | –                                                        | –                                                                        | +                                                                        | –                                                     | –                                               | –                                    | Third             |
| Paley et al. 1958                                    | –                                                              | –                                                        | –                                                                        | +                                                                        | +                                                     | –                                               | –                                    | Third             |
| <b>Outcome: hematological effects (oral only)</b>    |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| <i>Oral acute-duration exposure</i>                  |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Davis and Fields 1958                                | –                                                              | +                                                        | +                                                                        | +                                                                        | +                                                     | –                                               | +                                    | Second            |
| Hoffmeister et al. 2018                              | –                                                              | ++                                                       | ++                                                                       | ++                                                                       | ++                                                    | +                                               | ++                                   | First             |
| <i>Oral intermediate-duration exposure</i>           |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Davis and Fields 1958                                | –                                                              | +                                                        | +                                                                        | +                                                                        | +                                                     | –                                               | +                                    | Second            |
| Duckham and Lee 1976                                 | –                                                              | +                                                        | +                                                                        | +                                                                        | –                                                     | –                                               | +                                    | Second            |
| Finley et al. 2013                                   | –                                                              | +                                                        | +                                                                        | +                                                                        | +                                                     | –                                               | +                                    | Second            |

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**Table C-9. Summary of Risk of Bias Assessment for Cobalt—Human-Controlled Exposure Studies**

| Reference                                   | Risk of bias criteria and ratings                              |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      | Risk of bias tier |
|---------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|                                             | Selection bias                                                 |                                                          | Performance bias                                                         | Attrition/<br>exclusion bias                                             | Detection bias                                        |                                                 | Selective reporting bias             |                   |
|                                             | Was administered dose or exposure level adequately randomized? | Was the allocation to study groups adequately concealed? | 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? |                   |
| Hoffmeister et al. 2018                     | -                                                              | ++                                                       | ++                                                                       | ++                                                                       | ++                                                    | +                                               | ++                                   | First             |
| Holly 1955                                  | -                                                              | +                                                        | +                                                                        | +                                                                        | -                                                     | -                                               | +                                    | Second            |
| Taylor et al. 1977                          | -                                                              | +                                                        | +                                                                        | +                                                                        | -                                                     | -                                               | -                                    | Second            |
| Tvermoes et al. 2014                        | -                                                              | +                                                        | +                                                                        | +                                                                        | +                                                     | -                                               | +                                    | Second            |
| <b>Outcome: thyroid effects (oral only)</b> |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| <i>Oral acute-duration exposure</i>         |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Roche and Layrisse 1956                     | -                                                              | +                                                        | +                                                                        | +                                                                        | +                                                     | -                                               | +                                    | Second            |
| Paley et al. 1958                           | -                                                              | +                                                        | +                                                                        | -                                                                        | +                                                     | -                                               | -                                    | Third             |
| <i>Oral intermediate-duration exposure</i>  |                                                                |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Duckham and Lee 1976                        | -                                                              | +                                                        | +                                                                        | -                                                                        | +                                                     | -                                               | -                                    | Second            |
| Finley et al. 2013                          | -                                                              | +                                                        | +                                                                        | +                                                                        | +                                                     | -                                               | +                                    | Second            |
| Gross et al. 1955                           | -                                                              | -                                                        | -                                                                        | +                                                                        | +                                                     | +                                               | -                                    | Second            |
| Holly 1955                                  | -                                                              | +                                                        | +                                                                        | +                                                                        | -                                                     | -                                               | -                                    | Second            |
| Kriss et al. 1955                           | -                                                              | -                                                        | -                                                                        | +                                                                        | +                                                     | +                                               | -                                    | Second            |

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**Table C-9. Summary of Risk of Bias Assessment for Cobalt—Human-Controlled Exposure Studies**

| Reference            | Risk of bias criteria and ratings                              |                                                          |                                                                          |                                                                          |                                                       |                                                 |                                      | Risk of bias tier |
|----------------------|----------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|                      | Selection bias                                                 |                                                          | Performance bias                                                         | Attrition/<br>exclusion bias                                             | Detection bias                                        |                                                 | Selective reporting bias             |                   |
|                      | Was administered dose or exposure level adequately randomized? | Was the allocation to study groups adequately concealed? | 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? |                   |
| Paley et al. 1958    | -                                                              | +                                                        | +                                                                        | -                                                                        | +                                                     | -                                               | -                                    | Third             |
| Tvermoes et al. 2014 | -                                                              | +                                                        | +                                                                        | +                                                                        | +                                                     | -                                               | +                                    | Second            |

++ = definitely low risk of bias; + = probably low risk of bias; - = probably high risk of bias; -- = definitely high risk of bias

\*Key question used to assign risk of bias tier

## APPENDIX C

**Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies**

| Reference                                             | Risk of bias criteria and ratings                              |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      | Risk of bias tier |
|-------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|                                                       | Selection bias                                                 |                                                          | Performance bias                                            |                                                                          | Attrition/<br>exclusion<br>bias                                          | Detection bias                                        |                                                 | Selective<br>reporting<br>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? |                   |
| <b>Outcome: respiratory effects (inhalation only)</b> |                                                                |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| <i>Inhalation acute-duration exposure</i>             |                                                                |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Burzlauff et al. 2022a (rat)                          | ++                                                             | +                                                        | ++                                                          | +                                                                        | ++                                                                       | ++                                                    | +                                               | ++                                   | First             |
| Palmes et al. 1959 (rat)                              | –                                                              | +                                                        | +                                                           | –                                                                        | +                                                                        | –                                                     | –                                               | +                                    | Second            |
| Viegas et al. 2022a, 2022b (rat)                      | +                                                              | +                                                        | +                                                           | +                                                                        | +                                                                        | –                                                     | –                                               | +                                    | Second            |
| <i>Inhalation intermediate-duration exposure</i>      |                                                                |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Kerfoot 1974 (mini pig)                               | –                                                              | +                                                        | ++                                                          | –                                                                        | ++                                                                       | –                                                     | +                                               | +                                    | First             |
| Johansson et al. 1987 (rabbit)                        | –                                                              | +                                                        | ++                                                          | –                                                                        | ++                                                                       | –                                                     | +                                               | +                                    | First             |
| Johansson et al. 1991 (rabbit)                        | –                                                              | +                                                        | ++                                                          | –                                                                        | ++                                                                       | –                                                     | +                                               | +                                    | First             |
| Johansson et al. 1992 (rabbit)                        | –                                                              | +                                                        | ++                                                          | –                                                                        | ++                                                                       | –                                                     | +                                               | +                                    | First             |
| Burzlauff et al. 2022a, 2022b (rat)                   | ++                                                             | +                                                        | ++                                                          | +                                                                        | ++                                                                       | ++                                                    | +                                               | ++                                   | First             |

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**Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies**

| Reference                                                   | Risk of bias criteria and ratings                              |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      | Risk of bias tier |
|-------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|                                                             | Selection bias                                                 |                                                          | Performance bias                                            |                                                                          | Attrition/<br>exclusion<br>bias                                          | Detection bias                                        |                                                 | Selective<br>reporting<br>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? |                   |
| NTP 2014 (rat, mouse)                                       | +                                                              | +                                                        | ++                                                          | +                                                                        | ++                                                                       | ++                                                    | +                                               | ++                                   | First             |
| Bucher et al. 1990; NTP 1991 (rat, mouse)                   | +                                                              | +                                                        | ++                                                          | +                                                                        | ++                                                                       | ++                                                    | +                                               | ++                                   | First             |
| Palmes et al. 1959 (rat, guinea pig)                        | –                                                              | +                                                        | +                                                           | –                                                                        | +                                                                        | –                                                     | –                                               | +                                    | Second            |
| <i>Inhalation chronic-duration exposure</i>                 |                                                                |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Behl et al. 2015; NTP 2014 (rat, mouse)                     | +                                                              | +                                                        | ++                                                          | +                                                                        | +                                                                        | ++                                                    | +                                               | ++                                   | First             |
| Behl et al. 2015; Bucher et al. 1999; NTP 1998 (rat, mouse) | +                                                              | +                                                        | ++                                                          | +                                                                        | ++                                                                       | ++                                                    | +                                               | ++                                   | First             |
| Wehner et al. 1977 (hamster)                                | +                                                              | +                                                        | ++                                                          | –                                                                        | ++                                                                       | –                                                     | +                                               | ++                                   | First             |

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**Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies**

| Reference                                            | Risk of bias criteria and ratings                                    |                                                             |                                                                |                                                                                |                                                                                |                                                          |                                                    |                                         | Risk of bias tier |
|------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------|-----------------------------------------|-------------------|
|                                                      | Selection bias                                                       |                                                             | Performance bias                                               |                                                                                | Attrition/<br>exclusion<br>bias                                                | Detection bias                                           |                                                    | Selective<br>reporting<br>bias          |                   |
|                                                      | Was administered dose or<br>exposure level adequately<br>randomized? | Was the allocation to study<br>groups adequately concealed? | Were experimental conditions<br>identical across study groups? | Were the research personnel<br>blinded to the study group during<br>the study? | Were outcome data complete<br>without attrition or exclusion from<br>analysis? | Is there confidence in the<br>exposure characterization? | Is there confidence in the<br>outcome assessment?* | Were all measured outcomes<br>reported? |                   |
| <b>Outcome: gastrointestinal effects (oral only)</b> |                                                                      |                                                             |                                                                |                                                                                |                                                                                |                                                          |                                                    |                                         |                   |
| <i>Oral acute-duration exposure</i>                  |                                                                      |                                                             |                                                                |                                                                                |                                                                                |                                                          |                                                    |                                         |                   |
| Akinrinde et al.<br>2016c (rat)                      | -                                                                    | +                                                           | -                                                              | +                                                                              | -                                                                              | -                                                        | +                                                  | -                                       | Second            |
| Richardson et al.<br>2018 (rat)                      | -                                                                    | +                                                           | +                                                              | +                                                                              | +                                                                              | -                                                        | -                                                  | +                                       | Second            |
| Salami et al. 2023<br>(rat)                          | -                                                                    | +                                                           | +                                                              | +                                                                              | -                                                                              | -                                                        | +                                                  | +                                       | Second            |
| <i>Oral intermediate-duration exposure</i>           |                                                                      |                                                             |                                                                |                                                                                |                                                                                |                                                          |                                                    |                                         |                   |
| Danzeisen et al.<br>2020a (rat)                      | +                                                                    | +                                                           | ++                                                             | +                                                                              | +                                                                              | ++                                                       | ++                                                 | -                                       | First             |
| Domingo et al.<br>1984                               | -                                                                    | +                                                           | -                                                              | +                                                                              | -                                                                              | -                                                        | +                                                  | -                                       | Second            |
| Holly 1955                                           | -                                                                    | +                                                           | -                                                              | +                                                                              | -                                                                              | -                                                        | +                                                  | -                                       | Second            |



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**Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies**

| Reference | Risk of bias criteria and ratings                                                                                              |                                                                                                                                             |                                                                          |                                                                                                              |                                      | Risk of bias tier |
|-----------|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------|-------------------|
|           | Selection bias                                                                                                                 | Performance bias                                                                                                                            | Attrition/<br>exclusion<br>bias                                          | Detection bias                                                                                               | Selective<br>reporting<br>bias       |                   |
|           | Was administered dose or exposure level adequately randomized?<br><br>Was the allocation to study groups adequately concealed? | Were experimental conditions identical across study groups?<br><br>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?<br><br>Is there confidence in the outcome assessment?* | Were all measured outcomes reported? |                   |

**Outcome: hematological effects (oral only)***Oral acute-duration exposure*

|                                  |   |   |    |   |   |   |   |    |       |
|----------------------------------|---|---|----|---|---|---|---|----|-------|
| Shrivastava et al. 2008 (rat)    | + | + | ++ | + | + | + | + | ++ | First |
| Shrivastava et al. 2010 (rat)    | + | + | ++ | + | + | + | + | ++ | First |
| Domingo and Llobet 1984 (rat)    | – | + | ++ | + | + | + | + | +  | First |
| Paternain and Domingo 1988 (rat) | – | + | +  | + | – | + | + | +  | First |

*Oral intermediate-duration exposure*

|                              |   |   |    |   |   |    |   |    |        |
|------------------------------|---|---|----|---|---|----|---|----|--------|
| Chetty et al. 1979 (rat)     | – | + | +  | + | + | –  | + | ++ | First  |
| Corrier et al. 1985 (rat)    | + | + | +  | + | – | –  | + | ++ | First  |
| Domingo et al. 1984 (rat)    | – | + | ++ | + | – | –  | – | ++ | Second |
| Danzeisen et al. 2020a (rat) | + | + | ++ | + | + | ++ | + | ++ | First  |

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**Table C-10. Summary of Risk of Bias Assessment for Cobalt—Experimental Animal Studies**

| Reference                                   | Risk of bias criteria and ratings                              |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      | Risk of bias tier |
|---------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|--------------------------------------|-------------------|
|                                             | Selection bias                                                 |                                                          | Performance bias                                            |                                                                          | Attrition/<br>exclusion<br>bias                                          | Detection bias                                        |                                                 | Selective<br>reporting<br>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? |                   |
| Holly 1955 (rat)                            | -                                                              | +                                                        | -                                                           | +                                                                        | -                                                                        | -                                                     | +                                               | -                                    | Second            |
| Krasovskii and Fridlyand 1971 (rat)         | -                                                              | +                                                        | -                                                           | +                                                                        | -                                                                        | -                                                     | -                                               | -                                    | Third             |
| Murdock 1959 (rat)                          | -                                                              | +                                                        | -                                                           | +                                                                        | -                                                                        | -                                                     | +                                               | +                                    | Second            |
| Pedigo et al. 1988 (mouse)                  | -                                                              | +                                                        | +                                                           | +                                                                        | +                                                                        | -                                                     | +                                               | +                                    | First             |
| Stanley et al. 1947 (rat)                   | -                                                              | +                                                        | -                                                           | +                                                                        | +                                                                        | -                                                     | +                                               | +                                    | First             |
| <b>Outcome: thyroid effects (oral only)</b> |                                                                |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| <i>Oral intermediate-duration exposure</i>  |                                                                |                                                          |                                                             |                                                                          |                                                                          |                                                       |                                                 |                                      |                   |
| Danzeisen et al. 2020a (rat)                | +                                                              | +                                                        | ++                                                          | +                                                                        | +                                                                        | ++                                                    | +                                               | -                                    | First             |
| Holly 1955                                  | -                                                              | +                                                        | -                                                           | +                                                                        | -                                                                        | -                                                     | +                                               | -                                    | Second            |
| Shrivastava et al. 1996                     | -                                                              | +                                                        | +                                                           | +                                                                        | -                                                                        | -                                                     | +                                               | -                                    | First             |

++ = definitely low risk of bias; + = probably low risk of bias; - = probably high risk of bias; - = definitely high risk of bias

\*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 HHS, 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, 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 Tables C-11, C-12, and C-13, 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".

## APPENDIX C

**Table C-11. Key Features of Study Design for Observational Epidemiology Studies**

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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

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**Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies**

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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

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**Table C-13. Key Features of Study Design for Experimental Animal Studies**

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A concurrent control group was used  
A sufficient number of animals per group were tested  
Appropriate parameters were 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 studies examining respiratory effects from inhalation studies and hematological, gastrointestinal, and thyroid effects observed in the observational epidemiology, controlled-exposure human studies, and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

## APPENDIX C

**Table C-14. Presence of Key Features of Study Design for Cobalt—  
Observational Epidemiology Studies**

| Reference                                             | Key features        |                           |                                          |                  | Initial study confidence |
|-------------------------------------------------------|---------------------|---------------------------|------------------------------------------|------------------|--------------------------|
|                                                       | Controlled exposure | Exposure prior to outcome | Outcomes assessed on an individual level | Comparison group |                          |
| <b>Outcome: Respiratory effects (inhalation only)</b> |                     |                           |                                          |                  |                          |
| <i>Cohort studies</i>                                 |                     |                           |                                          |                  |                          |
| Al-Abcha et al. 2021                                  | No                  | Yes                       | Yes                                      | Yes              | Moderate                 |
| Andersson et al. 2020                                 | No                  | Yes                       | Yes                                      | Yes              | Moderate                 |
| Linna et al. 2003                                     | No                  | Yes                       | Yes                                      | Yes              | Moderate                 |
| Gennart and Lauwerys 1990                             | No                  | Yes                       | No                                       | Yes              | Low                      |
| Kusaka et al. 1986a                                   | No                  | Yes                       | Yes                                      | Yes              | Moderate                 |
| Kusaka et al. 1986b                                   | No                  | Yes                       | Yes                                      | Yes              | Moderate                 |
| Rehfishch et al. 2012                                 | No                  | Yes                       | Yes                                      | Yes              | Moderate                 |
| Verougstraete et al. 2004                             | No                  | Yes                       | Yes                                      | Yes              | Moderate                 |
| <i>Case-control</i>                                   |                     |                           |                                          |                  |                          |
| Roto 1980                                             | No                  | No                        | Yes                                      | Yes              | Low                      |
| <i>Case series</i>                                    |                     |                           |                                          |                  |                          |
| Al-Abcha et al. 2021                                  | No                  | Yes                       | Yes                                      | No               | Low                      |
| Demedts et al. 1984                                   | No                  | Yes                       | Yes                                      | No               | Low                      |
| Sauni et al. 2010                                     | No                  | Yes                       | Yes                                      | No               | Low                      |
| Walters et al. 2014                                   | No                  | Yes                       | Yes                                      | No               | Low                      |
| <i>Cross-sectional studies</i>                        |                     |                           |                                          |                  |                          |
| Walters et al. 2012                                   | No                  | No                        | Yes                                      | Yes              | Low                      |
| Hamzah et al. 2014                                    | No                  | No                        | Yes                                      | Yes              | Low                      |
| Meyer-Bisch et al. 1989                               | No                  | No                        | Yes                                      | Yes              | Low                      |
| Roto 1980                                             | No                  | No                        | Yes                                      | Yes              | Low                      |
| Swennen et al. 1993                                   | No                  | No                        | Yes                                      | Yes              | Low                      |
| Nemery et al. 1992                                    | No                  | No                        | Yes                                      | Yes              | Low                      |
| Deng et al. 1991                                      | No                  | No                        | Yes                                      | Yes              | Low                      |
| <b>Outcome: Thyroid effects (oral only)</b>           |                     |                           |                                          |                  |                          |
| <i>Case series</i>                                    |                     |                           |                                          |                  |                          |
| Chamberlain 1961                                      | No                  | Yes                       | Yes                                      | No               | Low                      |
| Little and Sunico 1958                                | No                  | Yes                       | Yes                                      | No               | Low                      |
| Washburn and Kaplan 1964                              | No                  | Yes                       | Yes                                      | No               | Low                      |

## APPENDIX C

**Table C-15. Presence of Key Features of Study Design for Cobalt—Human-Controlled Exposure Studies**

| Reference                                             | Key features             |                               |                                                   |                                        | Initial study confidence |
|-------------------------------------------------------|--------------------------|-------------------------------|---------------------------------------------------|----------------------------------------|--------------------------|
|                                                       | Concurrent control group | Sufficient number of subjects | Appropriate parameters to assess potential effect | Adequate data for statistical analysis |                          |
| <b>Outcome: Respiratory effects (inhalation only)</b> |                          |                               |                                                   |                                        |                          |
| <i>Inhalation acute-duration exposure</i>             |                          |                               |                                                   |                                        |                          |
| Kusaka et al. 1986a                                   | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| <b>Outcome: Gastrointestinal effects (oral only)</b>  |                          |                               |                                                   |                                        |                          |
| <i>Oral acute-duration exposure</i>                   |                          |                               |                                                   |                                        |                          |
| Paley et al. 1958                                     | Yes                      | No                            | No                                                | No                                     | Very Low                 |
| <i>Oral intermediate-duration exposure</i>            |                          |                               |                                                   |                                        |                          |
| Duckham and Lee 1976                                  | Yes                      | No                            | No                                                | No                                     | Very Low                 |
| Holly 1955                                            | Yes                      | No                            | No                                                | No                                     | Very Low                 |
| Paley et al. 1958                                     | Yes                      | No                            | No                                                | No                                     | Very Low                 |
| <b>Outcome: Hematological effects (oral only)</b>     |                          |                               |                                                   |                                        |                          |
| <i>Oral acute-duration exposure</i>                   |                          |                               |                                                   |                                        |                          |
| Davis and Fields 1958                                 | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| Hoffmeister et al. 2018                               | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| <i>Oral intermediate-duration exposure</i>            |                          |                               |                                                   |                                        |                          |
| Davis and Fields 1958                                 | Yes                      | No                            | Yes                                               | No                                     | Low                      |
| Duckham and Lee 1976                                  | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| Finley et al. 2013                                    | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| Hoffmeister et al. 2018                               | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| Holly 1955                                            | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| Taylor et al. 1977                                    | Yes                      | No                            | No                                                | Yes                                    | Low                      |
| Tvermoes et al. 2014                                  | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| <b>Outcome: Thyroid effects (oral only)</b>           |                          |                               |                                                   |                                        |                          |
| <i>Oral acute-duration exposure</i>                   |                          |                               |                                                   |                                        |                          |
| Roche and Layrisse 1956                               | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| Paley et al. 1958                                     | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| <i>Oral intermediate-duration exposure</i>            |                          |                               |                                                   |                                        |                          |
| Duckham and Lee 1976                                  | Yes                      | No                            | Yes                                               | No                                     | Low                      |
| Finley et al. 2013                                    | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |
| Gross et al. 1955                                     | Yes                      | No                            | Yes                                               | No                                     | Low                      |
| Holly 1955                                            | Yes                      | No                            | No                                                | No                                     | Very Low                 |
| Kriss et al. 1955                                     | Yes                      | No                            | Yes                                               | No                                     | Low                      |
| Paley et al. 1958                                     | Yes                      | No                            | Yes                                               | No                                     | Low                      |
| Tvermoes et al. 2014                                  | Yes                      | No                            | Yes                                               | Yes                                    | Moderate                 |

**Table C-16. Presence of Key Features of Study Design for Cobalt—Experimental Animal Studies**

| Reference                                                   | Key feature              |                                        |                                                   |                                        | Initial study confidence |
|-------------------------------------------------------------|--------------------------|----------------------------------------|---------------------------------------------------|----------------------------------------|--------------------------|
|                                                             | Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis |                          |
| <b>Outcome: Respiratory effects (inhalation only)</b>       |                          |                                        |                                                   |                                        |                          |
| <i>Inhalation acute-duration exposure</i>                   |                          |                                        |                                                   |                                        |                          |
| Burzlauff et al. 2022a (rat)                                | Yes                      | Yes                                    | Yes                                               | No                                     | Moderate                 |
| Palmes et al. 1959 (rat)                                    | Yes                      | Yes                                    | No                                                | No                                     | Low                      |
| Viegas et al. 2022a, 2022b (rat)                            | Yes                      | Yes                                    | Yes                                               | No                                     | Moderate                 |
| <i>Inhalation intermediate-duration exposure</i>            |                          |                                        |                                                   |                                        |                          |
| Kerfoot 1974 (mini pig)                                     | Yes                      | No                                     | Yes                                               | Yes                                    | Moderate                 |
| Johansson et al. 1987 (rabbit)                              | Yes                      | No                                     | Yes                                               | Yes                                    | Moderate                 |
| Johansson et al. 1991 (rabbit)                              | Yes                      | No                                     | Yes                                               | Yes                                    | Moderate                 |
| Johansson et al. 1992 (rabbit)                              | Yes                      | No                                     | Yes                                               | Yes                                    | Moderate                 |
| Burzlauff et al. 2022a, 2022b (rat)                         | Yes                      | Yes                                    | Yes                                               | No                                     | Moderate                 |
| NTP 2014 (rat, mouse)                                       | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Bucher et al. 1990; NTP 1991 (rat, mouse)                   | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Palmes et al. 1959 (rat, guinea pig)                        | Yes                      | Yes                                    | Yes                                               | No                                     | Moderate                 |
| <i>Inhalation chronic-duration exposure</i>                 |                          |                                        |                                                   |                                        |                          |
| Behl et al. 2015; NTP 2014 (rat, mouse)                     | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Behl et al. 2015; Bucher et al. 1999; NTP 1998 (rat, mouse) | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Wehner et al. 1977 (hamster)                                | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| <b>Outcome: Gastrointestinal effects (oral only)</b>        |                          |                                        |                                                   |                                        |                          |
| <i>Oral acute-duration exposure</i>                         |                          |                                        |                                                   |                                        |                          |
| Akinrinde et al. 2016c                                      | No                       | Yes                                    | Yes                                               | No                                     | Low                      |
| Richardson et al. 2018 (rat)                                | Yes                      | Yes                                    | No                                                | Yes                                    | Moderate                 |
| Salami et al. 2023                                          | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| <i>Oral intermediate-duration exposure</i>                  |                          |                                        |                                                   |                                        |                          |
| Danzeisen et al. 2020a                                      | Yes                      | Yes                                    | Yes                                               | No                                     | Moderate                 |
| Domingo et al. 1984                                         | Yes                      | No                                     | Yes                                               | No                                     | Low                      |
| Holly 1955                                                  | No                       | Yes                                    | Yes                                               | No                                     | Low                      |

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**Table C-16. Presence of Key Features of Study Design for Cobalt—Experimental Animal Studies**

| Reference                                         | Key feature              |                                        |                                                   |                                        | Initial study confidence |
|---------------------------------------------------|--------------------------|----------------------------------------|---------------------------------------------------|----------------------------------------|--------------------------|
|                                                   | Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis |                          |
| <b>Outcome: Hematological effects (oral only)</b> |                          |                                        |                                                   |                                        |                          |
| <i>Oral acute-duration exposure</i>               |                          |                                        |                                                   |                                        |                          |
| Shrivastava et al. 2008 (rat)                     | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Shrivastava et al. 2010 (rat)                     | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Domingo and Llobet 1984 (rat)                     | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Paternain and Domingo 1988 (rat)                  | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| <i>Oral intermediate-duration exposure</i>        |                          |                                        |                                                   |                                        |                          |
| Chetty et al. 1979 (rat)                          | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Corrier et al. 1985 (rat)                         | Yes                      | No                                     | Yes                                               | Yes                                    | Moderate                 |
| Domingo et al. 1984 (rat)                         | Yes                      | No                                     | Yes                                               | Yes                                    | Moderate                 |
| Danzeisen et al. 2020a (rat)                      | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Holly 1955 (rat)                                  | Yes                      | No                                     | Yes                                               | No                                     | Low                      |
| Krasovskii and Fridlyand 1971 (rat)               | Yes                      | No                                     | Yes                                               | No                                     | Low                      |
| Murdock 1959 (rat)                                | Yes                      | No                                     | Yes                                               | No                                     | Low                      |
| Pedigo et al. 1988 (mouse)                        | Yes                      | Yes                                    | Yes                                               | Yes                                    | High                     |
| Stanley et al. 1947 (rat)                         | Yes                      | No                                     | Yes                                               | No                                     | Low                      |
| <b>Outcome: Thyroid effects (oral only)</b>       |                          |                                        |                                                   |                                        |                          |
| <i>Oral intermediate-duration exposure</i>        |                          |                                        |                                                   |                                        |                          |
| Danzeisen et al. 2020a                            | Yes                      | Yes                                    | Yes                                               | No                                     | Moderate                 |
| Holly 1955                                        | No                       | Yes                                    | Yes                                               | No                                     | Low                      |
| Shrivastava et al. 1996                           | Yes                      | Yes                                    | Yes                                               | No                                     | Moderate                 |

A summary of the initial confidence ratings for each outcome is presented in Table C-17. 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; any exceptions were noted in Table C-17.



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**Table C-17. Initial Confidence Rating for Cobalt Health Effects Studies**

|                                                             | Initial study confidence | Initial confidence rating |
|-------------------------------------------------------------|--------------------------|---------------------------|
| <b>Outcome: Respiratory effects (inhalation only)</b>       |                          |                           |
| <i>Inhalation acute-duration exposure</i>                   |                          |                           |
| Animal studies                                              |                          |                           |
| Burzlauff et al. 2022a (rat)                                | Moderate                 | Moderate                  |
| Palmes et al. 1959 (rat)                                    | Low                      |                           |
| Viegas et al. 2022a, 2022b (rat)                            | Moderate                 |                           |
| Human studies                                               |                          |                           |
| Kusaka et al. 1986a                                         | Moderate                 | Moderate                  |
| <i>Inhalation intermediate-duration exposure</i>            |                          |                           |
| Animal studies                                              |                          |                           |
| Kerfoot 1974 (mini pig)                                     | Moderate                 | High                      |
| Johansson et al. 1987 (rabbit)                              | Moderate                 |                           |
| Johansson et al. 1991 (rabbit)                              | Moderate                 |                           |
| Johansson et al. 1992 (rabbit)                              | Moderate                 |                           |
| Burzlauff et al. 2022a, 2022b (rat)                         | Moderate                 |                           |
| NTP 2014 (rat, mouse)                                       | High                     |                           |
| Bucher et al. 1990; NTP 1991 (rat, mouse)                   | High                     |                           |
| Palmes et al. 1959 (rat, guinea pig)                        | Moderate                 |                           |
| <i>Inhalation chronic-duration exposure</i>                 |                          |                           |
| Animal studies                                              |                          |                           |
| Behl et al. 2015; NTP 2014 (rat, mouse)                     | High                     | High                      |
| Behl et al. 2015; Bucher et al. 1999; NTP 1998 (rat, mouse) | High                     |                           |
| Wehner et al. 1977 (hamster)                                | High                     |                           |
| Human studies                                               |                          |                           |
| Al-Abcha et al. 2021 (cohort)                               | Moderate                 | Moderate                  |
| Al-Abcha et al. 2021 (case-series)                          | Low                      |                           |
| Andersson et al. 2020                                       | Moderate                 |                           |
| Linna et al. 2003                                           | Moderate                 |                           |
| Deng et al. 1991                                            | Low                      |                           |
| Gennart and Lauwerys 1990                                   | Low                      |                           |
| Kusaka et al. 1986a                                         | Moderate                 |                           |
| Kusaka et al. 1986b                                         | Moderate                 |                           |
| Rehfishch et al. 2012                                       | Moderate                 |                           |
| Verougstraete et al. 2004                                   | Moderate                 |                           |
| Roto 1980 (case-control)                                    | Low                      |                           |
| Demedts et al. 1984                                         | Low                      |                           |
| Sauni et al. 2010                                           | Low                      |                           |
| Walters et al. 2012                                         | Low                      |                           |
| Walters et al. 2014                                         | Low                      |                           |

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**Table C-17. Initial Confidence Rating for Cobalt Health Effects Studies**

|                                                      | Initial study confidence | Initial confidence rating |
|------------------------------------------------------|--------------------------|---------------------------|
| Hamzah et al. 2014                                   | Low                      |                           |
| Meyer-Bisch et al. 1989                              | Low                      |                           |
| Roto 1980 (cross-sectional)                          | Low                      |                           |
| Swennen et al. 1993                                  | Low                      |                           |
| Nemery et al. 1992                                   | Low                      |                           |
| <b>Outcome: Gastrointestinal effects (oral only)</b> |                          |                           |
| <i>Oral acute-duration exposure</i>                  |                          |                           |
| Animal studies                                       |                          |                           |
| Akinrinde et al. 2016c                               | Low                      | High                      |
| Richardson et al. 2018 (rat)                         | Moderate                 |                           |
| Salami et al. 2023                                   | High                     |                           |
| Human studies                                        |                          |                           |
| Paley et al. 1958                                    | Very Low                 | Very Low                  |
| <i>Oral intermediate-duration exposure</i>           |                          |                           |
| Animal studies                                       |                          |                           |
| Danzeisen et al. 2020a                               | Moderate                 | Moderate                  |
| Domingo et al. 1984                                  | Low                      |                           |
| Holly 1955                                           | Low                      |                           |
| Human studies                                        |                          |                           |
| Duckham and Lee 1976                                 | Very Low                 | Very Low                  |
| Holly 1955                                           | Very Low                 |                           |
| Paley et al. 1958                                    | Very Low                 |                           |
| <b>Outcome: Hematological effects (oral only)</b>    |                          |                           |
| <i>Oral acute-duration exposure</i>                  |                          |                           |
| Animal studies                                       |                          |                           |
| Shrivastava et al. 2008 (rat)                        | High                     | High                      |
| Shrivastava et al. 2010 (rat)                        | High                     |                           |
| Domingo and Llobet 1984 (rat)                        | High                     |                           |
| Paternain and Domingo 1988 (rat)                     | High                     |                           |
| Human studies                                        |                          |                           |
| Davis and Fields 1958                                | Moderate                 | Moderate                  |
| Hoffmeister et al. 2018                              | Moderate                 |                           |
| <i>Oral intermediate-duration exposure</i>           |                          |                           |
| Animal studies                                       |                          |                           |
| Chetty et al. 1979 (rat)                             | High                     |                           |
| Corrier et al. 1985 (rat)                            | Moderate                 |                           |
| Domingo et al. 1984 (rat)                            | High                     |                           |
| Danzeisen et al. 2020a (rat)                         | Moderate                 |                           |
| Holly 1955 (rat)                                     | Low                      |                           |
| Krasovskii and Fridlyand 1971 (rat)                  | Low                      |                           |

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**Table C-17. Initial Confidence Rating for Cobalt Health Effects Studies**

|                                             | Initial study confidence | Initial confidence rating |
|---------------------------------------------|--------------------------|---------------------------|
| Murdock 1959 (rat)                          | Low                      |                           |
| Pedigo et al. 1988 (mouse)                  | High                     |                           |
| Stanley et al. 1947 (rat)                   | Low                      |                           |
| Human studies                               |                          |                           |
| Davis and Fields 1958                       | Moderate                 | Moderate                  |
| Duckham and Lee 1976                        | Low                      |                           |
| Finley et al. 2013                          | Moderate                 |                           |
| Hoffmeister et al. 2018                     | Moderate                 |                           |
| Holly 1955                                  | Low                      |                           |
| Taylor et al. 1977                          | Low                      |                           |
| Tvermoes et al. 2014                        | Moderate                 |                           |
| <b>Outcome: Thyroid effects (oral only)</b> |                          |                           |
| <i>Oral acute-duration exposure</i>         |                          |                           |
| Human studies                               |                          |                           |
| Roche and Layrisse 1956                     | Moderate                 | Moderate                  |
| Paley et al. 1958                           | Moderate                 |                           |
| <i>Oral intermediate-duration exposure</i>  |                          |                           |
| Animal studies                              |                          |                           |
| Danzeisen et al. 2020a                      | Moderate                 | Moderate                  |
| Holly 1955                                  | Low                      |                           |
| Shrivastava et al. 1996                     | Moderate                 |                           |
| Human studies                               |                          |                           |
| Chamberlain 1961                            | Low                      | Moderate                  |
| Duckham and Lee 1976                        | Low                      |                           |
| Finley et al. 2013                          | Moderate                 |                           |
| Gross et al. 1955                           | Low                      |                           |
| Holly 1955                                  | Very Low                 |                           |
| Kriss et al. 1955                           | Low                      |                           |
| Little and Sunico 1958                      | Low                      |                           |
| Paley et al. 1958                           | Low                      |                           |
| Tvermoes et al. 2014                        | Moderate                 |                           |
| Washburn and Kaplan 1964                    | 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 effects following inhalation exposure and hematological, gastrointestinal, and thyroid effects following oral exposure are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then

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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-19.

**Table C-18. Adjustments to the Initial Confidence in the Body of Evidence**

|                                                       | Initial confidence | Adjustments to the initial confidence rating                            | Final confidence |
|-------------------------------------------------------|--------------------|-------------------------------------------------------------------------|------------------|
| <b>Outcome: Respiratory effects (inhalation only)</b> |                    |                                                                         |                  |
| Human studies                                         | Moderate           | +1 Consistency in body of evidence                                      | High             |
| Animal studies                                        | High               | +1 Consistency in body of evidence                                      | High             |
| <b>Outcome: Gastrointestinal effects (oral only)</b>  |                    |                                                                         |                  |
| Human studies                                         | Very low           | -2 Risk of bias                                                         | Very low         |
| Animal studies                                        | High               | -1 Risk of bias<br>-1 Unexplained inconsistency                         | Low              |
| <b>Outcome: Hematological effects (oral only)</b>     |                    |                                                                         |                  |
| Human studies                                         | Moderate           | -1 Risk of bias<br>+1 Consistency in body of evidence                   | Moderate         |
| Animal studies                                        | High               | -1 Risk of bias<br>+1 Consistency in body of evidence                   | High             |
| <b>Outcome: Thyroid effects (oral only)</b>           |                    |                                                                         |                  |
| Human studies                                         | Moderate           | -1 Risk of bias<br>-1 Imprecision<br>+1 Consistency in body of evidence | Low              |
| Animal studies                                        | Moderate           |                                                                         | Moderate         |

**Table C-19. Confidence in the Body of Evidence for Cobalt**

| Outcome                               | Confidence in body of evidence |                |
|---------------------------------------|--------------------------------|----------------|
|                                       | Human studies                  | Animal studies |
| Respiratory effects (inhalation only) | High                           | High           |
| Gastrointestinal effects (oral only)  | Very low                       | Low            |
| Hematological effects (oral only)     | Moderate                       | High           |
| Thyroid effects (oral only)           | Low                            | Moderate       |

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 (Tables C-5, C-6, and C-7). 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

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- **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  $\geq 10$  for tests of ratio measures (e.g., odds ratios) and  $\geq 100$  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

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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

## 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

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- **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-20.

**Table C-20. Level of Evidence of Health Effects for Cobalt**

| Outcome                          | Confidence in body of evidence | Direction of health effect | Level of evidence for health effect |
|----------------------------------|--------------------------------|----------------------------|-------------------------------------|
| <b>Human studies</b>             |                                |                            |                                     |
| Respiratory effects (inhalation) | High                           | Health effect              | High                                |
| Gastrointestinal effects (oral)  | Very low                       | Health effect              | Inadequate                          |
| Hematological effects (oral)     | Moderate                       | Health effect              | Moderate                            |
| Thyroid effects (oral)           | Low                            | Health effect              | Low                                 |
| <b>Animal studies</b>            |                                |                            |                                     |
| Respiratory effects (inhalation) | Moderate                       | Health effect              | Moderate                            |
| Gastrointestinal effects (oral)  | Low                            | Health effect              | Low                                 |
| Hematological effects (oral)     | High                           | Health effect              | High                                |
| Thyroid effects (oral)           | Moderate                       | Health effect              | Moderate                            |

## 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:

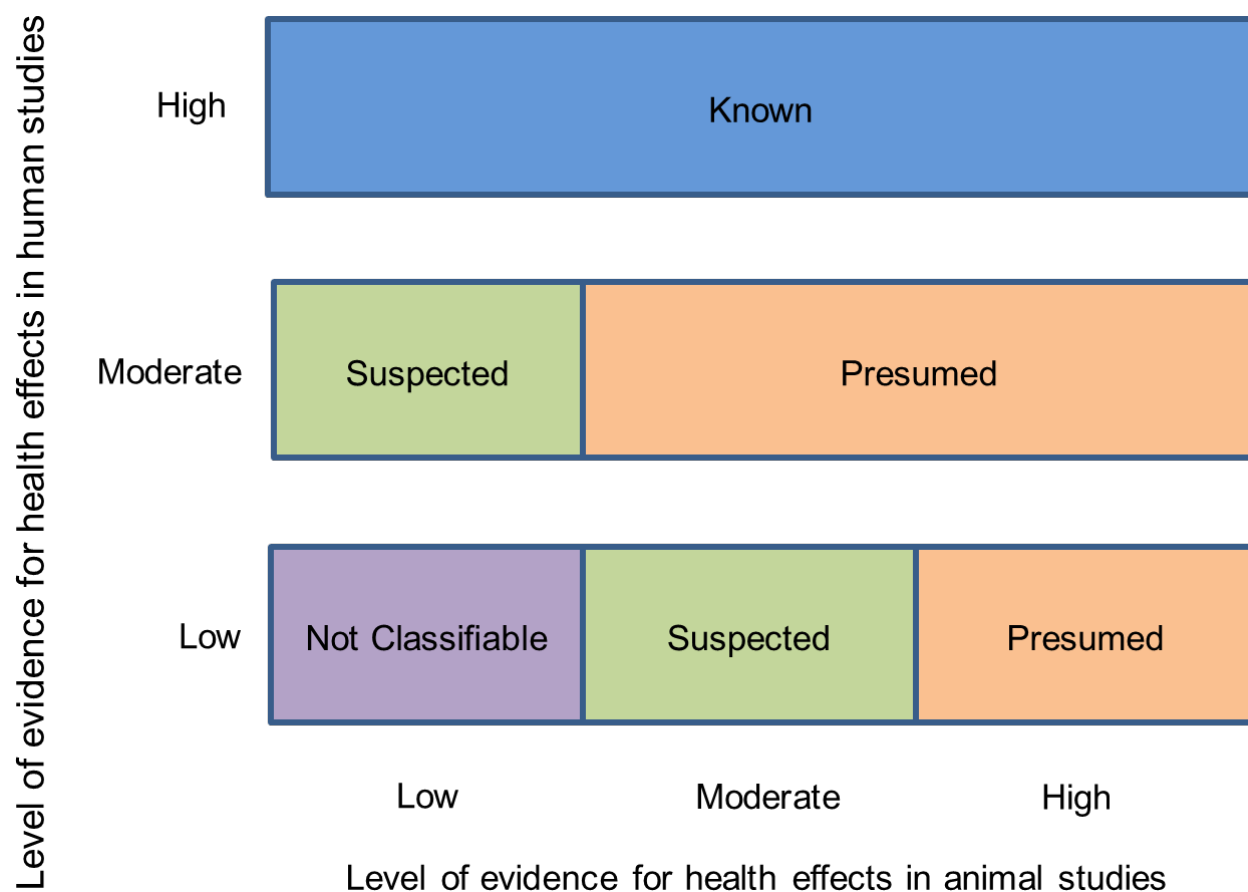
- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** 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

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- **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**
  - 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

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.

**Figure C-1. Hazard Identification Scheme**



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



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category of “inadequate” was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for cobalt are listed below and summarized in Table C-21.

**Known Health Effects**

- Respiratory effects following inhalation exposure
  - High level of evidence in epidemiological studies of humans occupationally exposed to cobalt by inhalation.
    - Exposed workers showed altered spirometry and increased evidence of pulmonary irritation and dyspnea (Gennart and Lauwerys 1990; Hamzah et al. 2014; Kusaka et al. 1986a; Linna et al. 2003; Meyer-Bisch et al. 1989; Nemery et al. 1992; Swennen et al. 1993; Verougstraete et al. 2004).
    - Some occupational studies reported increased risk of asthma in cobalt-exposed workers (Kusaka et al. 1986b; Linna et al. 2003; Roto 1980; Walters et al. 2012).
    - There is also limited evidence of impaired lung function after acute-duration inhalation exposure in humans (Kusaka et al. 1986a).
  - High level of evidence in studies of rodents exposed to cobalt and its compounds by inhalation.
    - Acute-duration exposure is associated with inflammatory responses at low concentrations (Burzlaff et al. 2022a; Viegas et al. 2022a) and severe lung damage at lethal concentrations (Palmes et al. 1959; Viegas et al. 2022a).
    - Widespread respiratory damage was consistently observed in rats and mice following intermittent intermediate- or chronic-duration inhalation exposure, with severity of lesions increasing in a dose- and duration-dependent manner (Burzlaff et al. 2022a; NTP 1991, 1998, 2014).
    - In other species, intermediate-duration inhalation exposure resulted in inflammatory changes in rabbit lungs (Johansson et al. 1987) and decreased respiratory compliance, a metric of mechanical ventilation, in pigs (Kerfoot 1974).
  - Based on high evidence from human and animal studies, respiratory effects following inhalation exposure to cobalt and cobalt compounds are classified as known health effects.

**Presumed Health Effects**

- Hematological effects following oral exposure
  - Moderate level of evidence in human studies that showed polycythemia after acute- and intermediate-duration oral exposure to cobalt in healthy individuals (Davis and Fields 1958). Cobalt supplementation has also been shown to elevate red blood cell count when given to anemic patients (Duckham and Lee 1976; Taylor et al. 1977).
  - High level of evidence in animal studies after oral exposure to cobalt and its compounds. Increased erythrocytes, hematocrit, and/or hemoglobin were observed in rats following acute-duration exposure (Domingo and Llobet 1984; Paternain and Domingo 1988; Shrivastava et al. 2008, 2010) and intermediate-duration oral exposure (Corrier et al. 1985; Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955; Murdock 1959; Stanley et al. 1947).
  - Mechanistic data indicate that cobalt can mimic hypoxic conditions via interference with HIF-1 $\alpha$ , which would stimulate erythropoiesis (Hoffmeister et al. 2018; Yuan et al. 2003).
  - Based on moderate level of evidence from human studies and high level of evidence from animal studies, with support from a plausible mechanism of action, an increase in erythrocytes is classified as a presumed health effect following oral exposure.

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**Suspected Health Effects**

- Thyroid effects following oral exposure
  - Low level evidence in human studies.
    - There is limited evidence from case reports of goiter or impaired thyroid function in some patients taking cobalt as a treatment for anemia associated with sickle-cell anemia, pregnancy, or chronic renal disease (Chamberlain 1961; Duckham and Lee 1976; Gross et al. 1955; Kriss et al. 1955; Little and Sunico 1958; Washburn and Kaplan 1964).
    - Transient impairments in thyroid function were observed following acute- or intermediate-duration oral exposure to cobalt in some controlled human studies (Paley et al. 1958; Roche and Layrisse 1956). Other studies at similar or lower doses showed no effects (Finley et al. 2013; Holly 1955; Tvermoes et al. 2014).
  - Data from animal studies are limited but provide a moderate level of evidence based on severity of histopathological changes in the thyroid of mice following intermediate-duration exposure to high cobalt doses (Shrivastava et al. 1996).
  - A proposed mechanism for thyroid effects is decreased iodine uptake resulting from cobalt blocking the organic binding of iodine (Paley et al. 1958).
  - Based on low level of evidence from human studies and moderate level of evidence from animal studies, with support from a plausible mechanism of action, impaired thyroid function is classified as a suspected health effect following oral exposure.

**Not Classifiable Effects**

- Gastrointestinal effects following oral exposure
  - Data in humans pertaining to gastrointestinal effects are considered inadequate. While reported at low administered doses, evidence is restricted to subjective reports of gastrointestinal intolerance in humans following oral exposure to cobalt as a potential treatment for anemia or hyperthyroidism (Duckham and Lee 1976; Holly 1955; Paley et al. 1958).
  - A low level of evidence in animals is provided by a studies reporting alterations to the structure of the walls of the small intestine and delays in gastric emptying time in rats following acute-duration exposure to cobalt (Akinrinde et al. 2016c; Salami et al. 2023). However, intermediate-duration studies did not report any damage to the gastrointestinal tract in rats following oral exposure to cobalt (Danzeisen et al. 2020a; Domingo et al. 1984; Holly 1955).
  - Based on inadequate data in humans and a low level of evidence from animals, gastrointestinal effects are not classifiable as toxic effects following oral exposure to cobalt.

**Table C-21. Hazard Identification Conclusions for Cobalt**

| Outcome                                   | Hazard identification |
|-------------------------------------------|-----------------------|
| Respiratory effects (inhalation exposure) | Known                 |
| Gastrointestinal effects (oral exposure)  | Not classifiable      |
| Hematological effects (oral exposure)     | Presumed              |
| Thyroid effects (oral exposure)           | Suspected             |

## 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

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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 ( $\geq 365$  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

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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), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), 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.

- (12) 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.

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- (13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.
- (14) 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<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (15) 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).
- (16) 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.
- (17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

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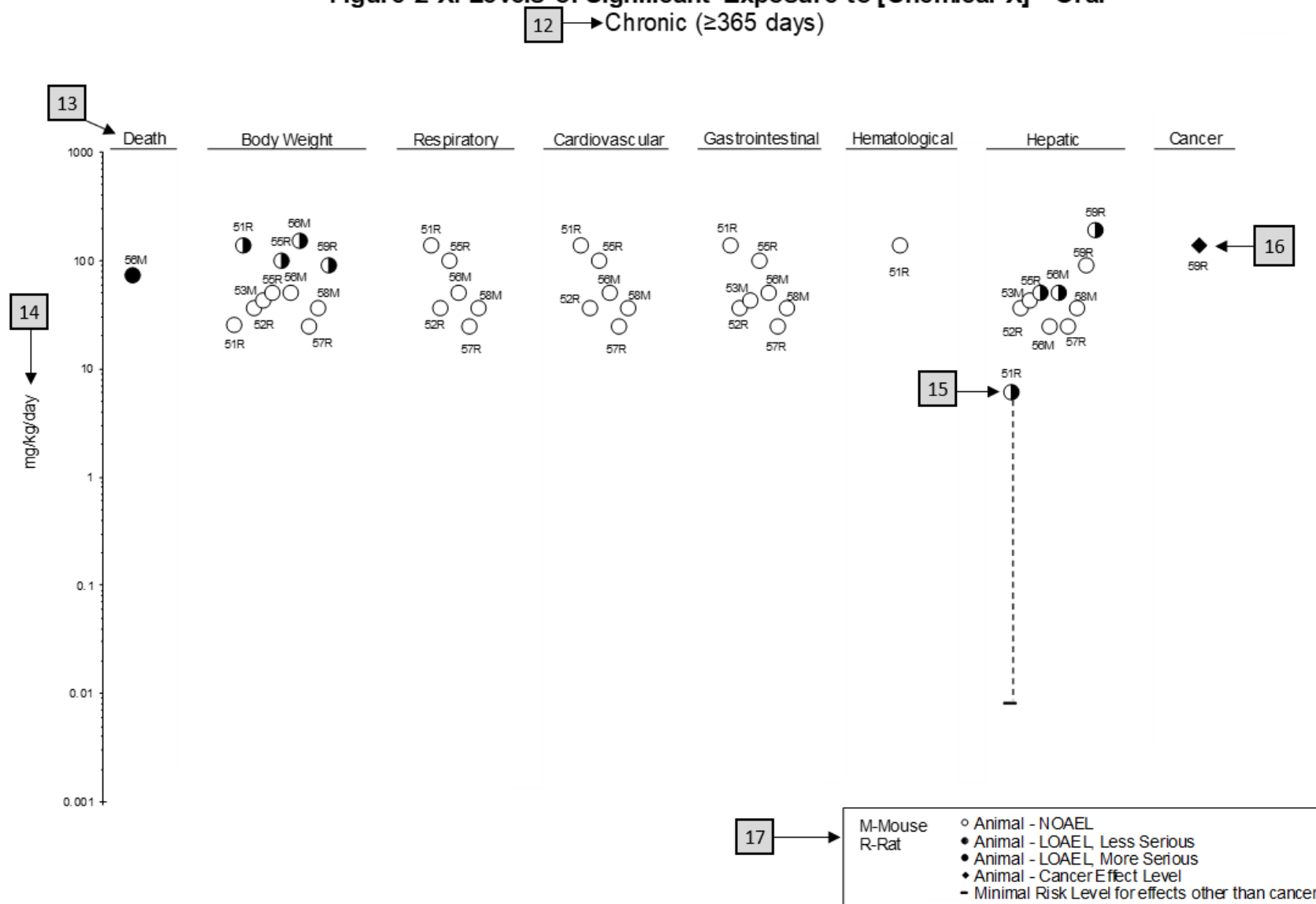
| Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral ← 1 |                                                          |                        |                                                        |                                  |                                |                      |                                         |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------|----------------------------------------------------------|------------------------|--------------------------------------------------------|----------------------------------|--------------------------------|----------------------|-----------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2                                                                    | 4                                                        | 5                      | 6                                                      | 7                                | 8                              | 9                    | Effect                                  |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                      | Species<br>Figure (strain)<br>key <sup>a</sup> No./group | Exposure<br>parameters | Doses<br>(mg/kg/day)                                   | Parameters<br>monitored          | Endpoint                       | NOAEL<br>(mg/kg/day) | Less<br>serious<br>LOAEL<br>(mg/kg/day) | Serious<br>LOAEL<br>(mg/kg/day) | Effect                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>CHRONIC EXPOSURE</b>                                              |                                                          |                        |                                                        |                                  |                                |                      |                                         |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 3                                                                    | 51<br>↑<br>Rat<br>(Wistar)<br>40 M,<br>40 F              | 2 years<br>(F)         | M: 0, 6.1,<br>25.5, 138.0<br>F: 0, 8.0,<br>31.7, 168.4 | CS, WI,<br>BW, OW,<br>HE, BC, HP | Bd wt<br><br>Hemato<br>Hepatic | 25.5<br><br>138.0    | 138.0<br><br>6.1 <sup>c</sup>           |                                 | Decreased body weight gain in<br>males (23–25%) and females (31–<br>39%)<br><br>Increases in absolute and relative<br>weights at ≥6.1/8.0 mg/kg/day after<br>12 months of exposure; fatty<br>generation at ≥6.1 mg/kg/day in<br>males and at ≥31.7 mg/kg/day in<br>females, and granulomas in<br>females at 31.7 and<br>168.4 mg/kg/day after 12, 18, or<br>24 months of exposure and in<br>males at ≥6.1 mg/kg/day only after<br>24 months of exposure |
|                                                                      | 10<br>↓<br>Aida et al. 1992                              |                        |                                                        |                                  |                                |                      |                                         |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                      | 52<br>Rat<br>(F344)<br>78 M                              | 104 weeks<br>(W)       | 0, 3.9, 20.6,<br>36.3                                  | CS, BW, FI,<br>BC, OW,<br>HP     | Hepatic<br>Renal<br><br>Endocr | 36.3<br>20.6<br>36.3 | 36.3                                    |                                 | Increased incidence of renal tubular<br>cell hyperplasia                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                      | George et al. 2002                                       |                        |                                                        |                                  |                                |                      |                                         |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                      | 59<br>Rat<br>(Wistar)<br>58M, 58F                        | Lifetime<br>(W)        | M: 0, 90<br>F: 0, 190                                  | BW, HP                           | Cancer                         |                      | 190 F                                   |                                 | Increased incidence of hepatic<br>neoplastic nodules in females only;<br>no additional description of the<br>tumors was provided                                                                                                                                                                                                                                                                                                                        |
|                                                                      | Tumasonis et al. 1985                                    |                        |                                                        |                                  |                                |                      |                                         |                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

<sup>a</sup>The number corresponds to entries in Figure 2-x.

<sup>b</sup>Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the BMDL<sub>05</sub> of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

<sup>c</sup>Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the BMDL<sub>10</sub> of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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**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.

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### *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**

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### *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:

*Clinician Briefs and Overviews* discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see [https://www.atsdr.cdc.gov/emes/health\\_professionals/clinician-briefs-overviews.html](https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html)).

*Managing Hazardous Materials Incidents* is a 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.html>).

*Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see <https://www.atsdr.cdc.gov/toxfaqs/Index.asp>).

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### ***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, 400 7<sup>th</sup> Street, S.W., Suite 5W, Washington, DC 20024 • 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](mailto: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 <http://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  $\leq 14$  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 ( $K_{oc}$ )**—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 ( $K_d$ )**—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  $BMD_{10}$  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 malignant 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.

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**Ceiling Value**—A concentration that must not be exceeded.

**Chronic Exposure**—Exposure to a chemical for  $\geq 365$  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.

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**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<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—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<sub>(LO)</sub> (LD<sub>LO</sub>)**—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<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—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 LOAEL**—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

**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.

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**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 exposure level 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 exposure level, they are not considered to be adverse.

**Octanol-Water Partition Coefficient ( $K_{ow}$ )**—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.

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**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<sup>3</sup> 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)  $\geq 1$  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.

## APPENDIX F

**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.

**Serious LOAEL**—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

**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                                        |
| BCF               | bioconcentration factor                                               |
| BMD/C             | benchmark dose or benchmark concentration                             |
| BMD <sub>x</sub>  | dose that produces a X% change in response rate of an adverse effect  |
| BMDL <sub>x</sub> | 95% lower confidence limit on the BMD <sub>x</sub>                    |
| 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                                                            |
| CPSC              | Consumer Products Safety Commission                                   |
| CWA               | Clean Water Act                                                       |
| 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                                          |
| FIFRA             | Federal Insecticide, Fungicide, and Rodenticide Act                   |
| FR                | Federal Register                                                      |

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|                  |                                                                                |
|------------------|--------------------------------------------------------------------------------|
| FSH              | follicle stimulating hormone                                                   |
| g                | gram                                                                           |
| GC               | gas chromatography                                                             |
| gd               | gestational day                                                                |
| GGT              | $\gamma$ -glutamyl transferase                                                 |
| GRAS             | generally recognized as safe                                                   |
| HEC              | human equivalent concentration                                                 |
| HED              | human equivalent dose                                                          |
| HHS              | Department of Health and Human Services                                        |
| HPLC             | high-performance liquid chromatography                                         |
| HSDB             | Hazardous Substances Data Bank                                                 |
| IARC             | International Agency for Research on Cancer                                    |
| IDLH             | immediately dangerous to life and health                                       |
| IRIS             | Integrated Risk Information System                                             |
| K <sub>d</sub>   | adsorption ratio                                                               |
| kg               | kilogram                                                                       |
| kgg              | kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton |
| K <sub>oc</sub>  | organic carbon partition coefficient                                           |
| K <sub>ow</sub>  | octanol-water partition coefficient                                            |
| L                | liter                                                                          |
| LC               | liquid chromatography                                                          |
| LC <sub>50</sub> | lethal concentration, 50% kill                                                 |
| LC <sub>Lo</sub> | lethal concentration, low                                                      |
| LD <sub>50</sub> | lethal dose, 50% kill                                                          |
| LD <sub>Lo</sub> | lethal dose, low                                                               |
| LDH              | lactate dehydrogenase                                                          |
| LH               | luteinizing hormone                                                            |
| LOAEL            | lowest-observed-adverse-effect level                                           |
| LSE              | Level of Significant Exposure                                                  |
| LT <sub>50</sub> | 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                            |

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|        |                                                                                     |
|--------|-------------------------------------------------------------------------------------|
| 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 limit                                                          |
| REL-C  | recommended exposure limit-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                                                     |

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|       |                                    |
|-------|------------------------------------|
| 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                  |
| $\alpha$      | alpha                    |
| $\beta$       | beta                     |
| $\gamma$      | gamma                    |
| $\delta$      | delta                    |
| $\mu\text{m}$ | micrometer               |
| $\mu\text{g}$ | microgram                |
| $q_1^*$       | cancer slope factor      |
| –             | negative                 |
| +             | positive                 |
| (+)           | weakly positive result   |
| (–)           | weakly negative result   |

**October 13<sup>th</sup> , 2025**

**Call to Order & Determination of Quorum:**

The Winneshiek County Area Solid Waste Agency meeting was called to order by Chairperson Mark Vick at 5:00 p.m. on Monday, October 13<sup>th</sup>, 2025 at the Winneshiek County Annex Building. Voting members present were; Mark Vick, Steve Kelsay, Don DiLaura, Mark Faldet, Leon Kipp, Todd Ihde, Dan Langreck, Keith Frana, Richard Hammel and Dennis Wilkins. A quorum was determined by the chairperson. Also present were; Counsel Jana Eversizer Olson, Landfill Director T.J Schissel, Landfill Operator Meghan Scheidel, Chris Oelkers Foth Engineering, Gina Wilming Foth Engineering, Hannah Dubbs Foth Engineering.

**Approval of Minutes & Agenda:**

Moved by Faldet, seconded by Wilkins, to approve the meeting minutes of 08/11/25. All voting approved.  
Moved by Faldet, seconded by Wilkins to approve the 10/13/25 agenda. All voting approved.

**Introduction of Guests:** Dave Mooney, Craig Kluesner, Bob Sersland, Roger Hammel, Kelly Ludeking, Julia Hageman, Brain Hageman, Jeremy Hirth, Lucas Merritt, Julian Merritt, Dan Christopher, Garrick Smith, Fallon Hammon, Ross Merritt

**Report from Secretary-Treasurer:**

8/31/25 Checking Balance: \$598,872.09

8/31/25 Checking Interest: \$4.24

8/31/25 Certificates of Deposit (Operating): \$2,447,334.90

8/31/25 Certificates of Deposit (Closure-Post Closure): \$7,305,022.81

8/31/25 Total Investments: \$9,752,357.71

9/30/25 Checking Balance: \$666,616.79

9/30/25 Checking Interest: \$4.68

9/30/25 Certificates of Deposit (Operating):\$2,447,334.90

9/30/25 Certificates of Deposit (Closure-Post Closure):\$7,305,022.81

9/30/25 Total Investments: \$9,752,357.71

**Public Comment:**

There was no public comment.

**Approve Claims Paid:**

Moved by DiLaura, seconded by Langreck to approve the August claims of \$226,232.00 and September claims of \$181,706.30. All voting approved. Motion carried.

**Committee Reports:**

**Landfill Director's Report**

Cover dirt was hauled; the recirculation area was covered with black dirt and seeded. Chris Oelkers on site conducting gas monitoring. TJ met with Jeff Kuboushek at Recycling and attended the Fall Solid Waste Conference.

**Engineer's Report**

Gas monitoring is completed; ACM next steps will be implemented. Chris will be on site next week completing the semi-annual review to include new aerials of the site, fall sampling will begin next week.

**Committee Reports:**

1. Item 6.1- Groundwater Assessment of Corrective Measures. Gina Wilming with Foth Engineering presented the Groundwater Assessment of Corrective Measures and answered questions.
2. Item 6.5- Hawkeye Sanitation clarification of Landfill rules and policy. Discussion of rules and policies with a plan for further discussion at the November meeting.
3. Item 6.6-Discussion to enter into agreement with Allamakee County. Discussion regarding accepting Allamakee County waste with plan to for further discussion in the future.

**Establish Time & Date of Next Meeting:**

The WCASWA will meet on November 10<sup>th</sup>, 2025 at 5:00 pm at the Winneshiek County Annex Building.

**Adjournment:**

Moved by Faldet, seconded by Kipp to adjourn 6:35 pm. All voting approved.

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**Leon Kipp, Secretary**