

CHAPTER 6. ADEQUACY OF THE DATABASE

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

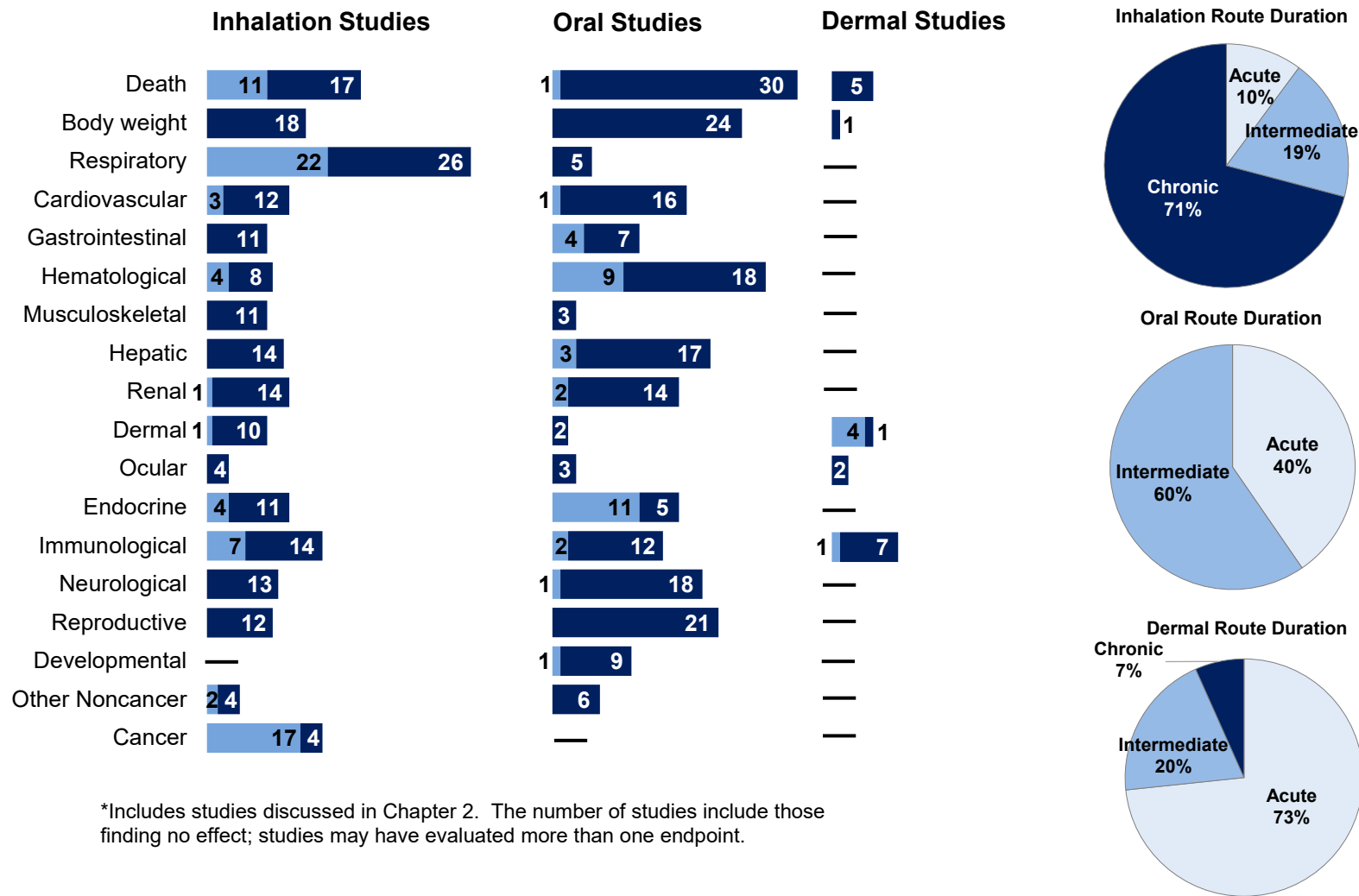
As shown in Figure 6-1, studies on the health effects in humans and animals exposed to cobalt primarily examine oral ingestion and inhalation. Many of these studies are case reports of individuals who intentionally or accidentally ingested cobalt or cobalt-containing substances. Controlled-exposure studies 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**



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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/m³, but at a lower dose of 0.1 mg Co/m³, 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)