

Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo*

CAS No. 7440-48-4 (Cobalt metal)

No separate CAS No. assigned for cobalt compounds as a class
Reasonably anticipated to be human carcinogens

Introduction

This listing of the class of cobalt and cobalt compounds that release cobalt ions *in vivo* (as defined below) supersedes the previous listing of cobalt sulfate in the Report on Carcinogens. The compound cobalt sulfate was first listed in the *Eleventh Report on Carcinogens* in 2004 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals.

Carcinogenicity

Cobalt and cobalt compounds that release cobalt ions *in vivo* are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data from studies on mechanisms of carcinogenesis. Mechanistic data indicate that the release of cobalt ions *in vivo* is a key event for cobalt-induced carcinogenicity. The available data show that cobalt metal and cobalt compounds that release cobalt ions *in vivo* (regardless of their solubility in water) act via similar modes of action to cause similar types of effects, including cell death, DNA damage, and cancer, and that the cobalt ion is largely responsible for the toxicity and carcinogenicity (NTP 1998, 2014, IARC 2006).

Both water-soluble cobalt compounds and poorly water-soluble cobalt particles are included in this class, as both types of cobalt species can release cobalt ions *in vivo*, although they differ in the mechanisms by which the cobalt ions enter cells. Vitamin B₁₂, which is an essential cobalt-containing nutrient, does not meet the criteria for this listing, because the vitamin does not release cobalt ions, but passes through the body intact while bound to specific carrier proteins (Neale 1990). It is not possible to determine the quantitative carcinogenic risk from cobalt ions released from surgical implants because of limitations in the available cancer studies of cobalt

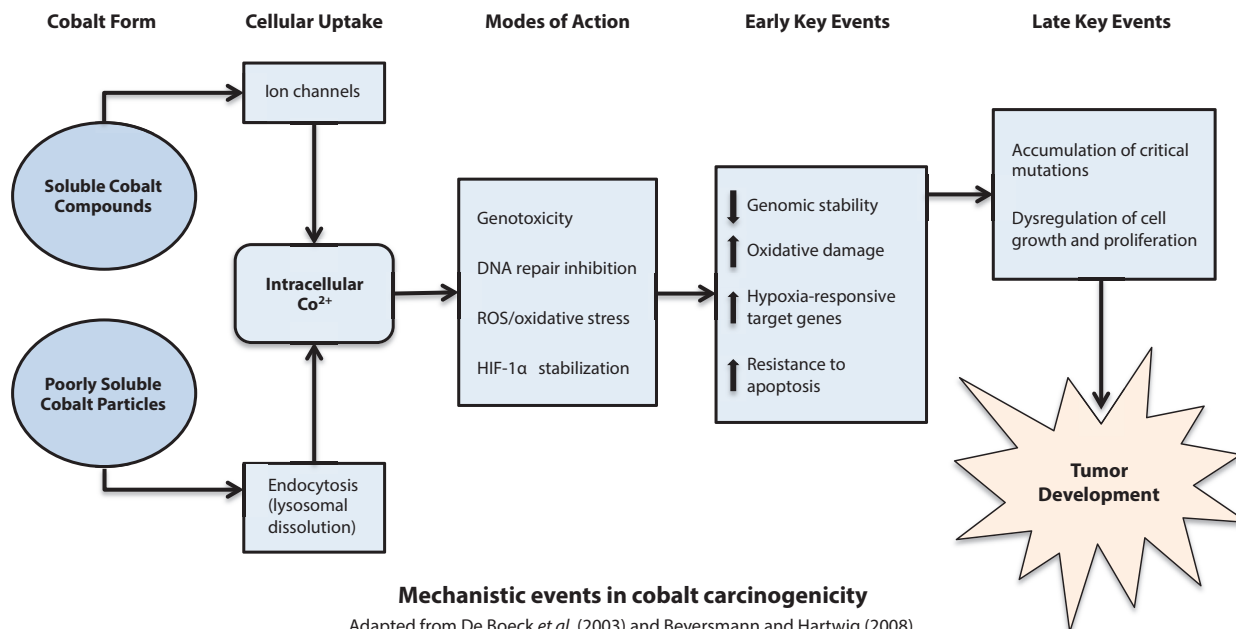
alloy implants in experimental animals and of patients with cobalt-containing surgical implants.

Mechanisms of Carcinogenesis and Other Relevant Data

The key events related to toxicity and carcinogenicity are thought to include cellular uptake of cobalt, intracellular release of cobalt ions from particles, and immediate and downstream biological responses related to the proposed modes of action. The first step in the carcinogenicity or toxicity process is the release of cobalt ions *in vivo*. Water-soluble cobalt compounds release cobalt ions into fluids outside the cell, and the ions enter the cell through ion channels within the cell membrane. In contrast, poorly soluble particulate cobalt compounds are taken up by specific organelles (lysosomes) in the cell via a process called endocytosis; cobalt is then solubilized in the acidic environment in the lysosomes, and the ions are released inside the cell. Evidence for cellular uptake of the different forms of cobalt is provided by studies evaluating their solubility in biological fluids *in vitro* (e.g., in gastric and lysosomal fluids) (see Properties) and *in vitro* studies measuring levels of cobalt ions within cells (Peters *et al.* 2007, Ortega *et al.* 2014, Sabbioni *et al.* 1994, Smith *et al.* 2014).

Although the mechanism(s) of action for cobalt-induced carcinogenic effects are not completely understood, several key events have been identified that are related to biologically plausible modes of action and are applicable to all cobalt forms that release cobalt ions *in vivo*. These events include inhibition of DNA repair, genotoxicity, generation of reactive oxygen species (ROS) resulting in oxidative damage, and stabilization of hypoxia-inducible factor 1 α (HIF-1 α), a protein that increases the expression of genes that promote survival of cells when they receive less oxygen. The proposed modes of action are summarized in the diagram below.

Cobalt is considered to be a clastogen, because in *in vitro* assays in mammalian cells, it primarily causes chromosome damage and DNA strand breaks. Only a few genotoxicity studies in experimental animals were available, but the results were generally consistent with those of *in vitro* studies. Two potential mechanisms for genotoxicity include (1) direct induction of oxidative damage to DNA by cobalt(II) ions and (2) an indirect effect through inhibition of DNA repair (Smith *et al.* 2014, Lison 2015).



Cobalt is one of a group of metals (transition metals, like iron and nickel) that promote oxidation and reduction (redox) reactions through transfer of electrons. *In vitro* studies have shown that cobalt particles and ions can induce ROS in mammalian cells, with cobalt metal and cobalt oxide particles having a greater effect than ions. It has been proposed that ROS can play a role in the tumor development process at several stages, including initiating the process by inducing mutations and promoting proliferation of these mutated cells by deregulating controls on cell growth, leading to tumors. Studies in rats have shown that cobalt causes oxidative stress and oxidative DNA damage in several tissues, including kidney, liver, and lung (Kasprzak *et al.* 1994), which supports this proposed pathway for cobalt-induced carcinogenicity. Also, a higher frequency of a specific mutation in the *K-ras* oncogene, a gene with the potential to cause cancer, was found in cobalt-induced lung tumors in mice and rats than in spontaneous lung tumors (NTP 1998, 2014, IARC 2006). This mutation involves substitution of one nucleotide for another in a G to T transversion, which is a mutation commonly associated with oxidative DNA damage. In addition, cobalt-induced oxidative stress (via the production of ROS) can activate genes and proteins (specifically, the transcription factors NF- κ B, AP1, p53, and Nrf2) that in turn regulate the expression of many genes that play a role in carcinogenicity, such as those involved in inflammation and control of the cell cycle (Valko *et al.* 2005, 2006, Beyersmann and Hartwig 2008, Shukla *et al.* 2012, Davidson *et al.* 2015, PubChem 2015).

Finally, a well-established biological effect of cobalt is to mimic oxygen deficiency in cells by stabilizing HIF-1 α (Maxwell and Salnikow 2004, Greim *et al.* 2009, Saini *et al.* 2010a,b, Galán-Cobo *et al.* 2013, Gao *et al.* 2013, Nyga *et al.* 2015). HIF-1 α plays a central role in regulating more than 100 hypoxia-responsive genes and is a major regulator of the adaptation of cancer cells to oxygen deficiency. HIF-1 α overexpression has been linked to cancer initiation and progression and is a common characteristic of many human cancers (Paul *et al.* 2004, Galanis *et al.* 2008, 2009, Cheng *et al.* 2013).

Although most of the toxicological effects of cobalt are attributed to the cobalt ion, direct toxic effects of cobalt particles also contribute, as evidenced by the greater toxicity of cobalt metal than of cobalt sulfate in National Toxicology Program (NTP) rodent bioassays (NTP 1998, 2014, Behl *et al.* 2015). Differences in the relative toxicity reported for cobalt particles and ions may be partially explained by differences in the mechanisms by which cobalt enters the cell and in the subsequent accumulation and distribution of cobalt within the cell, as well as a synergistic effect between the particles and metal on ROS production (Peters *et al.* 2007, Sabbioni *et al.* 2014, Smith *et al.* 2014).

Cancer Studies in Experimental Animals

Exposure of experimental animals to cobalt metal or cobalt compounds caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. This conclusion is based on studies in rats and mice exposed to cobalt metal (five studies), water-soluble cobalt compounds (two studies with cobalt sulfate and one study with cobalt chloride), and poorly water-soluble cobalt compounds (four studies with cobalt oxide). Studies of cobalt alloys and radioactive cobalt in experimental animals were not considered to be informative, because of potential confounding by other carcinogens.

Inhalation exposure of rats and mice to cobalt metal (NTP 2014) or cobalt sulfate (NTP 1998) or intratracheal instillation of cobalt oxide in rats (Steinhoff and Mohr 1991) caused lung tumors (alveolar/bronchiolar adenoma and carcinoma). In addition, inhalation exposure of rats to cobalt metal caused squamous-cell tumors of the

lung (primarily cystic keratinizing epithelioma) in females and possibly in males.

In inhalation studies of cobalt metal in rats (NTP 2014), tumors were also induced at sites distant from the lung, including tumors of the pancreas (islet-cell adenoma or carcinoma combined) in males and of the hematopoietic system (mononuclear-cell leukemia) in females, indicating a systemic effect. Increased incidences of kidney tumors (adenoma or carcinoma combined) in male rats and pancreas (carcinoma) in female rats may have been related to cobalt metal inhalation; however, the findings were not conclusive. Inhalation exposure to cobalt metal (NTP 2014) or cobalt sulfate (NTP 1998) induced adrenal-gland tumors (benign and malignant pheochromocytoma), which could have been caused by direct or indirect mechanisms.

In rats, local injection of cobalt at various anatomic locations caused tumors at the injection sites. Although these studies were less robust than the inhalation studies, and sarcomas are common in rats following injection of a variety of compounds, the consistency of the tumor types and findings across different cobalt forms provides supporting evidence for the carcinogenicity of cobalt. Intraperitoneal or intramuscular injection of the poorly water-soluble compound cobalt oxide caused histiocytoma or sarcoma at the injection site (Gilman and Ruckerbauer 1962, Steinhoff and Mohr 1991), and subcutaneous injection of the water-soluble compound cobalt chloride caused fibrosarcoma (Shabaan *et al.* 1977). Intramuscular or intrathoracic injection of cobalt metal (Heath 1956, Heath and Daniel 1962) or nanoparticles (Hansen *et al.* 2006) caused various types of sarcoma (primarily rhabdomyofibrosarcoma, rhabdomyosarcoma, or fibrosarcoma). In the study of nanoparticles, no tumors were observed after implantation of substances (e.g., titanium dioxide and silicon dioxide) with the same physical characteristics (i.e., surface-to-volume ratio) as cobalt, suggesting that the tumors were due to carcinogenic properties of cobalt and not just to a reaction to any physical implant.

A few studies in rodents (Gilman and Ruckerbauer 1962, Jasmin and Riopelle 1976, Wehner *et al.* 1977) found no tumors at certain tissue sites following exposure to the same forms of cobalt that caused tumors in other studies; however, these studies generally lacked sensitivity to detect an effect, because of the use of a less sensitive animal model, shorter study duration, or lower exposure levels.

Cancer Studies in Humans

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to cobalt and cobalt compounds that release cobalt ions *in vivo*. The data relevant to the evaluation were from studies primarily evaluating lung cancer in five independent cohorts of workers in different types of industries and two population-based case-control studies of esophageal cancer and other cancers of the respiratory and upper digestive (aerodigestive) tract, one in Ireland (O'Rorke *et al.* 2012) and the other in the state of Washington (Rogers *et al.* 1993). Studies of cobalt alloys in humans (primarily joint implants) were not considered to be informative, because they were not specific to cobalt exposure, and the extent of any cobalt exposure was unknown.

Although increased risks of lung cancer were found in most of the cohort studies, it is unclear that the excess risks were due to exposure specifically to cobalt, because of potential confounding from exposures to known lung carcinogens or other study limitations. In the cohort studies, hard-metal (Moulin *et al.* 1998, Wild *et al.* 2000) and nickel-refinery workers (Grimrud *et al.* 2005) were also exposed to known lung carcinogens. The findings of an increased risk of lung cancer among porcelain painters exposed to cobalt was complicated by a somewhat similar increase in risk among female pottery workers

who were not thought to be exposed to cobalt (Tüchsen *et al.* 1996). In studies of a cohort of cobalt production workers, the excess risk found in the first report of this cohort (Mur *et al.* 1987) was no longer present in an update of the cohort (Moulin *et al.* 1993). No association between cobalt exposure and lung cancer was found in a study of stainless- and alloyed-steel workers in France (Moulin *et al.* 2000). Most of the studies had limited sensitivity to detect a true risk, because of small numbers of lung-cancer cases among exposed workers, crude methods of exposure assessment, or potential healthy-worker-related effects (due to the fact that workers are healthier on average than the general population).

Increased risks of esophageal cancer were suggested in two case-control studies; however, it is unclear whether cobalt exposure contributed to the cancer excess. In both studies, cobalt exposure was assessed from a single sample of toenail clippings taken at or several months after diagnosis of esophageal cancer. Measurements of cobalt in toenails reflect an integrated exposure that occurred 12 to 18 months before clipping, raising the question of whether levels found in toenails close to or, in many cases, after cancer diagnosis reflected the relevant period of exposure for long-latency cancer.

Properties

As a class, cobalt and cobalt compounds that release cobalt ions *in vivo* are related largely by their chemical properties, specifically bioavailability. (The different valence states of cobalt are described below, under Chemical Characteristics.)

Bioavailability

The carcinogenic and toxic effects of cobalt and cobalt compounds begin with the release of cobalt ions *in vivo*. The bioavailability of a

metal species can be predicted by its solubility in biological fluids, such as synthetic equivalents of gastric and intestinal fluids (for ingestion exposure) or lung (alveolar, interstitial, and lysosomal) fluids (for inhalation exposure), and by studies in cultured cells. Results from studies testing solubility in synthetic biological fluids are shown in the table below, along with other chemical and physical properties of cobalt metal and these cobalt compounds. These studies demonstrated that cobalt metal and both water-soluble and poorly water-soluble cobalt compounds can dissolve and release cobalt ions in some biological fluids (Brock and Stopford 2003, Stopford *et al.* 2003, Cobalt Development Institute personal communication 21 Jul and 19 Oct 2015), suggesting that they will release ions *in vivo*.

Very low values ($\leq 2\%$) for bioaccessibility have been reported for the sulfide and mixed (II,III) oxide (Co_3O_4), and intermediate values (14% to 55%) for stearate and oxalate under the same test conditions. However, other, more informative tests with more physiologically relevant test conditions (e.g., two-week studies with 0.3- μm particles in culture medium in the presence of alveolar macrophages) have reported 50% solubility for Co_3O_4 . In addition, Ortega *et al.* (2014) found that intracellular concentrations of solubilized cobalt ions were similar for Co_3O_4 and cobalt chloride in human lung cells *in vitro*, suggesting that Co_3O_4 would release cobalt ions *in vivo*. Results with other biological fluids, such as serum and intestinal, alveolar, and interstitial fluids, indicate that the species of cobalt compound, particle size and surface area, and pH of the surrogate fluid all can affect the solubility of cobalt in biological fluids.

The solubility of cobalt compounds in water depends largely on pH, and cobalt is generally more mobile in acidic solutions than in alkaline solutions (IARC 1991, Paustenbach *et al.* 2013). Sulfates, nitrates, and chlorides of cobalt tend to be soluble in water, whereas oxides

Physical and chemical properties of cobalt metal and some cobalt compounds

Form ^a	CAS No.	Formula	Molec. weight	Physical form	Density or specific gravity	Water solubility (g/100 cc) ^b	Bioaccessibility (% solubility in gastric/lysosomal fluids)
<i>Cobalt metal</i>	7440-48-4	Co ^c	58.9 ^c	grey hexagonal or cubic metal ^c	8.92 ^c	0.00029 ^d	100/100 ^e
Water-soluble compounds							
<i>Acetate (org.)</i>	71-48-7	Co(C ₂ H ₃ O ₂) ₂ ^f	249.1 ^f	red-violet, monoclinic ^f	1.70 ^f	34.8 ^d	98/80 ^d
<i>Chloride</i>	7646-79-9	CoCl ₂ ^g	129.8 ^g	blue hexagonal leaflets ^g	3.36 ^g	45 ^g	100/100 ^e
<i>Nitrate</i>	10141-05-6	CoN ₂ O ₆ ^c	182.9 ^c	red powder or crystals ^c	2.49 ^c	67.0 ^d	96/100 ^d
<i>Sulfate heptahydrate</i>	10026-24-1	CoSO ₄ ·7H ₂ O ^f	281.1 ^f	red pink, monoclinic ^f	1.95 ^f	60.4 ^f	100/100 ^e
Poorly water-soluble compounds							
<i>Carbonate (org.)</i>	513-79-1	CoCO ₃ ^f	118.9 ^f	red, trigonal ^f	4.13 ^f	0.00114 ^d	100/100 ^e
<i>2-Ethylhexanoate (org.)</i>	136-52-7	Co(C ₈ H ₁₅ O ₂) ₂ ^f	173.7 ^h	blue liquid (12% Co) ^f	1.01 ^f	0.630 ^d	100/100 ^e
<i>Hydroxide</i>	21041-93-0	Co(OH) ₂ ^f	93.0 ^f	rose-red, rhombic ^f	3.60 ^f	0.00032 ^f	95/98 ^d
<i>Naphthenate (org.)</i>	61789-51-3	Co(C ₁₁ H ₇ O ₂) ₂ ^c	401.3 ^c	purple liquid (6% Co) ^f	0.97 ^f	0.0293 ^d	100/100 ^e
<i>Oxalate (org.)</i>	814-89-1	CoC ₂ O ₄ ^f	147.0 ^f	white or reddish ^f	3.02 ^f	0.00322 ^d	37/55 ^d
<i>Oxide</i>	1307-96-6	CoO ^f	74.9 ^f	green-brown cubic ^f	6.45 ^f	0.00049 ^d	100/92.4 ^e
<i>(II,III) Oxide</i>	1308-06-1	Co ₃ O ₄ ^f	240.8 ^f	black, cubic ^f	6.07 ^f	0.00016 ^d	2/2 ^d (50%) ⁱ
<i>Propionate (org.)</i>	1560-69-6	Co(C ₃ H ₃ O ₂) ₂ ^c	205.1 ^c	reddish solid ^d	–	7.49 ^d	91/94 ^d
<i>Stearate (org.)</i>	1002-88-6	Co(C ₁₈ H ₃₅ O ₂) ₂ ^c	625.9 ^c	grey solid ^d	–	0.00705 ^d	14/16 ^d
<i>Sulfide</i>	1317-42-6	CoS ^f	91.0 ^f	reddish octahedral ^f	5.45 ^f	0.00038 ^f	1/1 ^d

^aCobalt compounds selected for inclusion in the table are those with toxicological data or of commercial importance. All compounds contain Co(II) except where noted. Forms in italics have been tested for carcinogenicity or genetic toxicity or have mechanistic data; org. = organic compound; all others are inorganic.

^bSolubility data were converted to grams per 100 cubic centimeters as necessary.

^cPubChem 2015, ^dCobalt Development Institute personal communication 21 Jul and 19 Oct 2015, ^eStopford *et al.* 2003, ^fCDI 2006, ^gHSDB 2012, ^hHSDB 2004.

ⁱKreyling *et al.* 1990. Bioaccessibility was assessed by release of cobalt ions into culture medium in the presence of canine alveolar macrophages after two weeks of culture.

(including the mixed oxide, Co_3O_4), hydroxides, and sulfides tend to be poorly soluble or insoluble in water (Lison 2015). Organic cobalt compounds can be either soluble, as is cobalt(II) acetate, or insoluble, as are cobalt(II) carbonate and cobalt(II) oxalate (CDI 2006). In addition to low pH, solubilization of some poorly water-soluble compounds in biological fluids may be enhanced in the presence of binding proteins (IARC 2006).

Chemical Characteristics

Cobalt (Co) is a naturally occurring transition element with magnetic properties. It is the 33rd most abundant element, making up approximately 0.0025% of the weight of Earth’s crust. Cobalt is a component of more than 70 naturally occurring minerals, including arsenides, sulfides, and oxides. The only stable and naturally occurring cobalt isotope is ^{59}Co (ATSDR 2004, WHO 2006). Metallic cobalt, $\text{Co}(0)$, exists in two crystalline forms, hexagonal and cubic, which are stable at room temperature (IARC 1991, ATSDR 2004, WHO 2006). Cobalt predominantly occurs in two oxidation states, $\text{Co}(II)$ and $\text{Co}(III)$. $\text{Co}(II)$ is much more stable than $\text{Co}(III)$ in aqueous solution (Nilsen *et al.* 1985, Paustenbach *et al.* 2013) and is present in the environment and in most commercially available cobalt compounds (e.g., cobalt chloride, sulfide, and sulfate). $\text{Co}(III)$ also is present in some commercially available cobalt compounds, including the mixed oxide (Co_3O_4) (IARC 1991, Paustenbach *et al.* 2013, Lison 2015) and some simple salts of $\text{Co}(III)$ (e.g., Co_2O_3). Important salts of carboxylic acids include formate, acetate, citrate, naphthenate, linoleate, oleate, oxalate, resinate, stearate, succinate, sulfamate, and 2-ethylhexanoate.

Use

Cobalt and cobalt compounds are used in numerous commercial, industrial, and military applications. On a global basis, the largest use of cobalt is in rechargeable battery electrodes (Shedd 2014b); however, U.S. production of rechargeable batteries has been very limited (Brodd 2005). In 2012, the reported U.S. consumption of cobalt and cobalt compounds was approximately 8,420 metric tons, the majority used for superalloys (Shedd 2014b). Major uses for metallic cobalt include production of superalloys, cemented carbides, and bonded diamonds. Cobalt nanoparticles are used in medical applications (e.g., sensors, magnetic resonance imaging contrast enhancement, and drug delivery), and cobalt nanofibers and nanowires are used in industrial applications. Cobalt compounds are used as pigments for glass, ceramics, and enamels (oxides, sulfate, and nitrate), as driers for paints, varnishes, or lacquers (hydroxide, oxides, propionate, acetate, tallate, naphthenate, and 2-ethylhexanoate), as catalysts (hydroxide, oxides, carbonate, nitrate, acetate, oxalate, and sulfide), as adhesives and enamel frits (naphthenate, stearate, and oxides), and as trace mineral additives in animal diets (carbonate, sulfate, nitrate, oxides, and acetate). U.S. consumption of cobalt and cobalt compounds in 2012 is summarized in the following table.

The fastest-growing use for cobalt in recent years has been in high-capacity, rechargeable batteries, including nickel-cadmium, nickel-metal hydride, and lithium-ion batteries for electric vehicles and portable electronic devices such as smartphones and laptops (Maverick 2015). Many other uses for cobalt exist, including in integrated circuit contacts and semiconductor production. An emerging use is as a key element in several forms of “green” energy technology applications, including gas-to-liquids and coal-to-liquids processes, oil desulfurization, clean coal, solar panels, wind and gas turbines, and fuel cells, and in cobalt-based catalysts for sunlight-driven water-splitting to convert solar energy into electrical and chemical energy.

End use	Metric tons of cobalt content	Percent of total consumption
Superalloys	4,040	48.0
Chemicals and ceramics	2,300	27.3
Cemented carbides	774	9.2
Other alloys ^a	699	8.3
Steels	548	6.5
Miscellaneous and unspecified	63	0.7

Source: Shedd 2014b.

^aIncludes magnetic, nonferrous, and wear-resistant alloys and welding materials.

Production

Cobalt metal is produced as a by-product from ores associated with copper, nickel, zinc, lead, and platinum-group metals and is most often chemically combined in its ores with sulfur and arsenic (Davis 2000, CDI 2006). The largest cobalt reserves are in the Congo (Kinshasa), Australia, Cuba, Zambia, Canada, Russia, and New Caledonia, with very limited production in the United States in recent years (Shedd 2014a). Except for a negligible amount of by-product cobalt produced from mining and refining of platinum-group metal ores, the United States did not refine cobalt in 2012 (Shedd 2014b). Cobalt has not been mined in the United States in over 30 years (ATSDR 2004); however, a primary cobalt mine, mill, and refinery were being established in Idaho in 2015 (Farquharson 2015). In 2012, 2,160 metric tons of cobalt was recycled from scrap. No cobalt has been sold from the National Defense Stockpile since 2009.

Metallic cobalt and several cobalt compounds are high-production-volume chemicals, based on their annual production or importation into the United States in quantities of at least 1 million pounds. Recent volumes of U.S. production, imports, and exports of cobalt metal and high-production-volume cobalt compounds are listed in the following table.

Cobalt category	Quantity (lb)		
	Production (2012)	Imports (2013)	Exports (2013)
Metal (excluding alloys)	23,384,002	16,151,599	— ^a
Compounds			
Acetates	1 million to < 10 million	342,918	520,996
Carbonates	1,038,821	1,193,856	— ^a
Chlorides	— ^b	215,661	14,304
2-Ethylhexanoate	4,294,523	—	—
Hydroxide	4,709,137	—	—
Oxides	1 million to < 10 million	5,300,984 ^c	902,467 ^c
Propionate	1 million to < 10 million	—	—
Sulfate	1 million to < 10 million	1,319,004	— ^a

Sources: EPA 2014 (production), USITC 2014 (imports and exports).

— = no data found.

^aNo specific Schedule B code was identified. (Schedule B codes are 10-digit numbers used by the U.S. Commerce Department to collect and publish statistics on physical goods exported from the United States.)

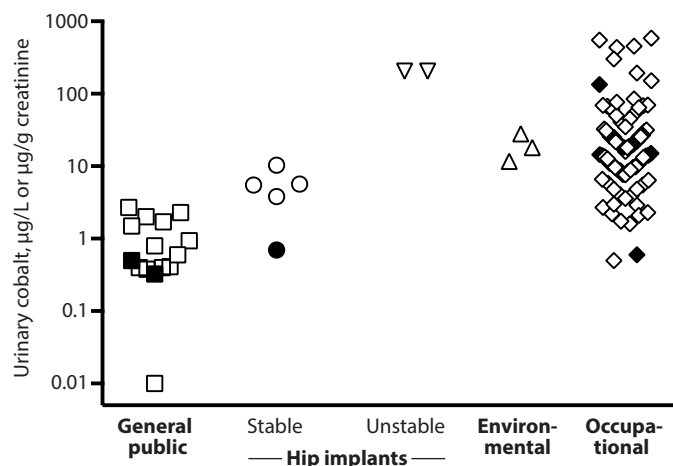
^bCobalt chloride production data for 2012 were withheld by the manufacturer.

^cThe reported value is for cobalt hydroxide and oxides combined.

Exposure

A significant number of people living in the United States are exposed to cobalt, based on several lines of evidence, including biological monitoring data demonstrating exposure in occupationally and non-occupationally exposed populations. Data from the U.S. Environmental Protection Agency’s Toxics Release Inventory (TRI) indicate that production- and use-related releases of cobalt compounds have occurred at numerous industrial facilities in the United States.

In biomonitoring studies that measured cobalt in the urine of people exposed to cobalt from various sources, the highest levels generally were due to occupational exposures and failed hip implants; lower levels were due to exposure from normal implants or the environment. The lowest levels were observed in the general population (with unknown sources of exposure). The graph below shows the mean or median levels of urinary cobalt for the general population and for groups with known exposures. Data are reported for both U.S. and non-U.S. exposures; occupational and medical implant exposures outside the United States can be informative because of the similarity of production methods and implant compositions worldwide.



Urine levels of cobalt for various exposed groups

Source: NTP 2015.
 Filled symbols = U.S. data; open symbols = non-U.S. data.
 Each data point represents a different study.

Urinary cobalt measurements in the U.S. general population have remained consistent since 1999, with geometric mean values between 0.316 and 0.379 µg/L, according to the National Health and Nutrition Examination Survey (NHANES) (CDC 2014). Urinary cobalt is considered a good indicator of absorbed cobalt (IARC 2006, WHO 2006), especially from recent exposures (ATSDR 2004). Levels of cobalt in blood (including whole blood, plasma, and serum) show a pattern similar to that for urinary cobalt levels.

Occupational Exposure

The primary route of occupational exposure to cobalt is via inhalation of dust, fumes, mists, or gaseous cobalt carbonyl. Dermal contact with cemented carbide (i.e., hard-metal) powders and cobalt salts can result in systemic uptake. Occupational exposure to cobalt occurs in the following industries: (1) production of cobalt metal or salts, (2) metallurgical-related industries, (3) cemented carbides and bonded diamonds, (4) chemicals and pigments, and (5) electronics, “green” energy, and recycling. Occupational exposure has been documented by measurements of cobalt in ambient workplace air (as shown in the following table) and in blood, urine (as shown in the figure above), nails, and hair, and lung tissue from workers or deceased workers (IARC 1991, ATSDR 2004, IARC 2006, CDC 2013). The highest levels of cobalt in workplace air were generally for hard-metal manufacture involving cobalt metal powders (> 1,000 µg/m³ in some instances) (NTP 2009), production of cobalt salts, and metallurgical-related industries (> 10,000 µg/m³ in some instances) (IARC 2006). The highest cobalt levels in urine, blood, hair, and nails also were associated with exposure to cobalt powders.

Industry	Cobalt in workplace air (range, µg/m ³)
Production of cobalt metal or salts	2–50,000
Metallurgical-related industries ^a	ND–21,000 ^b
Cemented carbides and bonded diamonds ^a	ND–1,622
Chemicals and pigments ^a	ND–80
Electronics, “green” energy, and recycling ^a	ND–10

Sources: IARC 2006, NIOSH 2015. ND = not detected.
^aThe range for cobalt in workplace air includes U.S. data from NIOSH Hazard Evaluation and Technical Assistance surveys.
^bOne higher value was reported; however, the Occupational Safety and Health Administration noted that the sample appeared to have been tampered with.

Surgical Implants

Total hip implants consist of (1) a femoral head attached to a stem that is inserted in the thigh bone (usually made of ceramic or metal) and (2) a socket or cup that is anchored in the pelvis (made of metal, ceramic, or polyethylene). Cobalt-chromium-molybdenum (CoCrMo) alloy is the predominant alloy used in metal-containing implants, such as metal-on-metal implants (in which both articulating surfaces are metal), polyethylene-on-metal implants, and metal-on-ceramic implants. Other metals, such as nickel, tungsten, iron, aluminum, and titanium, may also be used in implants. Knee implants may also contain cobalt metal; however, unlike some hip implants with metal-to-metal contact, knee implants are designed so that metal surfaces do not contact each other. Cobalt ions may be released into the body throughout the lifetime of a cobalt-containing device (Sampson and Hart 2012, Devlin *et al.* 2013). Urinary levels of cobalt identified from studies of hip implants reported as stable or that did not specifically address stability ranged from approximately 0.7 to 12 µg/L, compared with a range of 0.01 to 4.2 µg/L for the general population (as shown in the previous graph). Implants may fail because of excessive wear or corrosion by body fluids, increasing the levels of cobalt released from the implants (Sampson and Hart 2012). Dunstan *et al.* (2005) reported blood cobalt levels of 19 and 52 µg/L in two individuals with unstable (radiologically loose) metal-on-metal implants. In rare cases, high levels of cobalt from failed implants may be associated with toxicity. Recommended levels of blood cobalt for further clinical investigation and action were set at 7 µg/L in the United Kingdom (MHRA 2012) and 10 µg/L in the United States by the Mayo Clinic (2015).

Environmental Exposure

The TRI reported that in 2013, on- and off-site industrial releases of cobalt and cobalt compounds totaled approximately 5.5 million pounds from 723 facilities in the United States (TRI 2014a). Calculations based on media-specific release data from the TRI indicate that releases to land accounted for 82% of total releases in 2013 (TRI 2014b,c). Worldwide, approximately 75,000 metric tons of cobalt enters the environment annually, with similar amounts coming from natural sources (40,000 metric tons) and sources related to human activities (35,000 metric tons) (Shedd 1993, CDI 2006). Recycling of electronic and electrical waste can result in release of cobalt to the environment; however, releases from this source are less of a concern in the United States than in other global regions where recycling is more common and less controlled (Julander *et al.* 2014).

The average concentration of cobalt in ambient air in the United States has been reported to be approximately 0.4 ng/m³ (ATSDR 2004). Levels can be orders of magnitude higher near source areas (e.g., near facilities processing cobalt-containing alloys and compounds) reported from outside the United States. The median co-

balt concentration in U.S. drinking water has been reported to be less than 2.0 µg/L; however, levels as high as 107 µg/L have been reported (ATSDR 2004). Cobalt concentrations have been reported to range from 0.01 to 4 µg/L in seawater and from 0.1 to 10 µg/L in fresh water and groundwater (IARC 2006). Studies have reported cobalt soil concentrations ranging from 0.1 to 50 ppm. However, soils near ore deposits, phosphate rock, or ore-smelting facilities or soils contaminated by airport or highway traffic or near other source areas may contain higher concentrations (IARC 2006).

Data for individuals exposed to cobalt from the environment are limited, but a study of metal exposure from mining and processing of nonferrous metals in Katanga, Democratic Republic of Congo, found that geometric mean urinary cobalt concentrations were 4.5-fold higher for adults and 6.6-fold higher for children in urban and rural communities near mines and metal smelters than in rural communities without mining or industrial activities (Cheyns *et al.* 2014).

Other Sources of Exposure of the General Population

The general population can be exposed to low levels of cobalt primarily through consumption of food and to a lesser degree through inhalation of ambient air and ingestion of drinking water (ATSDR 2004). The daily cobalt intake from food in the United States was estimated to range from 3.4 to 11.6 µg based on analyses of 234 foods in the 1984 U.S. Food and Drug Administration Total Diet Study (Pennington and Jones 1987). Although this amount includes cobalt as part of both vitamin B₁₂ and other cobalt compounds (ATSDR 2004), green, leafy vegetables and fresh cereals generally contain the most cobalt (IARC 1991), and these plant sources of cobalt do not contain vitamin B₁₂. In the 1960s, some breweries added cobalt salts to beer to stabilize the foam (resulting in cobalt exposures of 0.04 to 0.14 mg/kg of body weight), but cobalt is no longer added to beer (ATSDR 2004). Higher cobalt intake may result from consumption of over-the-counter or prescription mineral preparations containing cobalt compounds.

Other potential sources of exposure include consumer products and tobacco smoking. Cobalt is present in only a few consumer products, including cleaners, detergents, soaps, car waxes, and a nickel metal hydride battery (5% to 10% cobalt) (ATSDR 2004, HPD 2014). Various brands of tobacco have been reported to contain cobalt at concentrations ranging from less than 0.3 to 2.3 µg/g of dry weight, and 0.5% of the cobalt content is transferred to mainstream smoke (WHO 2006). However, urinary cobalt levels (unadjusted for creatinine) for cigarette-smoke-exposed and unexposed NHANES participants for survey years 1999 to 2004 did not differ significantly (Richter *et al.* 2009).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of cobalt naphthenate in solvent naphtha on ships and barges.

Department of Transportation (DOT)

Numerous cobalt compounds are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Cobalt compounds are listed as hazardous air pollutants.

Clean Water Act

Cobalt discharge limits are imposed for numerous processes during the production of cobalt at secondary cobalt facilities processing tungsten carbide scrap raw materials. Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities; for numerous processes during the production of batteries; and for numerous processes during the production of cobalt salts.

Discharge limits for cobalt are imposed for wastewater discharges from centralized waste treatment facilities except discharges and activities exempted in 40 CFR 437.1(b), (c), and 40 CFR 421, Subpart AC.

Cobaltous bromide, formate, and sulfamate are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb for cobaltous bromide, formate, and sulfamate.

Emergency Planning and Community Right-To-Know Act

EPCRA Section 302: Threshold planning quantity (TPQ) = 100 lb for cobalt, ((2,2'-(1,2-ethanediyldibis(nitriolomethylidene))bis(6-fluorophenolato))(2-)-N,N',O,O')- (also called fluomine) (solids in powder form with particle size < 100 µm or solution or molten form); = 10,000 lb for all other forms of fluomine; = 10 lb for cobalt carbonyl (solids in powder form with particle size < 100 µm or solution or molten form); = 10,000 lb for all other forms of cobalt carbonyl.

EPCRA Section 304: Reportable quantity (RQ) = 100 lb for fluomine; = 10 lb for cobalt carbonyl.

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Boiled linseed oil (containing no more than 0.33% manganese naphthenate and no more than 0.33% cobalt naphthenate) is exempt from the requirement of a tolerance when used as a coating agent for 5-ethyl hexahydro-1H-azepine-1-carbothioate. No more than 15% of the pesticide formulation may consist of boiled linseed oil, and this exemption is limited to use on rice before edible parts form.

Food and Drug Administration (FDA, an HHS agency)

Cobaltous salts are prohibited from use in human food.

All drugs containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives) have been withdrawn from the market because they were found to be unsafe or not effective, and they may not be compounded.

Chromium–cobalt–aluminum oxide used as a color additive for linear polyethylene surgical sutures used in general surgery must comprise no more than 2% by weight of the suture material, not migrate to surrounding tissue, and conform to labeling requirements in 21 CFR 70.25.

Chromium cobalt-aluminum oxide may be used as a color additive in contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

Ferric ammonium ferrocyanide and ferric ferrocyanide used to color externally applied drugs (including those for use in the area of the eye) must not contain more than 200 ppm cobalt (as Co) and conform to labeling requirements in 21 CFR 70.25.

21 CFR 369 contains recommended drug labeling statements for over-the-counter cobalt preparations containing ≥ 0.5 mg cobalt as a cobalt salt per dosage unit and which recommend administration rates of ≥ 0.5 mg per dose and ≥ 2 mg per 24-hour period.

An approved new drug application is required for marketing cobalt preparations intended for use by man.

21 CFR 872, 874, and 888 identify class designations (Class I, II, or III) of various cobalt-containing dental prosthetic device alloys, cobalt–chromium–alloy-based facial prosthetics, and cobalt–chromium–molybdenum orthopedic devices that determine the type of premarketing submission or application required for FDA clearance to market.

Cobalt naphthenate may be used in quantities that do not exceed those reasonably required as an accelerator in the production of cross-linked polyester resins used as articles or components of articles intended for repeated use in contact with food.

Cobalt aluminate may be safely used as a colorant in the manufacture of articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding of food at levels not to exceed 5% by weight of all polymers except in resinous and polymeric coatings complying with 21 CFR 175.300, melamine-formaldehyde resins in molded articles complying with 21 CFR 177.1460, xylene-formaldehyde resins complying with 21 CFR 175.380, ethylene-vinyl acetate copolymers complying with 21 CFR 177.1350, and urea-formaldehyde resins in molded articles complying with 21 CFR 177.1900.

Occupational Safety and Health Administration (OSHA)

This legally enforceable PEL was adopted from the 1968 ACGIH TLV-TWA shortly after OSHA was established; it may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) (8-h TWA) = 0.1 mg/m³ for cobalt metal, dust, and fume (as Co).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m³ for cobalt and inorganic compounds; = 0.1 mg/m³ for cobalt carbonyl and cobalt hydrocarbonyl.

Biological exposure index (BEI) = 15 µg/L for cobalt in urine for cobalt and inorganic compounds, including cobalt oxides but not combined with tungsten carbide, for end of shift at end of workweek.

Consumer Product Safety Commission (CPSC)

The CPSC has issued guidance regarding the potential hazards of specific cobalt- or cobalt-compound-containing art and craft materials (e.g., glazes, glass colorants, paints, toners, pigments, and dyes) and specific precautions to take when using them.

Environmental Protection Agency (EPA)

Regional Screening Levels (formerly Preliminary Remediation Goals): residential soil = 23 mg/kg; industrial soil = 350 mg/kg; residential air = 0.00031 µg/m³; industrial air = 0.0014 µg/m³; tap water = 6 µg/L.

National Institute for Occupational Safety and Health (NIOSH, an HHS agency)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m³ for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m³ for cobalt metal dust and fume (as Co); = 0.1 mg/m³ for cobalt carbonyl (as Co) and cobalt hydrocarbonyl (as Co).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m³ for cobalt metal dust and fume (as Co).

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