

**NTP Executive Committee Working Group for the Report on Carcinogens (RG2)
Commentary on Human Exposure to Cobalt Sulfate**

At the May 1, 2002 RG2 review of the cobalt sulfate nomination for listing in the RoC the RG2 recommended that the human exposure information presented in Section 2 of the cobalt sulfate background document be revised so that the human exposure information could be updated using the information in the most recent ATSDR Toxicological Profile for Cobalt (September 2001). It was also recommended that this section be reorganized according to information specific for cobalt sulfate followed by information on cobalt compounds. There is more information available for human exposure to cobalt compounds in general than information for exposure to specific cobalt compounds. The RG2 wanted the information to be presented so that it clearly defined what type of information (e.g. production, occupational exposure) was available specifically for cobalt sulfate and generally for cobalt compounds.

This commentary is not meant to be a new draft of Section 2 of this background document. The information on human exposure to cobalt sulfate specifically and cobalt compounds in general has been updated to include any new information contained in the September 2001 ATSDR Toxicological Profile for Cobalt and reorganized so that information specific for cobalt sulfate is clearly discernable from information on cobalt compounds as a class.

Human Exposure

Information on human exposure has been divided into information specific for cobalt sulfate and information on cobalt compounds.

1 Cobalt sulfate

1.1 Use

Cobalt sulfate is used in the electroplating and electrochemical industries, where it is added to nickel plating baths in order to improve the smoothness, brightness, hardness, and ductility of the deposits. It also is used as a drier for lithographic inks, varnishes, paints, and linoleum and in storage batteries. Cobalt sulfate is employed as a coloring agent in ceramics, enamels, and glazes to prevent discoloring and as a co-pigment for decorating porcelain. In addition, cobalt sulfate has been used in animal feeds as a mineral supplement (Budavari *et al.* 1996, Kirk and Othmer 1999).

Cobalt sulfate has been mixed, in small quantities, with fertilizers for use on pastures where the forage is cobalt deficient, to provide enough cobalt for ruminants to produce vitamin B₁₂. In the United States in 1996, the total amount of fertilizer consumed containing cobalt sulfate was two tons. All of the fertilizer use was in Washington State, where the highest concentrations of cobalt in fertilizers were 44.8 to 222 mg/kg (dry weight) (EPA 1999, Washington State 1999).

In the 1960s, some breweries added cobalt sulfate to their beers to improve the stability of the foam by counteracting the antifoaming activity of detergent residues left on poorly rinsed glasses. Although only a small amount (1 ppm) was used in the beer, this practice was stopped after an epidemic of “beer drinker’s cardiomyopathy” was linked to the cobalt (NTP 1998).

Cobalt sulfate has also been used in veterinary medication to prevent and treat cobalt deficiency in ruminants, which causes reduction in feed intake and body weight, accompanied by emaciation, anemia, and debility. Cobalt sulfate had been used in the past to improve hematocrit, hemoglobin, and erythrocyte levels in human patients with refractory anemia, including sickle-cell disease, thalassemia, chronic infection or renal disease, anemia associated with neoplastic disease, and various other refractory anemias of unknown cause. In 1985, cobalt was used clinically only in the treatment of normochromic, normocytic anemia associated with severe renal failure (HSDB 2000, Hillman and Finch 1985). There is no listing for cobalt or cobalt sulfate in the current *Goodman & Gilman’s Pharmacological Basis of Therapeutics* (Goodman and Gilman 2001).

1.2 Production

Cobalt sulfate is formed by the interaction of cobalt oxide, hydroxide, or carbonate with sulfuric acid. Production of cobalt sulfate in the United States in 1983 was estimated at 450,000 lb (NTP 1998). Current production levels are not available. There are currently 11 U.S. suppliers of cobalt sulfate (ChemFinder 2001).

Import of cobalt sulfate in 1986 was reported to be 79,700 lb (HSDB 2000). U.S. imports for consumption of cobalt sulfates were 1,360 metric tons in 1999 and 1,040 metric tons in 1998, valued at \$9,840,000 and \$10,400,000, respectively. No specific information on cobalt sulfate exports was identified (USGS 2001).

Chem Sources identified 15 suppliers of cobalt(II) sulfate, four suppliers of cobalt(II) sulfate monohydrate, and 16 suppliers of cobalt(II) sulfate heptahydrate in the United States (Chem Sources 2001). The Hazardous Substances Data Bank listed seven manufacturers of cobaltous sulfate (HSDB 2000).

1.3 Analysis

No information was found that specifically identified analysis for cobalt sulfate.

1.4 Environmental occurrence

No information was found that specifically identified environmental occurrence to cobalt sulfate.

1.5 Environmental fate

Seawater formation of cobalt sulfate is not estimated because of the high concentration of chloride ion. No other information was found that specifically identified environmental fate to cobalt sulfate.

1.6 Environmental exposure

No information was found that specifically identified environmental exposure to cobalt sulfate.

1.7 Occupational exposure

No information was found that specifically identified occupational exposure to cobalt sulfate.

1.8 Biological indices of exposure

Cobalt sulfate, like other water-soluble metallic salts, dissolves directly into blood serum (362 g/L at 20°C) (Jensen and Tüchsen 1990). Cobalt can be detected in urine, blood, and tissues; however, there currently is no way to correlate cobalt sulfate exposure with cobalt levels observed in these matrices.

1.9 Regulations

No specific U.S. Environmental Protection Agency (EPA) regulations for cobalt sulfate were identified.

2 Cobalt compounds as a class

2.1 Use

The largest use of metallic cobalt is in super alloys that are used in gas turbine aircraft engines. Superalloys are alloys developed for applications where elevated temperature and high mechanical stress are encountered. Cobalt compounds are used as pigments in glass, ceramics, and paints; as catalysts in the petroleum industry; as paint driers; as trace element additives in agriculture and medicine.

2.2 Production

The United States did not mine or refine cobalt in 2000, although negligible amounts of cobalt were produced as a byproduct of mining operations. The U.S. supply of cobalt in 2000 included imports, stock releases, and secondary materials. Stock releases originated from the U.S. government reserve (National Defense Stockpile) for military, industrial, and civilian use during a national emergency. Sales of the National Defense Stockpile of cobalt began in March of 1993. Seven companies were known to be active in the production of cobalt compounds. It was estimated that 45% of U.S. cobalt usage was in superalloys, 9% in cemented carbides, 9% in magnetic alloys, and the remaining 37% in various other metallic and chemical uses (USGS 2001). Table D-1 summarizes recent patterns of cobalt production, import, export, and consumption in the United States.

Table 1-1. Cobalt production, consumption, import, and export

| Salient statistics | Metric tons of cobalt | |
|--------------------------|-----------------------|--------|
| | 1999 | 2000 |
| United States: | | |
| Production: | | |
| Mine | NR | NR |
| Secondary | 2,720 | 2,800 |
| Consumption: | | |
| Reported | 8,420 | 8,400 |
| Apparent | 10,700 | 10,900 |
| Imports for consumption | 8,150 | 8,000 |
| Exports | 1,550 | 2,300 |
| World production: | | |
| Mine | 29,900 | 32,300 |
| Refinery | 31,200 | NR |

Sources: Shedd 1999, USGS 2001.

NR = not reported.

Reported 1999 U.S. cobalt consumption was 2,530 metric tons for chemical and ceramic uses and 64 metric tons for miscellaneous and unspecified uses. Reported 1999 U.S. consumption of cobalt chemical compounds (organic and inorganic) was 1,910 metric tons. Imports of cobalt sulfates and other cobalt salts (acetates, carbonates, and chlorides) from 10 countries totaled \$12,400,000. Most imports were from Finland. The United States exported \$49,700,000 of cobalt and cobalt compounds in 1999. Table D-2 summarizes U.S. cobalt consumption patterns in early 2001.

Table 1-2. Patterns of cobalt consumption in the United States in 2001

| Consumption information | Date | Metric Tons | Compounds and uses |
|---|-------------|--------------------|--|
| Reported consumption of cobalt materials | Jan–May | 669 | oxide and other chemical compounds |
| Reported consumption of cobalt by end use | Jan–May | 883 | chemical uses including catalysts, driers in paints, feed or nutritive additive, glass decolorizer, ground coat frit, pigments, other uses |
| Reported consumption of cobalt by end use | Jan–May | 127 | miscellaneous and unspecified uses |
| Imports by consumption | Jan–April | 498 | salts and compounds including acetates, carbonates, chlorides, and sulfates |
| Exports | Jan–April | 74 | salts and compounds |

Source: USGS 2001.

2.3 Analysis

Determination of cobalt, especially in biological samples containing low levels of cobalt, is accurate only if samples are not contaminated. Contamination from disposable syringes and technical-grade anticoagulants was responsible for erroneous reports in earlier literature of grossly high levels of cobalt in biological specimens. The common classical methods used for determining cobalt concentration in biological samples are polarographic and colorimetric methods. However, these older methods are unsuitable for determining low levels of cobalt in many biological samples, and samples must be chemically pretreated before quantification. The most common single-element instrumental techniques used are electrothermal atomic absorption spectrometry (AAS) and voltammetric techniques (ATSDR 2001). Analytical methods for determining cobalt in biological matrices are summarized in Table 2-3. The samples analyzed in the studies presented in this table were primarily from cobalt-exposed and non-exposed workers (Heinrich and Angerer 1984, Ichikawa *et al.* 1985, Alexandersson 1988). However, one study used samples from laboratory volunteers (Bouman *et al.* 1986), and another used hospital patients with knee or hip prostheses (Sunderman *et al.* 1989). IARC (1991) reported that serum cobalt concentrations in humans were in the range of 0.1 to 0.3 µg/L. As shown in Table 2-3, the detection limit for cobalt in serum by direct injection into electrothermal AAS with Zeeman background correction is 0.02 µg/L.

Table 1-3. Analytical methods for determining cobalt in biological materials

| Matrix | Analytical method | Detection limit |
|---------------|--|------------------------|
| Urine | electrothermal Atomic Absorption Spectroscopy (AAS) with Zeeman background correction — direct injection | 0.3 µg/L |
| | | 0.1 µg/L |
| | electrothermal AAS with Zeeman background correction — chemical preparation | 2.4 µg/L |
| | electrothermal AAS with deuterium background correction — chemical preparation | 0.1 µg/L |
| | differential pulse cathodic stripping voltametry (DPCSV) — chemical preparation | 0.2 µg/L |
| Whole blood | electrothermal AAS with deuterium background correction | 2 µg/L |
| | DPCSV — chemical preparation | 0.8 µg/L |
| | colorimetry — chemical preparation | 0.15 µg/L |
| Serum | electrothermal AAS with Zeeman background correction — direct injection | 0.02 µg/L |
| Blood | inductively coupled plasma-atomic emission spectrometry (ICP–AES) — chemical preparation | 10 µg/g |
| Tissue | ICP–AES — chemical preparation | 0.2 µg/g |

Source: ATSDR 2001.

Because of its rapidity, accuracy, and low detection limit, electrothermal AAS with Zeeman background correction is the method most commonly used to quantify cobalt levels in environmental samples. To meet detection limits of some of the analytical methods, preconcentration may be necessary for some environmental samples (e.g., seawater). As with biological samples, contamination of environmental samples during collection, storage, and treatment are concerns (ATSDR 2001). Analytical methods for determining cobalt in environmental samples are detailed in Table 4.

Table 1-4. Analytical methods for determining cobalt in environmental samples.

| Matrix | Analytical method | Detection limit | Recovery^a |
|----------------------------|---|------------------------|--|
| Air (workroom) | □-spectrometry with lithium-drifted germanium detector | 0.17 µg/m ³ | – |
| Air (occupational) | flame AAS with background correction | 0.4 µg/m ³ | 98% with 12- to 96-µg spiked filter |
| | ICP–AES | 0.5 µg/m ³ | 95%–100% with 2.5- to 1,000-µg spiked filter |
| Water (low ionic strength) | electrothermal AAS with Zeeman or deuterium background correction | < 0.5 µg/L | 93%–115% at 8.5–30 µg/L |
| Lake water | ICP-AES | < 0.004 µg/L | – |
| Rainwater | photon-induced X-ray emission | 0.08 µg/L | – |
| Seawater | electrothermal AAS with Zeeman background correction | 0.0002 µg/L | 90% |
| Water and waste water | flame AAS | 0.05 mg/L | 97%–98% at 0.2–5.0 mg/L |
| | electrothermal AAS with background correction | 1 µg/L | – |
| Groundwater or leachate | flame AAS with background correction | 0.05 mg/L | 97%–98% at 0.2–5.0 mg/L |
| Groundwater or leachate | electrothermal AAS with background correction | 1 µg/L | – |
| Food | electrothermal AAS with background correction | 1.88 µg/L | 100%–107% at 0.2–0.6 mg/kg in leaves and liver |

Source: ATSDR 2001.

^a – = no data available.

2.4 Environmental occurrence

2.4.1 Air

Sources of cobalt in the atmosphere are both natural and anthropogenic. Natural sources include wind-blown continental dust, seawater spray, volcanoes, forest fires, and continental and marine biogenic emissions. The worldwide emissions from natural sources have been estimated to range from 13 to 15 million pounds per year. Cobalt in the atmosphere probably exists in particulate form (ATSDR 2001).

In the United States, the average ambient atmospheric concentration of cobalt was reported to be approximately 0.4 ng/m³ (ATSDR 2001). Although the HSDB (2000) described the atmospheric concentration of cobalt in remote areas as being very low, the only value given was less than 1 ng/m³ for the Antarctic. The same source reported that the air concentration of cobalt can reach or exceed 81 ng/m³ in heavily industrialized cities. Near a beryllium-copper alloy facility, cobalt levels as high as 610 ng/m³ were observed (HSDB 2000).

Atmospheric cobalt concentrations are much higher near cobalt manufacturing and production facilities. In the ambient air of a facility that manufactured cobalt salts, cobalt concentrations measured by personal sampling ranged from 0.1 to 3.0 mg/m³, with a mean of 0.2 mg/m³, and mean concentrations measured by stationary sampling were 0.049 and 1.046 mg/m³. The cobalt concentration in the ambient air during painting of pottery with soluble cobalt salts ranged from 0.07 to 8.61 mg/m³ (HSDB 2000). In Illinois, levels of cobalt in urban air ranged from 0.0025 to 0.010 mg/m³.

2.4.2 Water

Concentrations of cobalt in uncontaminated freshwater have been reported to range from 0.1 to 10 µg/L (IARC 1991). The geometric mean and median cobalt levels from 6,805 ambient surface water stations were 2.9 and 2.0 µg/L, respectively. The average concentration in seawater ranged from 0.078 µg/L in the Caribbean Sea to 0.39 µg/L in the Indian Ocean (ATSDR 2001).

The National Community Water Supply Study found that cobalt concentrations in drinking water in the United States ranged from nondetectable to 19 µg/L, with 62% of the water samples containing a concentration less than 1 µg/L. The average cobalt concentration in drinking water was 2.2 µg/L (ATSDR 2001).

2.4.3 Soil

The average concentration of cobalt is 20-25 mg/kg in the earth's crust, 18 mg/kg in igneous rocks, and 7.2 mg/kg in U.S. soils. Soils with cobalt concentrations less than 3 mg/kg are considered cobalt deficient, because plants that grow in these soils will not contain enough cobalt to meet the dietary needs of cattle and sheep (< 0.08 – 0.1 mg/kg). Soils near ore deposits, phosphate rocks, ore traffic sites, or industrial pollution sites have been reported to contain cobalt at concentrations of up to 800 mg/kg (ATSDR 2001).

2.5 Environmental fate

2.5.1 Air

It is generally accepted that anthropogenic cobalt originating from combustion sources would primarily be in the form of the oxide, whereas cobalt arsenide and sulfide could be released during ore extraction processes. Very few data, however, were available on the potential transformation of these forms to other chemical species, such as the sulfate. It is speculated that chemical speciation of cobalt oxide in the air could lead to the formation of more-soluble forms such as cobalt sulfate, which would result in greater quantities being washed out of the atmosphere in rain (ATSDR 2001)

2.5.2 Water

Many factors will affect the speciation and transport of cobalt in natural waters and sediments. Dissolved cobalt appears to be precipitated in the adsorbed state with oxides of iron and manganese and with crystalline sediments such as aluminosilicate and goethite. In addition, cobalt precipitates out as carbonate and hydroxide in water (ATSDR 2001). In freshwater, it is estimated that speciation may yield 76% free Co^{+2} , 9.8% carbonate, 9.6% bicarbonate, 4% humic complexes, and 0.4% cobalt sulfate. Species of cobalt in seawater are CoCl^+ , free Co^{+2} , carbonate, or carbonate and sulfate. Organic waste concentration and pH play an important role in cobalt speciation (ATSDR 2001). Bioconcentration of cobalt in marine fish is expected to occur, with bottom-feeders accumulating high levels of cobalt (HSDB 2000, ATSDR 2001).

2.5.3 Soil

The speciation of cobalt is regulated primarily by pH, the concentration of chelating or complexing agents in the soil, and the redox potential of the soil. At low pH, cobalt is oxidized to trivalent cobalt and usually is associated with iron. In the process of weathering, cobalt is readily taken into solution. It also is adsorbed to a great extent by hydrolysate or oxidate sediments (HSDB 2000).

2.6 Environmental exposure

Exposure to cobalt occurs through inhalation of ambient air and ingestion of food and drinking water. The average intake of cobalt in foods by adults in Canada was 11 $\mu\text{g}/\text{day}$, with the intake varying between 4 and 15 $\mu\text{g}/\text{day}$ for various age groups. The median concentration of cobalt in U.S. drinking water is less than 2.0 $\mu\text{g}/\text{L}$ and the average concentration in ambient air is approximately 0.4 ng/m^3 (ATSDR 2001). The major source of cobalt is food, in the form of green leafy vegetables, which may contain as much as 0.5 mg/kg dry weight (HSDB 2000). Cobalt is an essential trace element in humans, because a cobalt atom is present in each molecule of vitamin B_{12} (cobalamin). Cobalt's presence in vitamin B_{12} is its only known essential function in humans (Anderson 2000). An adult human body contains approximately 1.1 mg of cobalt (NTP 1998).

The National Health and Nutrition Examination Survey in 1999 measured cobalt levels in the urine of 1,007 participants aged 6 years or older, to provide physicians with a reference range of cobalt in the urine of the U.S. population for use in determining whether individuals have been exposed to cobalt (CDC 2001). The geometric mean was 0.36 $\mu\text{g}/\text{L}$ of urine (95% CI = 0.32 to 0.40). The geometric mean of the creatinine-adjusted levels was 0.33 $\mu\text{g}/\text{g}$ of creatinine (95% CI = 0.29 to 0.36).

2.7 Occupational exposure

It has been estimated by Jensen and Tüchsen (1990) that more than a million workers in the United States potentially are exposed to cobalt or cobalt compounds, though for many, the degree of potential exposure is limited (HSDB 2000, NTP 1998). Occupational exposure to cobalt occurs principally in refining processes, in production of alloys, and in the tungsten carbide hard-metal industry (Kazantzis 1981). In addition, many workers are exposed to a limited degree when using cobalt-containing paint dryers. Occupational

exposure is primarily dermal or through inhalation of cobalt metal dusts or fumes (HSDB 2000, NTP 1998).

Cobalt metal has been reported in the air of metal manufacturing, welding, and grinding factories at concentrations ranging from 1 to 300 $\mu\text{g}/\text{m}^3$ and in the dust of an electric welding factory at 4.2 $\mu\text{g}/\text{g}$ (ATSDR 2001). Occupational exposure to cobalt also has been assessed from the concentrations of cobalt in workers' tissues and body fluids. Alexandersson (1988) reported a high degree of conformity between the concentration of cobalt in blood and urine and the average levels of cobalt in the air during a workweek. In workers exposed to high levels (0.09 mg/m^3), cobalt concentrations in the blood were 20 times those of the control group, while in the low-exposure workers (0.01 mg/m^3), the concentrations were only slightly higher than in the controls. Other studies have shown that lungs from occupationally exposed workers, such as coal miners and metal-industry workers, contained from 2.5 to 6 times as much cobalt as lungs from control groups (ATSDR 2001).

2.8 Biological indices of exposure

Cobalt can be detected in urine, blood, and tissues; however, there currently is no way to correlate cobalt sulfate exposure with cobalt levels observed in these matrices. Based on reports of accidental exposure to radioactive cobalt (^{60}Co) and intravenous or oral administration of ^{60}Co to volunteer human subjects (Smith *et al.* 1972), approximately 90% of inhaled, injected, or ingested cobalt is eliminated within a few days; however, the remaining 10% has a half-life in the body of two years after parenteral administration or 5 to 15 years after inhalation. No biological use of cobalt is known other than its presence in vitamin B₁₂ (HSDB 2000).

2.9 Regulations

See cobalt sulfate background document, Section 2.9

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