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_{12}; 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 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_{12}, also known as cyanocobalamin, which plays a crucial role in maintaining optimal health in humans and animals.

The general population can be exposed to low levels of cobalt by breathing air, eating food, or drinking water with food being the largest source of exposure. 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}Co decays in 5.27 years and half of ^{57}Co decays in 272 days. While the general population is rarely exposed to radioactive cobalt, radiation therapy patients may be exposed to radiation from cobalt located inside a therapy machine or during radiosurgery using a gamma knife that uses ^{60}Co. Workers at nuclear facilities, irradiation facilities, or nuclear waste storage sites may be exposed to small amounts of radioactive cobalt and its radiation from these sources. Additional details of exposure to radioactive cobalt and related health effects are discussed in the Toxicological Profile for Ionizing Radiation (ATSDR 1999).

1.2 SUMMARY OF HEALTH EFFECTS

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 (≤14 days), intermediate (15–364 days), and chronic (≥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_{12}, 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.

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

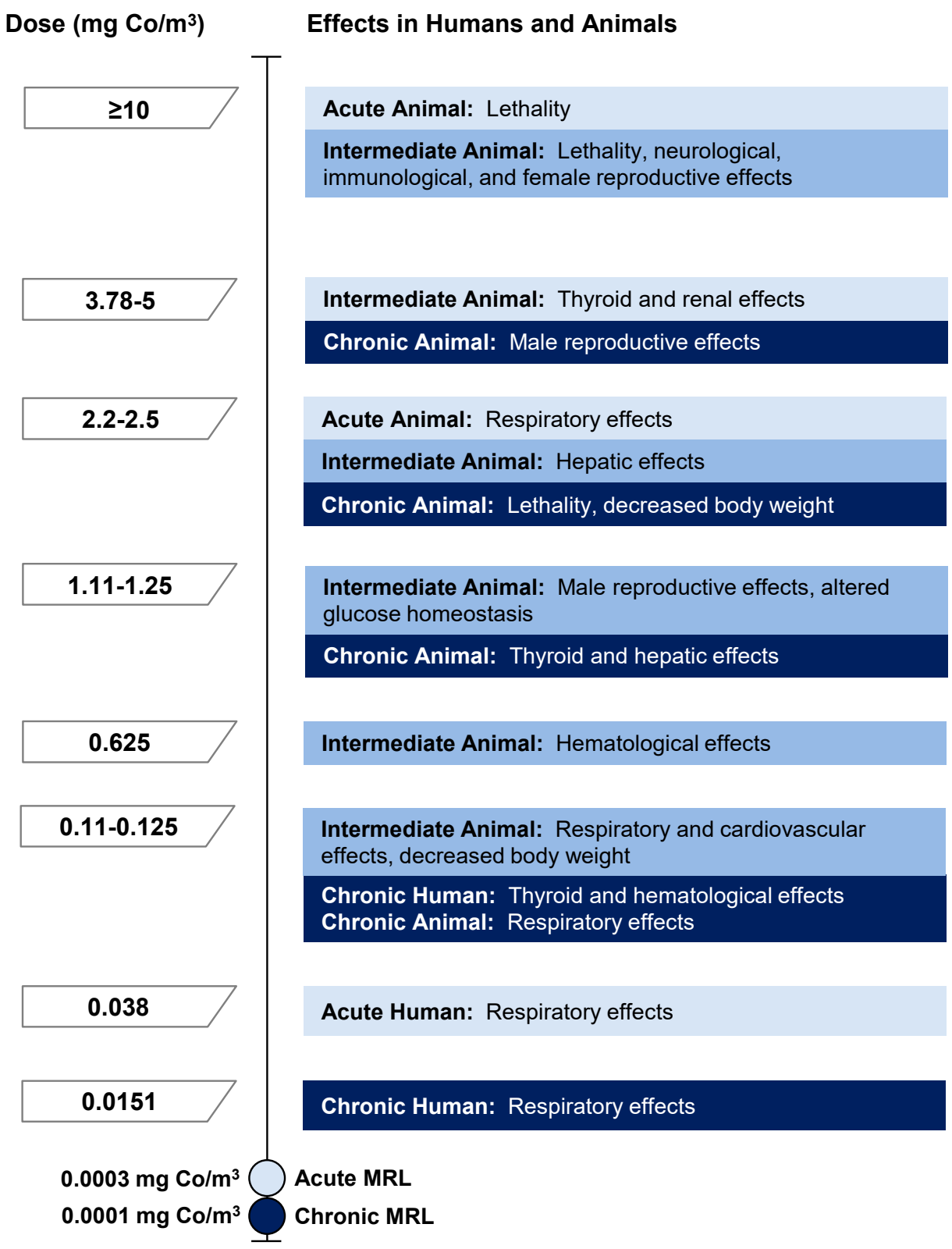
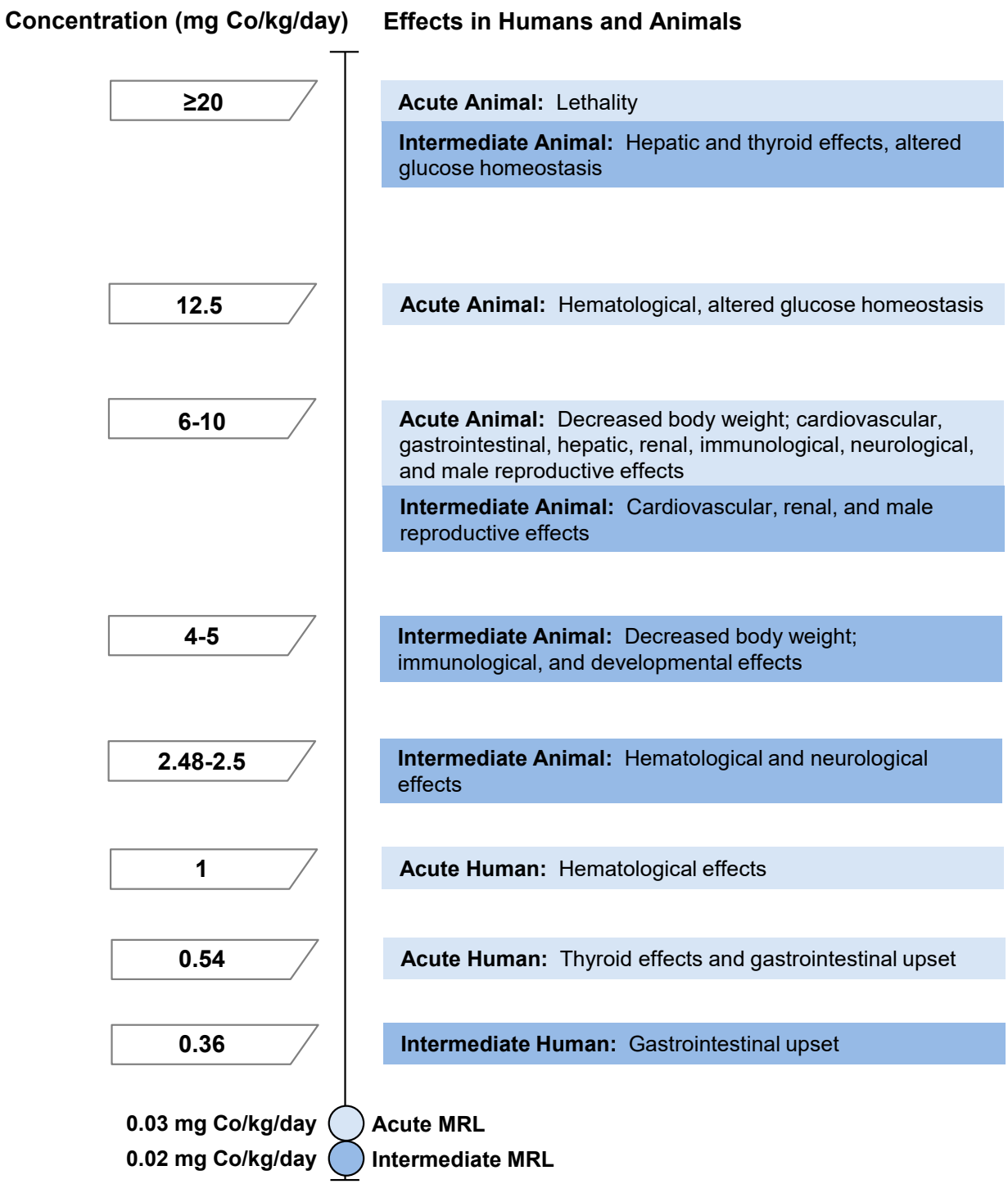


Figure 1-2. Health Effects Found in Humans and Animals Following Oral Exposure to Cobalt



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).

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-

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

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.

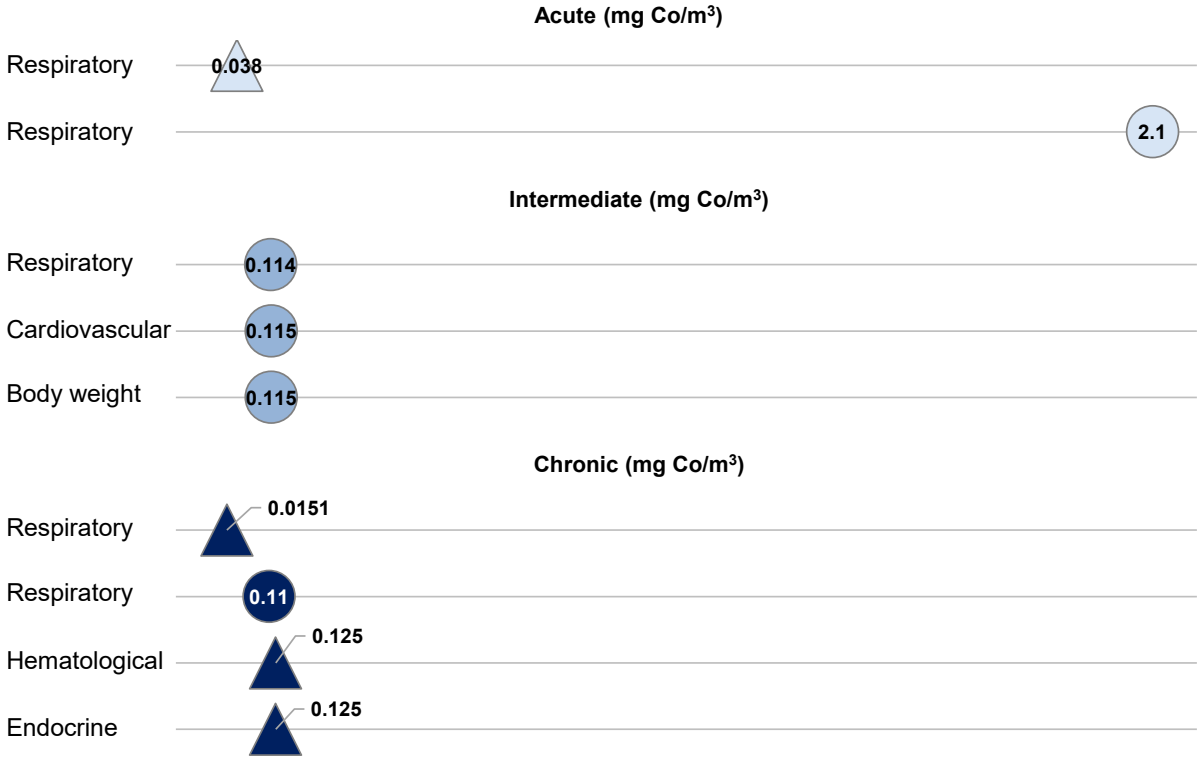


Figure 1-4. Summary of Sensitive Targets of Cobalt – Oral

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.

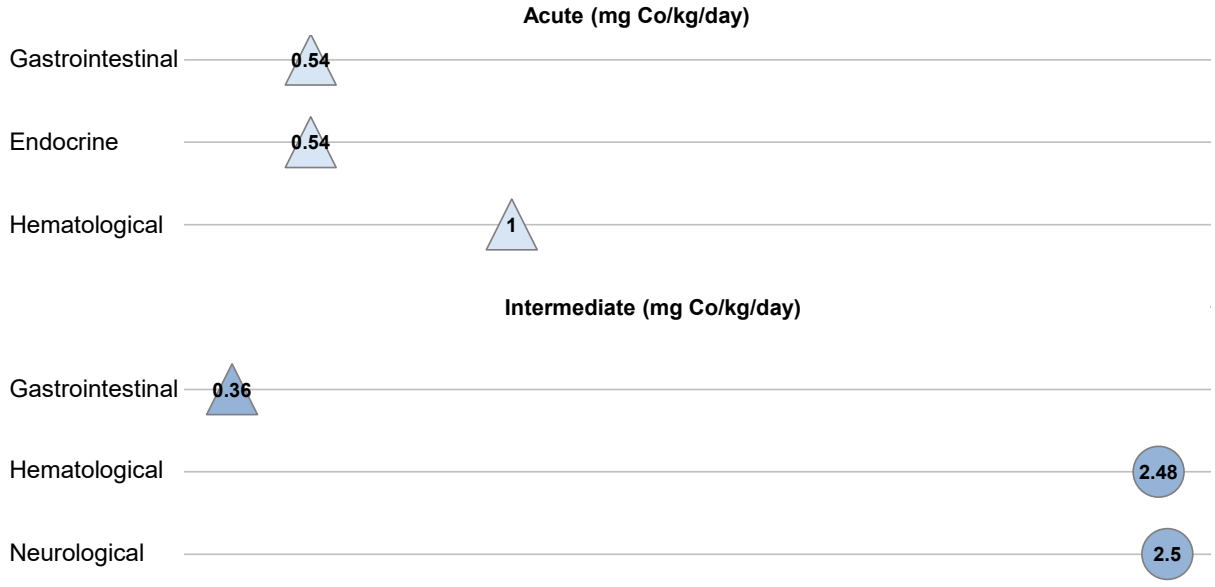


Table 1-1. Minimal Risk Levels (MRLs) for Cobalt[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**$3x10^{-4}$ mg Co/m^3**	Increased neutrophils in bronchoalveolar lavage fluid in female rats	$NOAEL_{HEC}$	0.01 mg Co/m^3	UF: 30	Viegas et al. 2022a, 2022b
	Intermediate	None	–	–	–	–	–
	Chronic	**$1x10^{-4}$ mg Co/m^3**	Reduced spirometry parameter values in workers	$NOAEL_{ADJ}$	0.0013 mg Co/m^3	UF: 10	Nemery et al. 1992
Oral	Acute	**0.03 mg Co/kg/day**	Production of polycythemia in human volunteers[b]	LOAEL	1.0 mg Co/kg/day	UF: 30	Davis and Fields 1958
	Intermediate	**0.02 mg Co/kg/day**	Elevated red blood cell count in male rats	$BMDL_{1SD}$	1.95 mg Co/kg/day	UF: 100	Danzeisen et al. 2020a
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.
[b]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