# Cobalt Dust
# [7440-48-4]

# Review of Toxicological Literature

**February 2002**

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*Prepared for*

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# Executive Summary

## Nomination

Cobalt dust was nominated for toxicology and carcinogenesis studies based on widespread occupational exposure and the occurrence of occupational disease, i.e. hard metal disease, associated with exposure to cobalt and its compounds, including cobalt tungsten carbide. The carcinogenicity of a soluble cobalt compound, cobalt sulfate heptahydrate, in experimental animals exposed by inhalation has been recently demonstrated. Limited data are available to assess the chronic toxicity and carcinogenic potential of inhaled insoluble cobalt compounds, particularly cobalt metal dust.

## Nontoxicological Data

Cobalt exists in two allotropic forms, the hexagonal form and the cubic form, both of which are stable at room temperature. It is stable in air and water at normal temperature. Specially prepared very fine cobalt dust (i.e., dust from the reduction of the oxides in hydrogen), however, will ignite at room temperature in air.

Cobalt metal is commercially available with a purity >95% as broken or cut cathodes or as electrolytic coarse powder, anodes, briquets, etc. Cobalt powders have been used in the formation of alloy phases, cobalt-based superalloys, fine-particle magnetic alloys, and bearing materials filled with low-friction substances (e.g., graphite and nylon). Extra fine cobalt powder is an important raw material for producing cemented carbides, diamond tools, and metal welding and spraying components.

Most cobalt used in the United States is imported. Between 1995 and 1999, 6440 to 8430 metric tons (14.2 to 18.6 million pounds) of cobalt was imported into the United States each year, and the reported consumption ranged from 7590 to 9130 metric tons (16.7 to 20.1 million pounds) cobalt content. Two U.S. companies produce extra fine cobalt metal powder from cobalt metal and scrap.

Typical workplace air concentrations range from 0.01 to 1.7 mg/m$^3$ (0.004-0.71 ppm). Cobalt compounds are released to the air from natural and anthropogenic sources, especially burning fossil fuels. Other sources of atmospheric cobalt emissions are vehicle exhaust and cigarette smoke. At unpolluted sites, mean atmospheric cobalt levels are generally <1 to 2 ng/m$^3$ (0.4-0.8 ppt), while near industrial settings, they may be >10 ng/m$^3$ (4.1 ppt). In the United States, the average cobalt concentration in ambient air is ~0.4 ng/m$^3$ (0.2 ppt).

Cobalt compounds are listed as Federal hazardous air pollutants and in Section 8(d) of the Toxic Substances Control Act (TSCA). The American Conference of Governmental Industrial Hygienists (ACGIH) has established a concentration of 0.05 mg Co/m$^3$ for cobalt metal dust and fume as the eight-hour time-weighted average (TWA) threshold limit value (TLV); the Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit (PEL) of 0.1 mg Co/m$^3$ for cobalt metal dust and fume as the TWA for general industry, the shipyard industry, and the construction industry; and the National Institute of Occupational Safety and Health (NIOSH) has recommended an exposure limit of 0.05 mg/m$^3$ as cobalt for the metal, dust, and fumes as the ten-hour TWA.

## Human Data

Exposure: The general public is primarily exposed to cobalt metal fume and dust via inhalation; other routes include contact with the eyes and skin, and ingestion, since cobalt is a common trace element in foods and drinking water. In the United States, more than a million workers are potentially exposed to cobalt or its compounds, with the greatest exposure in mining processes, the cemented WC industry, and in cobalt powder and alloys production. Occupational exposure to cobalt is primarily via inhalation of dusts, fumes, or mists containing cobalt, targeting the skin and the respiratory tract, and occur during the production of cobalt powder; the production, processing, and use of hard metal; the processing of asbestos

fiber; the grinding and sharpening of cemented carbide and steel tools, etc. In the NIOSH 1981-1983 National Occupational Exposure Survey (NOES), an estimated 79,652 workers were potentially exposed to cobalt in 16 industries.

Upon being absorbed by inhalation, cobalt (with a biological half-life of a few days) is eliminated in the urine. A study measuring the ambient air in cobalt powder production reported a concentration in ambient air ranging from 0.675 to 10 mg/m$^3$ (0.280-4.1 ppm) and a mean concentration of 35.1 µg/L (0.596 µM) cobalt in urine. In another study of cobalt powder and cobalt salt production, the mean concentration of cobalt in ambient air was 46 to 1046 µg/m$^3$ (0.019-0.434 ppm) (stationary samples); the mean concentration of cobalt in blood was 5 to 48 µg/L (0.08-0.81 µM), and the mean level in urine was 19 to 438 µg/L (0.32-7.43 µM). (Correlative analyses have indicated that exposure to 50 µg/m$^3$ (0.02 ppm) cobalt in air leads to blood and urine concentrations roughly equivalent to 2.5 and 30 µg/L [0.042 and 0.51 µM], respectively.) Male workers occupationally exposed to a dust mixture for at least two years had significantly higher levels of cobalt in the urine than non-exposed workers (geometric means of 23.6 and 1.1 µg Co/g creatinine [0.400 and 0.019 µmol/g], respectively). Airborne concentrations of cobalt during processes involving hard metal were mainly below 100 µg/m$^3$ (41.5 ppm).

Toxicity: Cobalt dust is a mild irritant to the eyes and the skin. Symptoms of ingestion include hypotension, pericardial effusion, vomiting, and convulsions. Inhalation of cobalt dust and fumes has caused shortness of breath, dermatitis with hyperemia, and vesiculation. Additionally, cardiac effects, congestion of the liver, kidneys, conjunctiva, and immunological effects have been observed.

Chronic exposure to cobalt as a metal, fumes, or dust has been reported to cause respiratory disease with symptoms ranging from cough to permanent disability and even death, respiratory hypersensitivity, progressive dyspnea, decreased pulmonary function, weight loss, dermatitis, and diffuse nodular fibrosis. Allergic sensitization and chronic bronchitis may also result from prolonged exposure to the powder.

Intense occupational exposure to cobalt powder for 20 months produced a progressive hearing loss and atrophy of the optic nerve. A case of giant cell interstitial pneumonitis induced by cobalt dust was also reported. In both cases, the patient improved with the termination of exposure. A 48-year-old worker handling cobalt powder experienced cardiac shock under anesthesia during an operation for a duodenal ulcer.

Carcinogenicity: Few epidemiological studies of cancer risk in cobalt-exposed workers exist. In studies that are available, confounding by nickel and arsenic exposures and the limited size of the exposed population limit their utility for assessing carcinogenic hazard. The International Agency for Research on Cancer (IARC) concluded that there was *inadequate evidence* for the carcinogenicity of cobalt and cobalt compounds in humans and categorized the compounds as Group 2B—*possibly carcinogenic to humans*.

Genotoxicity: In workers occupationally exposed for at least two years to a dust mixture containing cobalt, nickel, and chromium, the mean value of individual sister chromatid exchange (SCE) frequencies and the percentage of high-frequency cells (HFC) were significantly higher compared to controls, and both were statistically significantly affected by exposure status and smoking habit. However, because cobalt is a weak mutagen, the results suggested that the small amounts of chromium and nickel might have been sufficient enough to induce SCE. In another study, male workers exposed to cobalt dust from refineries and workers exposed to hard metal dust from two producing plants had no significant increase of genotoxic effects (i.e., initial DNA damage and definitive chromosome breakage or loss) when compared to each other as well as controls. In contrast, in an *in vitro* study using peripheral blood cells from a healthy volunteer, cobalt powder and tungsten carbide-cobalt mixture (WC-Co) both induced dose-dependent increases in chromosome and DNA damage; the effect of the latter mixture was greater than that of cobalt alone.

## Animal Data

Chemical Disposition, Metabolism, and Toxicokinetics: Rats exposed to cobalt (0.001-0.5 mg/m$^3$ [0.0004-0.2 ppm] for 24 hours/day for 3 months) had accumulated levels in the thyroid, liver, and kidneys. Cobalt accumulation was also found in the lungs at >0.001 mg/m$^3$ (0.415 ppb]. The degree of accumulation was proportional to the concentration and duration of exposure. When administered as WC-Co, cobalt levels in urine were significantly increased compared to administration of pure cobalt, suggesting a greater bioavailability of cobalt when combined with WC. Clearance patterns of cobalt from the lungs and from blood in the animals were biphasic—in the first phase, clearance was rapid, while in the second phase, the removal was slower. Rapid urinary excretion of cobalt was also observed in rats exposed to WC-Co (intratracheal [i.t.]; 0.50 mg/100 g [0.085 µmol/g] body weight), occurring as early as six hours after instillation but failing to increase any further after 12 hours. Animals receiving cobalt powder (0.03 mg/100 g [5.1 nmol/g] body weight) excreted cobalt at a rate about one order of magnitude lower than WC-Co rats at six hours. However, at 48 hours, both groups had excreted almost equal amounts, and on day 7, there was no significant difference between mean urinary excretions of cobalt. The mean lung cobalt concentration of rats given cobalt was two times more than that for WC-Co; by day 7, mean levels had decreased significantly to almost the same level in all exposed rats.

In miniature swine, cobalt (inhalation; 0.1-1.0 mg/m$^3$ [0.04-0.41 ppm] pure cobalt powder for 6 hours/day 5 days/week for 3 months) was excreted mostly by the kidneys. In tissue analysis, the highest cobalt level in the control group was found in the liver. Test animals had similar levels in the liver. In the kidney cortex, however, cobalt concentrations were higher in the exposed groups compared to that in the control group.

Acute Toxicity: In rats, an intraperitoneal $LD_{50}$ value of 100-200 mg/kg (1.70-3.39 mmol/kg body weight was calculated. An $LD_{50}$ value of 1500 mg/kg (25.45 mmol/kg) was also reported but the route was unspecified.

Metallic cobalt powder was found to have an "acute irritant action," leading to severe changes in capillaries in the lungs or peritoneum, accompanied with a significant amount of fluid and sometimes hemorrhages. In rats, i.t. instillation of a 5% sterile suspension of cobalt powder produced pulmonary hemorrhage and edema. In a comparison study, golden hamsters, adult cavies, rabbits, and mice were exposed to cobalt dust via inhalation (study details not provided). Animals showed gross edema and numerous hemorrhages in the lungs.

In SD-Jcl rats exposed to cobalt aerosol (2.72 mg/m$^3$ [1.13 ppm]) for five hours, a very slight increase in alveolar macrophages in the alveolar ducts was observed three days after exposure. When given for an extended period (2.12 mg/m$^3$ [0.880 ppm] for 5 hours/day for 4 days), early inflammatory changes in the lung were seen; the induced lesions, however, were reversible.

Short-term or Subchronic Toxicity: Inhalation studies with metallic cobalt aerosol (0.005-0.5 mg/m$^3$ [0.002-0.2 ppm] 24 hours/day for 3 months) produced increases in hemoglobin and erythrocyte levels and decreases in blood phospholipids, cholesterol, and β-lipoproteins in rats. Additionally, disturbances in protein and carbohydrate metabolism and enzyme system, activation of the hemopoietic system, and pathomorphological changes in several organs and tissues were observed. Inhalation of the powder (0.48 and 4.4 mg/m$^3$ [0.20 and 1.8 ppm] for 4 months) also affected mucosal tissue. At 200 mg/m$^3$ (83.0 ppm), damages occurred in the vascular system, respiratory system, and in kidneys. A single i.t. injection of cobalt (3, 5, 10, and 50 mg [0.05, 0.08, 0.17, and 0.85 mmol]) caused changes in the lungs of rats.

In guinea pigs, i.t. administration of cobalt dust (50 mg [0.85 mmol]) resulted in obliterative pleuritis and firm dust lesions. Miniature swine exposed to cobalt powder (0.1-1.0 mg/m$^3$ [0.04-0.41 ppm] 6 hours/day

5 days/week for 3 months) became lethargic after one month and exhibited a functional impairment in the lungs, weakened ventricular contraction, and repolarization abnormalities. Alveolar septa were significantly thickened with collagen, elastic tissue, and fibroblasts.

WC-Co was found to be more toxic to the lung than cobalt alone. In a study of the delayed lung effects of pure cobalt powder and hard metal powder, a single i.t. instillation of WC-Co (1, 5, or 10 mg/100 g [0.17, 0.85, or 1.7 µmol/g] body weight) induced an acute alveolitis, which persisted for a month, while cobalt alone (0.6 mg/100 g [0.1 µmol/g] body weight) produced only slight effects. Repeated administration of cobalt (0.06 mg/100 g [0.01 µmol/g] body weight 4x) failed to produce any significant parenchymal changes, but WC-Co (1 mg/100 g [0.17 µmol/g] body weight 4x) induced a pulmonary fibrosis reaction; this was different from the progressive inflammatory process induced by crystalline silica.

Synergistic or Antagonistic Effects: In an *in vitro* assay, titanium carbide, niobium carbide, and chromium carbide exerted a synergistic effect with cobalt powder on mouse peritoneal macrophage integrity (i.e., increased lactate dehydrogenase [LDH] release).

Cytotoxicity: In mouse peritoneal macrophages and rat alveolar macrophages, WC-Co (12-200 µg/mL) had a greater toxic affect than cobalt metal powder alone (0.6-12 µg/mL [10 µM-0.20 mM]); for example, glucose uptake and superoxide anion production were both more significantly reduced by WC-Co than by the metal. Cobalt powder and WC-Co (both at 3 µg Co/mL [0.05 mM]), however, did not stimulate the production of interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), or fibronectin by rat alveolar macrophages.

In an *in vivo* assay with rats, WC-Co (0.06 mg Co/100 g [0.01 µmol/g] body weight) showed greater toxicity than cobalt alone (same dose). Significant increases in bronchoalveolar lavage fluid (BALF) parameters and the cellularity of BALF occurred with WC-Co. In lung phagocytes, WC-Co and cobalt both significantly stimulated cystatin-c production.

In chick primary cultures and rodent fibroblast cell lines, cobalt released from cobalt metal, alloys or dissolved salts was cytotoxic at concentrations >7.5 µg/mL (0.13 mM); cell death, growth inhibition, and mitotic aberrations were observed.

Reproductive and Teratological Effects: In test animals (species not provided) exposed to cobalt by inhalation (dose and exposure duration not provided), adverse effects included testicular atrophy, decreased sperm motility, and an increased length of the estrus cycle. Oral exposure to the metal at levels causing maternal toxicity produced stunted growth and decreased survival of newborn pups.

Carcinogenicity: In rats, single or repeated intramuscular or intrathoracic injections of cobalt metal powder (28 mg [0.48 mmol]) produced tumors at the injection site, mostly rhabdomyosarcomas. In rats, guinea pigs, and miniature swine, no tumors were observed from exposure via inhalation (up to 1.5 $mg/m^3$ [0.62 ppm] in rabbits and swine; 200 $mg/m^3$ [83.0 ppm] in rats) and i.t. (2.5-50 mg [0.042-0.85 mmol]) and intrarenal (5 mg [0.08 mmol]) injections. In rats, cobalt metal powder has also produced tumors in the thyroid gland, as well as the injection site. In rabbits, injection of cobalt dust produced transplantable liposarcomas and hyperplasia of adipose tissue.

Genotoxicity: Incubation of human peripheral lymphocytes with cobalt (0.06-6.0 µg/mL [1.0 µM-0.10 mM]) or WC-Co (10-100 µg/mL) caused a time- and dose-dependent increase in the production of DNA single strand breaks. On the basis of an equivalent cobalt content, WC-Co had a more significant effect than cobalt alone. Addition of sodium formate (1 M) had a protective effect against the production of the breaks with both powders.

No chronic toxicity or immunotoxicity studies with cobalt powder or dust were available.

Miscellaneous Studies: In rats exposed for four months to metallic cobalt dust (dose not provided), blood pressure was reduced by 20-25%, beginning with the third month of exposure. In a separate experiment (study details not provided), significant prolongation of extensor chronaxie and a significant but smaller increase in flexor chronaxie were observed at the second month of exposure in the animals. In addition, the rheobase increased but not significantly. The findings were indicative of changes in the central nervous system.

In cultured rat myoblasts, cobalt metal powder in horse serum produced cytological changes resembling those found in cobalt-induced rhabdomyosarcomas *in vivo*.

Hard Metal Disease and Cobalt-Tungsten Carbide: Numerous reviews and original studies on cobalt-induced occupational disease (especially hard metal disease) are available. The major effects in hard metal workers exposed to cobalt-containing dust are pulmonary effects. Interstitial fibrosis (hard-metal pneumoconiosis) and occupational asthma are the two types of lung lesions that occur. A study of memory functioning found that adult WC workers with hard metal disease had memory deficits related to difficulties in attention and verbal memory.

In animal studies, a synergistic effect was observed when cobalt was combined with WC (see above data). Rat alveolar epithelial type II cells (AT-II) were found to be more sensitive to cobalt than macrophages, and human AT-II were less sensitive to cobalt than rat alveolar macrophages. The toxicity of cobalt was increased with WC. In human osteosarcoma (HOS) cells, a pure mixture of tungsten (92%), nickel (5%), and cobalt (3%) particles (r-WNiCo) as well as cobalt powder alone (both at concentrations from 0.75-200 µg/mL) had a dose-dependent decrease in cell survival during a 24-hour incubation period. The r-WNiCo particles also produced transformants showing morphological changes and anchorage-independent growth in soft agar, induced tumors at the injection site in nude mice, and produced alterations in *ras* oncogene expression. The mixture was genotoxic; DNA breakage and chromosomal aberrations were induced when cells were exposed to the mixture.

Rats exposed to repeated inhalation of a cobalt metal blend used by the cemented carbide industry (20 $mg/m^3$ [8.3 ppm] cobalt for three years) had hyperplasia of the bronchial epithelium and focal fibrotic lesions of the lungs with developing granulomata. An experiment in which the animals were exposed daily to cobalt metal fume of cobalt, cobalt oxide, and cobaltic-cobaltous oxide (almost equal parts) via inhalation produced no such reactions. In guinea pigs, repeated inhalation of a mixture of cobalt (25%) and WC (75%) produced acute pneumonitis, which then rapidly led to death.

**Structure-Activity Relationships**

The NTP (National Toxicology Program) evaluated the toxicity and carcinogenicity of cobalt sulfate heptahydrate and found *some evidence of carcinogenic activity* in male rats based on increased incidences of alveolar/bronchiolar neoplasms. Marginal increases in incidences of pheochromocytomas of the adrenal medulla may have been related to exposure to cobalt sulfate heptahydrate. There was *clear evidence* of carcinogenic activity in female rats based on increased incidences of alveolar/bronchiolar neoplasms and pheochromocytomas of the adrenal medulla in groups exposed to cobalt sulfate heptahydrate. There was *clear evidence* of carcinogenic activity of cobalt sulfate heptahydrate in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. Inhalation exposure to cobalt sulfate heptahydrate, cobalt oxide, and cobalt hydrocarbonyl caused various inflammatory, fibrotic, and proliferative lesions in the respiratory tracts of rats, mice, and hamsters.

# Table of Contents


**Executive Summary** ..... i

**1.0 Basis for Nomination** ..... 1

**2.0 Introduction** ..... 1
- **2.1 Chemical Identification and Analysis** ..... 1
- **2.2 Physical-Chemical Properties** ..... 2
- **2.3 Commercial Availability** ..... 2

**3.0 Production Processes** ..... 2

**4.0 Production and Import Volumes** ..... 3

**5.0 Uses** ..... 3

**6.0 Environmental Occurrence and Persistence** ..... 4

**7.0 Human Exposure** ..... 4

**8.0 Regulatory Status** ..... 5

**9.0 Toxicological Data** ..... 6
- **9.1 General Toxicology** ..... 6
  - **9.1.1 Human Data** ..... 6
  - **9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics** ..... 8
  - **9.1.3 Acute Exposure** ..... 9
  - **9.1.4 Short-term and Subchronic Exposure** ..... 9
  - **9.1.5 Chronic Exposure** ..... 17
  - **9.1.6 Synergistic/Antagonistic Effects** ..... 17
  - **9.1.7 Cytotoxicity** ..... 17
- **9.2 Reproductive and Teratological Effects** ..... 20
- **9.3 Carcinogenicity** ..... 20
- **9.4 Initiation/Promotion Studies** ..... 20
- **9.5 Anticarcinogenicity** ..... 20
- **9.6 Genotoxicity** ..... 23
- **9.7 Cogenotoxicity** ..... 23
- **9.8 Antigenotoxicity** ..... 23
- **9.9 Immunotoxicity** ..... 23
- **9.10 Other Data** ..... 23
- **9.10.1 Miscellaneous Studies** ..... 23
- **9.10.2 Hard Metal Disease and Cobalt-Tungsten Carbide** ..... 23

**10.0 Structure-Activity Relationships** ..... 26

**11.0 Online Databases and Secondary References ..... 26**
**11.1 Online Databases ..... 26**
**11.2 Secondary References ..... 27**

**12.0 References ..... 28**

**13.0 References Considered But Not Cited ..... 38**

**Acknowledgements ..... 40**

**Units and Abbreviations ..... 40**

**Appendix: Literature Search Strategy ..... 42**

**Tables:**
**Table 1 Acute Toxicity Values for Cobalt Dust ..... 9**
**Table 2 Acute Exposure to Cobalt Dust ..... 10**
**Table 3 Short-term and Subchronic Exposure to Cobalt Dust ..... 11**
**Table 4 Cytotoxicity Studies of Cobalt Dust ..... 18**
**Table 5 Carcinogenicity Studies of Cobalt Dust ..... 21**

## 1.0 Basis for Nomination

Cobalt dust was nominated for toxicology and carcinogenesis studies based on the widespread occupational exposure and the occurrence of occupational disease, i.e. hard metal disease, associated with exposure to cobalt and its compounds, including cobalt tungsten carbide.

The carcinogenicity of a soluble cobalt compound, cobalt sulfate heptahydrate, in experimental animals exposed by inhalation has been recently demonstrated. Limited data are available to assess the chronic toxicity and carcinogenic potential of inhaled insoluble cobalt compounds, particularly cobalt metal dust. Furthermore, the evidence for a difference in toxic and carcinogenic responses for insoluble and soluble metal compounds, e.g. nickel, warrants a further evaluation of cobalt dust.

## 2.0 Introduction

In this report, Sections 2.0 through 8.0 mainly contain nontoxicological data for "cobalt metal;" where available, data for "cobalt dust" were included (e.g., production processes). Toxicological data consist of studies specifically using cobalt metal dust or powder. When given, comparisons with tungsten carbide-cobalt powders are provided. In addition, a brief review of toxicology data for hard metal and other cobalt compounds is presented in Sections 9.10.2 and 10.0, respectively. Further toxicity information on cobalt, form unspecified, and cobalt compounds can be found in *Draft Toxicological Profile for Cobalt* (ATSDR, 2001).

### 2.1 Chemical Identification and Analysis

Cobalt ([Co]; CASRN 7440-48-4; mol. wt. = 58.9332) is also called:

| | |
|---|---|
| ACO 4 | Cobalt metal |
| Aquacat | Co 0138E |
| C.I. 77320 | NCI-C60311 |
| Cobalt element | Super cobalt |

Sources: Registry (2001); RTECS (2000)

Cobalt in air, water, food, biological materials (e.g., urine, blood, serum, and tissues), and in various working materials has been analyzed using gas chromatography (GC), graphite furnace-atomic absorption spectrometry (GF-AAS), flame-AAS (F-AAS), inductively coupled plasma emission spectrometry (ICP), neutron activation analysis (NAA), adsorption differential pulse voltammetry (ADPV), and differential pulse cathodic stripping voltammetry (DPCSV) (IARC, 1991). Several sampling procedures have been developed by the National Institute of Occupational Safety and Health (NIOSH) (e.g., methods 7027 and 7900) for the analysis of cobalt in air (HSDB, 2001). Cobalt metal fume and dust is first collected on a cellulose membrane filter and then treated with nitric acid; as a solution in acid, analysis is then done using an atomic absorption spectrophotometer (NIOSH, 1978). The Occupational Safety and Health Administration (OSHA) has also developed air sample methods for cobalt dust and fume (e.g., OSHA ID 125G and OSHA ID 121) (OSHA, 2001). The determination of cobalt in biological materials is used as a biological indicator of exposure to the metal (IARC, 1991).

## 2.2 Physical-Chemical Properties

| Property | Information | Reference(s) |
|---|---|---|
| Physical State: | | |
| cobalt metal | gray, hard, magnetic, ductile, and somewhat malleable metal | Budavari (1996) |
| cobalt metal fume and dust | black solid or finely divided particulate dispersed in air | NIOSH (1978) |
| Odor | odorless | HSDB (2001) |
| Boiling Point ($^oC$) | 3100 | Budavari (1996) |
| Melting Point ($^oC$) | 1493 | Budavari (1996) |
| Density ($g/cm^3$) @ 25 °C | 8.92 | Budavari (1996) |
| Water Solubility | practically insoluble | IARC (1991) |
| Soluble in: | dilute nitric acid, hydrofluoric acid, sulfuric acid, and hydrochloric acid | Budavari (1996); IARC (1991) |

Although a magnetic metal, cobalt loses this property at 1115 °C (HSDB, 2001). It exists in two allotropic forms, the hexagonal form and the cubic form, both of which are stable at room temperature. At ordinary temperature, it is stable in air and toward water (Budavari, 1996). Specially prepared very fine cobalt dust (i.e., dust from the reduction of the oxides in hydrogen), however, will ignite at room temperature in air. The reaction of cobalt powder or dust with bromine pentafluoride, fused ammonium nitrate, or other strong oxidizers is violent; ignition, explosion, and/or fire can occur (HSDB, 2001). When heated, cobalt is oxidized to the mixed oxide, Co(II,III) oxide ($Co_3O_4$); above 900 °C, Co(II) oxide (CoO) is the end product. Additionally, when heated, it combines with sulfur, phosphorus, and carbon (IARC, 1991). Under oxidizing conditions, it readily concentrates with manganese oxides (Donaldson, 1986).

## 2.3 Commercial Availability

Cobalt metal is commercially available as broken or cut cathodes or as electrolytic coarse powder, anodes, briquets, shots, single crystals, granules (99.5% cobalt), rondelles, powder (99.8 or 99.995% cobalt), ductile strips (95% cobalt), high-purity strips (99% cobalt), foil (99.95 or 99.99% cobalt), rods (99.998% cobalt), wire (>99.9 % cobalt), and mesh powder (up to 99.6% pure) (IARC, 1991; HSDB, 2001). The metal is also found in the following forms: cobalt brass (22-30% cobalt), cobalt steel (34.5% cobalt), cobalt chromium molybdenum steels (1.33% cobalt), cobaltron steel alloy (2.25% cobalt), and cobalt-based superalloys (up to 60% cobalt) (HSDB, 2001). Refined cobalt is sold primarily as broken or cut cathodes by primary refiners (92%); electrolytic coarse powder makes up 3% of the industrial market (IARC, 1991).

In 1999, Carolmet Cobalt Products (Laurinburg, NC) produced cobalt metal powder from cobalt metal, and Osram Sylvania, Inc. (Towanda, PA) produced the powder from scrap (Shedd, 2000). OM Group, Inc. (aka OMG) is the world's largest producer and refiner of cobalt; its 2000 production was between 7000 and 8000 metric tons (15.44 and 17.64 million pounds). It has manufacturing facilities in St. George, UT, and Kokkola, Finland, and supplies cobalt extra fine powders in seven grades (OMG, 2000).

## 3.0 Production Processes

Cobalt is recovered as a byproduct from the mining and processing of nickel, silver, lead, copper, gold, and zinc ores (primarily as a byproduct of nickel and copper ores). From ore concentrates, it is obtained by roasting and then thermal reduction of the oxides by aluminum, electrolytic reduction of a metal solution, or by leaching with ammonia or sulfuric acid under high

temperatures, followed with reduction by hydrogen (Donaldson, 1986; HSDB, 2001). Most cobalt used in the United States is imported.

Cobalt powder is produced for industrial use by several processes. Reduction of oxides (gray cobalt(II) oxide [CoO] or black cobalt(II, III) oxide [$Co_3O_4$]) yields a product with a purity of 99.5% and a particle size of approximately 4 µm, while pyrolysis of carboxylates (cobalt formate or oxalate) produces a product with about 99.9% purity and a particle size of approximately 1 µm. Reduction of cobalt ions in aqueous solutions (e.g., purified leach solutions with cobalt pentammine complex ions) with hydrogen under pressure and at a high temperature yields an irregular chainlike powder. Very pure cobalt powder can be obtained by the decomposition of cobalt carbonyls (Mond process) (Donaldson, 1986).

## 4.0 Production and Import Volumes

World cobalt metal production during the period from 1970 to 1988 ranged from 18,084 tons (39.9 million pounds) to 36,720 tons (81.0 million pounds). Cobalt mining in the United States began in the late 1930s and ended in 1971 (Roskill Information Services, 1989; Shedd, 1990; and Snedd, 1988; all cited by IARC, 1991). The United States, however, has been the world's largest consumer of cobalt (Bustow, 2000; cited by Shedd, 2000). ). U.S. cobalt production between 1964 to 1971 ranged from 690,000 to 1,215,000 lbs (345 to 608 tons; 313 to 551 metric tons) (Sibley, 1975). A negligible amount of byproduct cobalt is produced from some mining operations. Production is obtained from scrap; in 1998, 3,080 metric tons (6.79 million pounds) was recycled (ATSDR, 2001).

Between 1985 and 1988, 31% of the U.S. cobalt supply was imported from Zaire, 21% from Zambia, 21% from Canada, 10% from Norway, and 17% from other countries (e.g., Belgium, Germany, Japan, and the United Kingdom) (IARC, 1991). Between 1995 and 1999, 6440 to 8430 metric tons (14.2 to 18.6 million pounds) of cobalt was imported into the United States each year; reported consumption ranged from 7590 to 9130 metric tons (16.7 to 20.1 million pounds) cobalt content (Shedd, 2000).

## 5.0 Uses

About 80% of the cobalt produced worldwide is used in the metallic state (Grimsley, 2001). [The United States is the largest consumer.] Cobalt is used in several military and industrial applications (ATSDR, 2001). It is used in the production of alloys, in the manufacture of cobalt salts, and in nuclear technology (e.g., the cobalt bomb [hydrogen bomb surrounded by a cobalt metal shell]) (Budavari, 1996). It is an effective catalyst for many organic reactions, particularly in hydrotreating catalysts which have molybdenum and cobalt sulfides as active components. Applications of cobalt include its use in the production of cemented WC (hard metal) and as an alloying element in superalloys, magnetic and hard-facing alloys, cobalt-containing high-strength steels, electrodeposited alloys, and other alloys with special properties (IARC, 1991). Specifically, cobalt powders have been used in the formation of alloy phases (e.g., maraging steel by hot extension of prealloyed powders), cobalt-based superalloys, fine-particle magnetic alloys, and bearing materials filled with low-friction substances (e.g., graphite and nylon) (Donaldson, 1986). Extra fine cobalt powder is an important raw material for producing cemented carbides, diamond tools, and metal welding and spraying components (OMG, 2000). Because of the health hazards associated with cobalt in workers (see Section 9.1.1), the Indian National Trade

Union Congress and the Diamond Trading have requested a ban on the use of cobalt as a material input in the diamond industry (*The Times of India*, 2001).

Major uses of cemented carbide-coated tools are metal-cutting operations and mining and quarrying (Smith and Carson, 1981).

## 6.0 Environmental Occurrence and Persistence

Cobalt is ubiquitous, accounting for 0.001 to 0.002% (20 mg/kg [0.34 mmol/kg]) of the earth's crust. It is a major constituent of about 70 minerals and a minor or trace constituent of hundreds more. Concentrations of cobalt are found in mafic and ultramafic rocks (average: 270 mg/kg [4.58 mmol/kg] cobalt), sedimentary rocks (e.g., clays [40 mg/kg (0.68 mmol/kg)] and sandstone [4 mg/kg (0.07 mmol/kg)]), meteorites, plants, soils, seawater (0.1-1 ppb [0.002-0.02 µmol/kg]), and manganese-rich marine nodules (Donaldson, 1986; IARC, 1991; ATSDR, 2001).

Cobalt is released to the air from natural (e.g., volcanoes, wind-blown continental dust, and marine biogenic emissions) and anthropogenic sources (e.g., burning of fossil fuels and processing of cobalt-containing alloys). Annual global atmospheric emission of cobalt from natural sources is ~13 to 15 million pounds and that from anthropogenic sources is ~9.7 million pounds (Lantzy and Mackenzie, 1979; Nriagu, 1989; Barceloux, 1999; all cited by ATSDR, 2001). Anthropogenic cobalt from combustion sources is primarily the oxide (Schroeder et al., 1987; cited by ATSDR, 2001). Carson (1979) estimated U.S. releases of cobalt compounds from coal burning and coking coal were 240 metric tons per year and releases from burning residual fuel oils totaled 100 metric tons per year. During ore extraction processes, cobalt may exist as the arsenide or sulfide. Other sources of atmospheric cobalt are emissions from vehicle exhaust and cigarette smoke (ATSDR, 2001). According to the Toxic Chemical Release Inventory (TRI), total releases of cobalt and its compounds to the environment (i.e., air, water, soil, and underground injection) from 695 facilities producing, processing, or using the compounds were 15.6 million pounds in 1999. Of this amount, 103,232 pounds were released into the air, accounting for 0.7% of the total on-site environmental releases (TRI99, 2001; cited by ATSDR, 2001). Because cobalt compounds are expected to be particle-associated in air, the average lifetime of the chemicals is estimated to be about 5 to 15 days (Cal-ARB, 1997).

At unpolluted sites, mean atmospheric cobalt levels are generally <1 to 2 ng/m$^3$ (0.4-0.8 ppt), while in industrial settings, they may be >10 ng/m$^3$ (4.1 ppt) (Smith and Carson, 1981; Hamilton, 1994 [cited by ATSDR, 2001]). In the United States, the average cobalt concentration in ambient air is ~0.4 ng/m$^3$ (0.2 ppt) (Smith and Carson, 1981). In remote, rural, and U.S. urban sites, the levels range from 0.001 to 0.9 ng/m$^3$ (0.0004-0.4 ppt), from 0.08 to 10.1 ng/m$^3$ (0.03-4.19 ppt), and from 0.2 to 83 ng/m$^3$ (0.08-34 ppt), respectively (Schroeder et al., 1987; cited by ATSDR, 2001). In several open-ocean environments, geometric mean cobalt levels ranged from 0.0004 to 0.08 ng/m$^3$ (0.0002-0.03 ppt) (Chester et al., 1991; cited by ATSDR, 2001). Typical workplace air concentrations range from 0.01 to 1.7 mg/m$^3$ (0.004-0.71 ppm) (IARC, 1991; Barceloux, 1999; cited by ATSDR, 2001).

## 7.0 Human Exposure

General Population: The general public is primarily exposed to cobalt metal fume and dust via inhalation; other routes include contact with the eyes and skin, and ingestion, since cobalt is a common trace element in foods and drinking water (HSDB, 2001; NIOSH, 1978; ATSDR, 2001;

Grimsley, 2001). The average daily intake of cobalt for an adult in the United States has been estimated at about 300 µg (5.09 µmol) from foods, 6 µg (0.1 µmol) from water, and <0.1 µg (0.002 µmol) from community air (HSDB, 2001). Cobalt has also been detected in cigarette smoke. Smokers with no occupational exposure to cobalt were found to have a significantly higher mean cobalt concentration in urine (0.6 µg/L [0.01 µM]) than nonsmokers (0.3 µg/L [0.005 µM]); cobalt levels in blood were the same (Alexandersson, 1988; cited by IARC, 1991 and ATSDR, 2001).

Occupational: In the United States, more than a million workers are potentially exposed to cobalt or its compounds, with the greatest exposure in mining processes, the cemented WC industry (see Section 9.10.2 for further details), and in cobalt powder and alloys production. Occupational exposure to cobalt is primarily via inhalation of dusts, fumes, or mists containing cobalt, targeting the skin and the respiratory tract, and occur during the production of cobalt powder; the production, processing, and use of hard metal; the processing of asbestos fiber; the grinding and sharpening of cemented carbide and steel tools, etc. (IARC, 1991; Lauwerys and Lison, 1994; HSDB, 2001). Operations employed for the production of hard metal tools expose workers to cobalt-containing dust through the removal of cobalt in wear particles from these tools as the metal and in the oxide forms (Smith and Carson, 1981). In the NIOSH 1981-1983 National Occupational Exposure Survey (NOES), an estimated 79,652 workers were potentially exposed to cobalt in 16 industries (Pedersen et al., 2001).

A study measuring the ambient air in cobalt powder production reported a concentration of cobalt in ambient air ranging from 0.675 to 10 mg/m$^3$ (0.280-4.1 ppm) and a mean concentration of 35.1 µg/L (0.596 µM) cobalt in urine (Pellet et al., 1984; cited by IARC, 1991). In another study of cobalt powder and cobalt salt production, the mean concentration of cobalt in ambient air was 46 to 1046 µg/m$^3$ (0.019-0.434 ppm) (stationary samples); the mean concentration of cobalt in blood was 5 to 48 µg/L (0.08-0.81 µM), and the mean level in urine was 19 to 438 µg/L (0.32-7.43 µM) (Angerer et al., 1985; cited by IARC, 1991). [Correlative analyses have indicated that exposure to 50 µg/m$^3$ (0.02 ppm) cobalt in air leads to blood and urine concentrations roughly equivalent to 2.5 and 30 µg/L (0.042 and 0.51 µM), respectively.] Airborne concentrations of cobalt during processes involving hard metal were mainly below 100 µg/m$^3$ (0.04 ppm) (see Section 9.10.2) (IARC, 1991).

## 8.0 Regulatory Status

Cobalt compounds are listed as Federal hazardous air pollutants under the 1990 Clean Air Act Amendments, Section 112(b)(1) (1990) as promulgated in 42 U.S. Code Section 7412(b)(1) (2000) and cited in 40 CFR 63, Subpart C, Section 63.60 (U.S. EPA, 2001). Under AB 2728, the ARB identified the substances as toxic air contaminants in April 1993 (Cal-ARB, 1997). Cobalt is also listed in Section 8(d) of the Toxic Substances Control Act (TSCA) (40 CFR 712.30) (HSDB, 2001).

The American Conference of Governmental Industrial Hygienists (ACGIH) has established a concentration of 0.05 mg Co/m$^3$ for cobalt metal dust and fume as the eight-hour time-weighted average (TWA) threshold limit value (TLV); OSHA has set a permissible exposure limit (PEL) of 0.1 mg Co/m$^3$ for cobalt metal dust and fume as the TWA for general industry, the shipyard industry, and the construction industry (29 CFR 1910.1000, 29 CFR 1915.1000, and 29 CFR 1926.55, respectively); and NIOSH has recommended an exposure limit of 0.05 mg/m$^3$ as cobalt

for the metal, dust, and fumes as the ten-hour TWA (NIOSH, 1978; IARC, 1991; ATSDR, 2001; HSDB, 2001).

Under Proposition 65, California has determined that cobalt metal powder is a carcinogen (Cal-ARB, 1997).

## 9.0 Toxicological Data

## 9.1 General Toxicology

### 9.1.1 Human Data

Also see Section 9.10.2 for additional human data on effects of exposure to cobalt with other heavy metals.

Chemical Disposition, Metabolism, and Toxicokinetics: Upon being absorbed by inhalation, cobalt (with a biological half-life of a few days) is eliminated in the urine (Hoet and Lauwerys, 1998). In nonoccupationally exposed persons, normal concentrations of cobalt in blood and urine range from 0.1 to 2 µg/L (0.002-0.03 µM). In hair, levels between 0.4 to 500 µg/kg (0.007-8.48 µmol/kg) were reported. In uremic patients, increased levels of cobalt in serum have been found (Curtis et al., 1976; Lins and Pehrsson, 1984; Elinder et al., 1988; Iyengar and Woittiez, 1988; all cited by IARC, 1991). Workers exposed to cobalt dust and fumes in the production of cobalt powder had mean cobalt concentrations of 5 to 48 µg/L (0.08-0.81 µM) in blood and mean values of 19 to 438 g/L (0.32-7.43 M) in urine during sampling post shift (Seiler et al., 1988; cited by HSDB, 2001). Male workers occupationally exposed to a dust mixture for at least two years had significantly higher levels of cobalt in the urine than non-exposed workers (geometric means of 23.6 and 1.1 µg Co/g creatinine [0.400 and 0.019 µmol/g], respectively) (Gennart et al., 1993).

Toxicity: Cobalt dust is a mild irritant to the eyes and the skin. Symptoms of ingestion include hypotension, pericardial effusion, vomiting, and convulsions. Inhalation of cobalt dust and fumes has caused shortness of breath, dermatitis with hyperemia, and vesiculation (HSDB, 2001). Additionally, cardiac effects, congestion of the liver, kidneys, conjunctiva, and immunological effects have been observed (Cal-ARB, 1997).

Chronic exposure to cobalt as a metal, fumes, or dust has been reported to cause respiratory disease with symptoms ranging from cough to permanent disability and even death, respiratory hypersensitivity, progressive dyspnea, decreased pulmonary function, weight loss, dermatitis, and diffuse nodular fibrosis (Dorsit, 1970 [cited by Herndon et al., 1981]; NIOSH, 1978; Budavari, 1996). Allergic sensitization and chronic bronchitis may also result from prolonged exposure to the powder (Donaldson, 1986). Few "poorly documented" cases of interstitial lung disease have been reported from exposure to cobalt alone (Kochetkova, 1960; Reinl et al., 1979; both cited by Lison and Lauwerys, 1995). Case reports include workers exposed to cobalt dust in industries in Russia, who had skin lesions, acute dermatitis (numerous red papules and nodules), surface ulcerations, and edema on hands and other exposed body parts (Brakhnova, 1975; cited by Herndon et al., 1981). Workers exposed to industrial dusts containing <0.1 mg $Co/m^3$ (0.04 ppm) for an average of 12.6 years had diffuse, interstitial lung disease, cough, and dyspnea on exertion (Coates and Watson, 1971; cited by Herndon et al., 1981). Individuals exposed to fine cobalt metal dust in a cobalt plant in Olen, Belgium, had respiratory irritation and reversible bronchitis (Verhamme, 1973; cited by Herndon et al., 1981).

Intense occupational exposure to cobalt powder for 20 months produced a progressive hearing loss and atrophy of the optic nerve; the individual improved with the termination of exposure (Meecham and Humphrey, 1991; cited by Lauwerys and Lison, 1994). A case of giant cell interstitial pneumonitis induced by cobalt dust was also reported; the patient improved with the termination of exposure and treatment with oral corticosteriods (Sundaram et al., 2001). A 48-year-old worker handling cobalt powder experienced cardiac shock under anesthesia during an operation for a duodenal ulcer. The heart was dilated (400 g) and contained 7 µg Co/g (10 nmol/g) versus normal levels of 0.1-0.4 µg/g (2-7 nmol/g) (Kennedy et al., 1981; cited Jensen and Tüchsen, 1990).

Carcinogenicity: Few epidemiological studies of cancer risk in cobalt-exposed workers exist (Jensen and Tüchsen, 1990). A high incidence of pulmonary cancer was found in English cobalt miners; however, the etiology was not known (Schwartz et al., 1947; cited by Herndon et al., 1981). Epidemiological studies of cobalt miners in the United States, Canada, Zaire, and other countries found no association between cobalt and neoplasm; however, cobalt was the cause of hard metal respiratory disease (see Section 9.10.2 for further details) (Payne, 1977; cited by Herndon et al., 1981). In a mortality study of a cohort of 1143 workers in an electrochemical plant producing cobalt and sodium (110 engaged in cobalt production) for at least a year during 1950 to 1980, an increased number of deaths from lung cancers was observed in those producing cobalt; smoking may have been a factor (Mur et al., 1987). Confounding by nickel and arsenic exposures is also a major problem, as well as the limited size of the exposed population (Jensen and Tüchsen, 1990). The follow-up (1981-1988) did not support the proposed relationship between lung cancer and cobalt exposure (Moulin et al., 1993).

IARC (1991) concluded that there was *inadequate evidence* for the carcinogenicity of cobalt and cobalt compounds in humans and categorized the compounds in Group 2B—*possibly carcinogenic to humans*.

Genotoxicity: In 26 male workers occupationally exposed for at least two years to a dust mixture containing cobalt, nickel, and chromium, the mean value of individual sister chromatid exchange (SCE) frequencies and the percentage of high-frequency cells (HFC) were significantly higher compared to controls, and both were statistically significantly affected by exposure status and smoking habit. Because cobalt is a weak mutagen, the results suggested that the small amounts of chromium and nickel might have been sufficient enough to induce SCE (Gennart et al., 1993).

Male workers exposed to cobalt dust from refineries and workers exposed to hard metal dust from two producing plants had no significant increase of genotoxic effects (i.e., initial DNA damage and definitive chromosome breakage or loss) when compared to each other as well as controls. Urinary 8-hydroxydeoxyguanosine (8-OhdG) levels were similar in both exposure groups (20 µg [0.34 µmol] Co/g creatinine). Results of the alkaline comet assay on lymphocytes failed to show any statistical significantly differences among the worker groups; when combined with the formamidopyrimidine DNA glycosylase enzyme to detect oxidative DNA damage, the same outcome was observed. The frequency of micronucleated mononucleates (MNMC) did not differ among the worker groups, whereas the frequency of micronucleated binucleates (MNCB) was not statistically different between control and exposed workers, but was statistically significantly higher in cobalt workers compared to hard metal workers (De Boeck et al., 2000).

In an *in vitro* study using peripheral blood cells from a healthy volunteer, cobalt powder and tungsten carbide-cobalt mixture (WC-Co) both induced dose-dependent increases in chromosome and DNA damage; the effect of the latter mixture was greater than that of cobalt alone (Van Goethem et al., 1997).

Other Data: Cobalt (up to 150 mg [2.55 mmol]), in particulate form, exhibited a strong hemolytic effect in human erythrocytes. There was a rapid rise in hemolysis up to about one hour, and then a plateau was reached and fairly maintained up to about six hours. Preincubation with serum weakened the activity (Rae, 1978).

### 9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

Rats exposed to cobalt (0.001-0.5 mg/m$^3$ [0.0004-0.2 ppm] for 24 hours/day for 3 months) had accumulated levels in the thyroid, spleen, liver, and kidneys. Cobalt accumulation was also found in the lungs at >0.001 mg/m$^3$ [0.415 ppb]. The animals showed a dose-response relationship in cobalt accumulation and distribution. The degree of accumulation was proportional to the concentration and duration of exposure (Popov et al., 1977). When administered as WC-Co, cobalt levels in urine were significantly increased compared to administration of pure cobalt, suggesting a greater bioavailability of cobalt when combined with WC. At a cobalt concentration of 0.03 mg/100 g (5 nmol/g), urinary cobalt levels at 24 hours after intratracheal (i.t.) instillation were 6.81 µg (0.116 µmol) in rats given pure cobalt powder and 22.17 µg (0.3762 µmol) in rats given WC-Co. At 1.00 mg Co/100 g (0.170 µmol/g), the amounts were 49.14 and 371.07 µg (0.8339 and 6.2968 µmol), respectively (Lasfargues et al., 1992).

In SD-Jcl rats exposed to cobalt aerosol (2.12 mg/m$^3$; 0.880 ppm) for 5 hours/day for 4 days, the average cobalt content of the lungs at two hours after the last exposure was 6.42 µg/wet g (0.109 µmol/g); in blood, cobalt content was 28.94 µg/L (0.4911 µM). At 28 days after exposure, the values were 0.09 µg/wet g (1.5 nmol/g) and 0.40 µg/L (6.8 nM), respectively. The clearance patterns of cobalt from the lungs and from blood were biphasic—in the first phase, clearance was rapid, while in the second phase, the removal was slower. The biological half-times of cobalt in the lungs were 52.8 hours for the first phase and 156.0 hours for the second phase. In blood, the values were 52.8 and 172.8 hours, respectively. During the 28 days after exposure, the blood to lung cobalt concentration was almost constant (Kyono et al., 1992). Rapid urinary excretion of cobalt was also observed in rats exposed to WC-Co (i.t.; 0.50 mg/100 g [0.085 µmol/g] body weight), occurring as early as six hours after instillation but failing to increase any further after 12 hours. Animals receiving cobalt powder (0.03 mg/100 g [5.1 nmol/g] body weight) excreted cobalt at a rate about one order of magnitude lower than WC-Co rats at six hours. However, at 48 hours, both groups had excreted almost equal amounts, and on day 7, there was no significant difference between mean urinary excretions of cobalt. The mean lung cobalt concentration of rats given cobalt was two times more than that for WC-Co; by day 7, mean levels had decreased significantly to almost the same level in all exposed rats (Lison and Lauwerys, 1994).

In miniature swine, cobalt (inhalation; 0.1-1.0 mg/m$^3$ [0.04-0.41 ppm] pure cobalt powder for 6 hours/day 5 days/week for 3 months) was excreted mostly by the kidneys. Animals receiving the low dose excreted a slightly higher amount of cobalt in urine compared to controls (29 and 18 µg Co/L [0.49 and 0.31 µM], respectively), while those receiving the high dose excreted more than ten times the controls (220 µg/L; 3.73 µM). In tissue analysis, the highest cobalt level in the

control group was found in the liver (0.15 µg/g; 2.5 nmol/g). Test animals had similar levels in the liver (0.13 µg/g [2.2 nmol/g] for the low-dose group and 0.14 µg/g [2.4 nmol/g] for the high-dose group). In the kidney cortex, however, cobalt concentrations were higher in the exposed groups compared to that in the control group (0.16 µg/g [2.7 nmol/g] [low dose] and 0.19 µg/g [3.2 nmol/g] [high dose] versus 0.09 µg/g [1.5 nmol/g] [controls]) (Kerfoot, 1973; Kerfoot et al., 1975).

### 9.1.3 Acute Exposure

Acute toxicity values for cobalt dust are presented in **Table 1**. The details of studies discussed in this section are presented in **Table 2**. (Note: Although the exposure period for experiments with cobalt dust was "acute," studies were classified under short-term, subchronic, or chronic exposure based on the length of the observation period. See Sections 9.1.4 and 9.1.5.)

**Table 1. Acute Toxicity Values for Cobalt Dust**

| Route | Species (sex and strain) | $LD_{50}$ | Reference |
|---|---|---|---|
| i.p. | rat (sex n.p., white) | 100-200 mg/kg bw; 1.70-3.39 mmol/kg bw | Frederick and Bradley (1946; cited by Harding, 1950) |
| n.p. | rat (sex and strain n.p.) | 1500 mg/kg; 25.45 mmol/kg | Donaldson (1986) |

Abbreviations: bw = body weight; i.p. = intraperitoneal(ly); $LD_{50}$ = lethal dose for 50% of test animals; n.p. = not provided

Metallic cobalt powder was found to have an "acute irritant action," leading to severe changes in capillaries in the lungs or peritoneum, accompanied with a significant amount of fluid and sometimes hemorrhages. In rats, i.t. instillation of a 5% sterile suspension of cobalt powder produced pulmonary hemorrhage and edema. Some cobalt was found in the bronchi and atria and close to the alveolar wall, near bronchial ends. In a comparison study, golden hamsters, adult cavies, rabbits (all n=2), and mice (n=6) were exposed to cobalt dust via inhalation (study details not provided). Animals showed gross edema and numerous hemorrhages in the lungs. The hamsters showed the least severe symptoms during exposure; their lungs were congested and edematous and showed extensive desquamation of the bronchial epithelium. The toxicity of cobalt was related to its solubility in protein-containing fluids (Harding, 1950).

In SD-Jcl rats exposed to cobalt aerosol (2.72 mg/m$^3$; 1.13 ppm) for five hours, a very slight increase in alveolar macrophages in the alveolar ducts was observed three days after exposure. When given for an extended period (2.12 mg/m$^3$ [0.880 ppm] for 5 hours/day for 4 days), early inflammatory changes in the lung were seen; the induced lesions, however, were reversible (Kyono et al., 1992).

### 9.1.4 Short-term and Subchronic Exposure

The details of the following studies are presented in **Table 3**.

Inhalation studies with metallic cobalt aerosol (0.005-0.5 mg/m$^3$ [0.002-0.2 ppm] 24 hours/day for 3 months) produced increases in hemoglobin and erythrocyte levels and decreases in blood phospholipids, cholesterol, and β-lipoproteins in rats. Additionally, disturbances in protein and carbohydrate metabolism and enzyme system, activation of the hemopoietic system, and

## Table 2. Acute Exposure to Cobalt Dust

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference(s) |
|---|---|---|---|---|
| Rats, piebald (anesthetized with ether) (n=6) | 5% sterile suspension of cobalt dust, purity n.p. | i.t.; ~1 mL (0.2 mol) of suspension in physiological saline; observation period ≥6 h | Animals were lethargic, had difficulty in righting themselves when placed on their backs, were breathing quickly, had decreased body temperatures, and died within 15 minutes to 6 h. Lungs were grossly edematous and hemorrhagic. Microscopic examination showed some cobalt in the bronchi and atria and close to the alveolar wall, near bronchial ends. | Harding (1950) |
| Rats, SD-Jcl, 8-wk-old, 15M (2-5/group) | cobalt aerosols generated from an aqueous suspension of ultrafine cobalt powder, purity n.p. | inh; 2.72 mg/m$^3$ (1.13 ppm) for 5 h; observed at 3 days after exposure | At 3 days after exposure, a very slight increase in alveolar macrophages in the alveolar ducts was observed. | Kyono et al. (1992) |
| Rats, SD-Jcl, 8-wk-old, 15M (2-5/group) | cobalt aerosols generated from an aqueous suspension of ultrafine cobalt powder, purity n.p. | inh; 2.12 mg/m$^3$ (0.880 ppm) for 5 h/day for 4 days; rats sacrificed at 2 h and 3, 8, and 28 days after the end of exposure | In all rats, acute pulmonary changes were observed at 2 h and 3 days after exposure. Histopathological changes included focal hypertrophy and proliferation of the epithelium in the lower airways, macrophage damage, intracellular edema of type I alveolar epithelium, interstitial edema of the alveolar septa, proliferation of type II alveolar epithelium, and narrowing of capillaries; most were observed at 2 h after exposure. Some damaged type I cells were morphologically transformed to the juvenile form. At 8 days after exposure, bronchioles and alveoli returned to normal. At 28 days, recovery in the bronchioles was complete. | Kyono et al. (1992) |

Abbreviations: h = hour(s); inh = inhalation; i.t. = intratracheal(ly); M = male(s); n = number; n.p. = not provided; wk = week(s)

## Table 3. Short-term and Subchronic Exposure to Cobalt Dust

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference(s) |
|---|---|---|---|---|
| Rats, white | metallic cobalt aerosol, purity n.p. | inh; 0.001, 0.005, 0.05, and 0.5 mg/m$^3$ (0.0004, 0.002, 0.02, 0.2 ppm) 24 h/day for 3 mo; observation period ≥3 mo | With 0.005 mg/m$^3$, an increase in hemoglobin level was observed. With 0.05 and 0.5 mg/m$^3$, erythrocyte and hemoglobin levels were decreased at 2 wk; levels increased after 2.5 mo of continuous exposure. | Popov (1976; cited by Herndon et al., 1981) |
| Rats | metallic cobalt aerosol, purity n.p. | inh; 0.001, 0.005, 0.05, and 0.5 mg/m$^3$ (0.0004, 0.002, 0.02, 0.2 ppm) 24 h/day for 3 mo; observation period ≥3 mo | At ≥0.005 mg/m$^3$, blood phospholipids, cholesterol, and β-lipoproteins were decreased compared to controls.<br>At 0.5 mg/m$^3$, cobalt content was increased 12x in the thyroid, 2x in the kidney, and 1.2x in the liver (actual values not specified) from 1.5 to 3 mo of exposure (Popov and Markina, 1977; cited by Herndon et al., 1981). | Popov (1977; cited by Herndon et al., 1981) |
| Rats | metallic cobalt aerosol, purity n.p. | inh; 0.001, 0.005, 0.05, and 0.5 mg/m$^3$ (0.0004, 0.002, 0.02, 0.2 ppm) 24 h/day for 3 mo; observation period ≥3 mo | At ≥0.005 mg/m$^3$, disturbances in protein and carbohydrate metabolism and in the enzyme system, activation of the hemopoietic system, and pathomorphological changes in the respiratory system, liver, kidney, spleen, thyroid, and brain were observed. | Popov (1977b) |
| Rats, white | metallic cobalt aerosol, purity n.p. | inh; 0.001, 0.005, 0.05, and 0.5 mg/m$^3$ (0.0004, 0.002, 0.02, 0.2 ppm) 24 h/day for 3 mo; observations made at 1.5 and 3 mo after initiation and 3 mo after recovery | At ≥0.005 mg/m$^3$, the thyroid had large follicles with rounded epithelium and sporadic epithelial hyperplasia. Livers had reduced numbers of binuclear hepatocytes and hepatocytes with necrobiotic and necrotic changes. There was a decrease in splenic lymphoid cell reactivity and mild protein dystrophy in convoluted renal tubules. In lungs, a decrease in the reactivity of the bronchial mucous membranes, lymphoid tissue, and collagen fibers was found. The degree of severity of pathological and morphological changes correlated with exposure doses. | Popov et al. (1977) |
| Rats | cobalt metal powder, purity n.p. | inh; 0.48 mg/m$^3$ (0.20 ppm) for 4 mo; observation period ≥4 mo | Circulatory and dystrophic changes, epithelium cellular element damage, and some epithelial atrophy were observed in the mucosal tissue. | Georgiadi and Elkind (1978; cited by Herndon et al., 1981) |
| Rats | cobalt dust, purity n.p. | inh; 0.48 and 4.4 mg/m$^3$ (0.20 and 1.8 ppm) for 2 mo; observation period ≥2 mo | At the low dose, all respiratory mucosal enzymes were decreased. Further exposure resulted in the return of some enzyme activity. The high dose also decreased enzyme levels; some changes were sex-related (not specified). | Georgiadi (1978; cited by Herndon et al., 1981) |

## Table 3. Short-term and Subchronic Exposure to Cobalt Dust (Continued)

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference(s) |
|---|---|---|---|---|
| Rats, albino, age n.p., 15M and 15F per group | metallic cobalt aerosols, purity n.p. | inh; 0.48±0.09 and 4.4±1.1 mg/m$^3$ for 2 or 4 mo; examined monthly up to a recovery period | At the high dose, more expressed changes were observed. Breathing frequency and membrane sensitivity were lower. At the low dose, a reduced threshold of neuromuscular excitability occurred after mo 1 and 3. Additionally, after 2 mo of exposure, rats showed circulatory disturbance (dilatation and fullness of blood vessels), swelling of cutaneous epithelial cells, intercellular edema, and edema of the connective tissue of the submucous matrix. Enzyme activities of the respiratory tract mucous membranes were reduced. After 4 mo, proteinaceous dystrophy and the appearance of atrophy were observed in the cutaneous epithelia. An increased quantity of goblet cells was observed in the mucous membrane of the nasal cavities. Almost all sections of the respiratory tract showed partial epithelial layer exfoliation and epithelial cell desquamation.<br><br>M rats were more sensitive to cobalt than F. F rats had decreased diuresis after 2 mo and after the recovery period. After 2 mo, protein concentration in the urine was also increased. In M, the chloride concentration of the urine was increased after 1 and 3 mo. Broader regions of goblet-cell transformation of the cutaneous epithelia underwent atrophy, and round-cell infiltration was more massive. | Georgiada and Ivanov (1984) |
| Rats | cobalt dust, purity n.p. | inh; 200 mg/m$^3$ ($TC_{Lo}$; 83.0 ppm) for 17 wk intermittently; observation period ≥17 wk | Damages in the vascular system (i.e., regional or general arteriolar or venous dilation) and in the lungs, thorax, or respiration (changes not specified) were observed. Changes also occurred in tubules, which included acute renal failure and acute tubular necrosis. | RTECS (2000) |

## Table 3. Short-term and Subchronic Exposure to Cobalt Dust (Continued)

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference(s) |
|---|---|---|---|---|
| Rats | suspension of metallic cobalt powder, purity n.p. | i.t.; 3, 5, and 10 mg (0.05, 0.08, 0.17 mmol) in physiological solution; observed for 4, 6, or 8 mo after administration | The mid dose caused the death of some rats, while the high dose caused the death of all rats after 2-3 days. With 5 mg cobalt, severe congestion of the capillaries of the alveolar septa and swelling of the small and intermediate bronchi, with massive infiltration by lymphocytes and some eosinophils, occurred. Animals had round gland-like formations, often surrounded with pneumonic foci and lined with an epithelium of cylindrical cells. The lumen was filled with exudate and numerous leukocytes. In rats killed after 8 mo, fatty changes in the liver and hypertrophy in the connective tissue in the small and intermediate bronchi and blood vessels were observed. In the high-dose group, pulmonary edema and extensive toxic pneumonia were observed. Liver had acute fatty dystrophy and necrosis of cells, and the complex tubules of the kidney had granular dystrophy.<br>[Similar but less distinct changes were observed in the low-dose group and in rats inhaling 200 mg/m$^3$ (83.0 ppm) cobalt dust.] | Kaplun (1967) |
| Rats | metal cobalt particles, purity n.p. | i.t.; single injection of 50 mg (0.85 mmol); observed at 12 mo after administration | Diffuse central fibrocellular infiltration occurred in the lungs. | Schepers (1955b; cited by Herndon et al., 1981) |
| Guinea pigs (n=6/dose) | cobalt metal dust, purity n.p. | i.t.; single injections of 10, 25, and 50 mg (0.17, 0.42, and 0.85 mmol); observed up to 360 days after administration | All but one animal died in each of the low- and mid-dose groups. At the high dose, two rats survived; obliterative pleuritis and firm circumscribed dust lesions were observed. | Delahant (1955; cited by Herndon et al., 1981) |

## Table 3. Short-term and Subchronic Exposure to Cobalt Dust (Continued)

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference(s) |
|---|---|---|---|---|
| Miniature swine (n=5/dose) | "pure" cobalt metal powder, purity n.p. | inh; 0.1-1.0 mg/m$^3$ (0.04-0.4 ppm) for 6 h/day 5 days/wk for 1 wk (sensitizing dose), followed by a 10-day lapse period and then 3 mo of exposure; observation period ≥1 mo after exposure | During exposure, some animals developed wheezing. After 4 wk of exposure, all test animals were lethargic. At 3 wk of exposure, the high-dose group had increased red and white blood cell counts; 3 wk later, the numbers returned to normal and remained so until the end of exposure. Test animals had a functional impairment in the lungs; lung compliance decreased progressively from control (35.5 cm$^3$/cm water) to the low dose (23.3 cm$^3$/cm water) to the high dose (19.8 cm$^3$/cm water). At 1 and 2 mo postexposure, compliance values for test animals returned to control levels.<br><br>Animals had weakened ventricular contraction and repolarization abnormalities (EKG values were compatible with those in cases of cardiomyopathy). There were increases in α-, β-, and γ-globulins and TP and inversion of the albumin/globulin ratio. Alveolar septa were significantly thickened with collagen, elastic tissue, and fibroblasts. | Kerfoot (1973); Kerfoot et al. (1975) |
| ***Comparative Studies of Lung Toxicity of Pure Cobalt Powder and Cobalt-tungsten Carbide Mixture**** | | | | |
| Rats, F-344, ~10-wk-old, 24M/group | cobalt dust and WC-Co, purities n.p. | inh; exposures were based on 1 mg Co/m$^3$ (0.4 ppm) or 15 mg WC/m$^3$ for 6 h/day 5 days/wk for 13 wk; observed at 6 days after final exposure | Animals showed a normal weight gain throughout and after exposure. No significant effects on lung function were found; however, both cobalt and WC-Co produced small increases in hydroxyproline and elastin. With WC-Co, end-airway inflammation and mild-to-moderate interstitial thickening were greater than that with cobalt alone. With both dusts, wet and dry lung weights and protein increased "disproportionately" to DNA content. Foamy macrophages were also seen. | Costa et al. (1990 abstr.) |

## Table 3. Short-term and Subchronic Exposure to Cobalt Dust (Continued)

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference(s) |
|---|---|---|---|---|
| Rats (anesthetized with sodium pentobarbital), Sprague-Dawley, 2- to 3-mo-old, 10F/dose group | extra fine cobalt metal powder, 99.87% pure; WC-Co containing 6.3% cobalt, purity n.p. | i.t.; single doses of 0.03, 0.06, and 1.0 mg/100 g (5.1, 10, 170 nmol/g) bw suspension of cobalt or 0.50, 1.0, and 16.67 mg/100 g bw (corresponding to 0.03, 0.06, and 1.0 mg Co/100 g bw) suspension of WC-Co; animals killed on day 2 | Within 24 h following instillation of the high doses, mortality was 20 and 60% for cobalt metal powder and WC-Co, respectively. Prior to death, rats in the latter group experienced massive pulmonary edema (gasping, cyanosis, and fluid discharge from the mouth and nostrils). Both groups had significant increases in absolute (1415 and 2210 mg for cobalt and WC-Co, respectively) and relative (6.8 and 11.0 mg/g bw, respectively) lung weights compared to controls (saline) [1147 mg (absolute) and 5.9 mg/g bw (relative)]; increases in the WC-Co group were significantly higher than in the cobalt group.<br><br>In rats given WC-Co, an acute and diffuse inflammatory reaction with generalized edematous alveolitis occurred. The alveoli had macrophages and neutrophils filled with particles. Bronchiolar and alveolar walls had enlarged and vacuolated macrophages with large and prominent nuclei, and some bronchial and bronchiolar epithelia were abraded. Tracheal and bronchial lymph nodes had lymphoid hyperplasia. Rats given cobalt alone showed moderate inflammatory response compared to those given WC-Co. Both lungs had scattered sites of exudative alveolitis and cellular proliferation occurred at the origin of alveolar ducts. WC-Co also induced marked increases in macrophage and neutrophil numbers, LDH activity, TP, and albumin concentration, whereas cobalt alone had no significant effects. | Lasfargues et al. (1992) |

## Table 3. Short-term and Subchronic Exposure to Cobalt Dust (Continued)

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference(s) |
|---|---|---|---|---|
| Rats (anesthetized with sodium pentobarbital), Sprague-Dawley, 8F/dose | extra fine cobalt metal powder, 99.87% pure; WC-Co containing 6.3% cobalt, purity n.p. | i.t.; single doses of 0.06, 0.3, and 0.6 mg/100 g (10, 50, and 100 nmol/g) bw suspension of cobalt or 1.0, 5.0, and 10.0 mg/100 g bw suspension of WC-Co; observed up to 28 days after administration | With WC-Co, mean LDH, TP, NAG, and albumin levels were significantly increased at 24 h in a dose-dependent manner. On day 28, the mid and high doses continued to increase biochemical indicators; at the low dose, only mean NAG activity was markedly increased. Significant and dose-dependent increases in total cell number, macrophages, neutrophils, and lymphocytes occurred on days 1 and 28.<br><br>With the high dose of cobalt, slight increases in LDH, TP, and albumin were observed 24 h after administration compared to controls (saline). Significant increases in total cell number, macrophages, neutrophils, and lymphocytes were also seen. On day 28, with the mid dose, NAG was significantly increased, and with the high dose, LDH and NAG were significantly increased. TP and albumin levels and cellular parameters were not significantly affected. | Lasfargues et al. (1995) |
| Rats (anesthetized with Hypnorm), Sprague-Dawley, 15F/dose | extra fine cobalt metal powder, 99.87% pure; WC-Co containing 6.3% cobalt, purity n.p. | i.t.; 0.06 mg/100 g (10 nmol/g) bw suspension of cobalt or 1.0 mg/100 g bw suspension of WC-Co 1x/mo for 4 mo; observed up to 1 mo after last administration | No toxic effects, except a slight reduction in body weight gain, were seen. With WC-Co, a significant increase in hydroxyproline content was found compared to controls and groups given cobalt alone. Animals showed large wide fibrotic areas containing macrophages, some fibroblast-like cells, black particles in the lumen of and around terminal airways, and increased collagen. With cobalt, rare and localized changes caused by macrophages and slight thickening of the intra-alveolar septum were seen. | Lasfargues et al. (1995) |

* Tungsten carbide powder was also tested; data are not presented here. Generally, it had no effect on the examined parameters.

Abbreviations: bw = body weight; F = female(s); h = hour(s); inh = inhalation; i.t. = intratracheal(ly); LDH = lactate dehydrogenase; M = male(s); mo = month(s); n = number; NAG = *N*-acetyl-β-*D*-glucosaminidase; n.p. = not provided; $TC_{Lo}$ = toxic concentration, low; TP = total proteins; WC-Co = tungsten carbide-cobalt mixture; wk = week(s)

pathomorphological changes in several organs and tissues (e.g., liver and thyroid) were observed (Popov, 1976, 1977 [both cited by Herndon et al., 1981], 1977b; Popov et al., 1977). Inhalation of the powder (0.48 and 4.4 mg/m$^3$ [0.20 and 1.8 ppm] for 4 months) also affected mucosal tissue (Georgiadi, 1978; Georgiadi and Elkind, 1978 [both cited by Herndon et al., 1981]; Georgiadi and Ivanov, 1984). At 200 mg/m$^3$ (83.0 ppm), damages occurred in the vascular system, respiratory system, and in kidneys (RTECS, 2000). A single i.t. injection of cobalt (3, 5, 10, and 50 mg [0.05, 0.08, 0.17, and 0.85 mmol]) caused changes in the lungs of rats (Kaplun, 1967; Schepers, 1955b [cited by Herndon et al., 1981]).

In guinea pigs, i.t. administration of cobalt dust (50 mg [0.85 mmol]) resulted in obliterative pleuritis and firm dust lesions (Delahant, 1955; cited by Herndon et al., 1981). Miniature swine exposed to cobalt powder (0.1-1.0 mg/m$^3$ [0.04-0.4 ppm] 6 hours/day 5 days/week for 3 months) became lethargic after one month and exhibited a functional impairment in the lungs, weakened ventricular contraction, and repolarization abnormalities. Alveolar septa were significantly thickened with collagen, elastic tissue, and fibroblasts (Kerfoot, 1973; Kerfoot et al., 1975).

WC-Co was found to be more toxic to the lung than cobalt alone (Lasfargues et al., 1992). In a study of the delayed lung effects of pure cobalt powder and hard metal powder, a single i.t. instillation of WC-Co (1, 5, or 10 mg/100 g [0.02, 0.08, or 0.17 mmol/g] body weight) induced an acute alveolitis, which persisted for a month, while cobalt alone (0.6 mg/100 g [0.1 µmol/g] body weight) produced only slight effects. Repeated administration of cobalt (0.06 mg/100 g [0.01 µmol/g] body weight 4x) failed to produce any significant parenchymal changes, but WC-Co (1 mg/100 g [0.2 µmol/g] body weight 4x) induced a pulmonary fibrosis reaction; this was different from the progressive inflammatory process induced by crystalline silica (Lasfargues et al., 1995).

### 9.1.5 Chronic Exposure

No data were available (other than carcinogenicity studies described in Section 9.3).

### 9.1.6 Synergistic/Antagonistic Effects

In an *in vitro* assay, titanium carbide, niobium carbide, and chromium carbide exerted a synergistic effect with cobalt powder on mouse peritoneal macrophage integrity (i.e., increased LDH release) (Lison and Lauwerys, 1995). Cobalt has been observed in both *in vivo* and *in vitro* studies to act synergistically with antibiotics (Pratt et al., 1948; cited by Grimsley, 2001).

### 9.1.7 Cytotoxicity

Details of the following studies, except where noted, are presented in **Table 4**.

In mouse peritoneal macrophages and rat alveolar macrophages, WC-Co (12-200 µg/mL) had a greater toxic effect than cobalt metal powder alone (0.6-12 µg/mL [10 µM-0.20 mM]); for example, glucose uptake and superoxide anion production were both more significantly reduced by WC-Co than by the metal (Lison and Lauwerys, 1991). The cellular uptake of cobalt was greater with WC-Co in macrophages than with cobalt alone (Lison and Lauwerys, 1994). Enhanced cellular cobalt uptake was also observed with the addition of niobium carbide, titanium carbide, or silicon carbide to cobalt particles; uptake was increased by a factor of 4, 6, and 7, respectively (study details are not provided here) (Lison and Lauwerys, 1995). Cobalt

## Table 4. Cytotoxicity Studies of Cobalt Dust

| Test System or Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, and Duration | Results/Comments | Reference |
|---|---|---|---|---|
| ***In Vitro* Assays** | | | | |
| Mouse peritoneal macrophages and alveolar macrophages from adult Sprague-Dawley rats | extra fine cobalt metal powder, 99.87% pure; WC-Co containing 6.3% cobalt, purity n.p. | incubation with 0.6, 3, 6, and 12 µg/$10^6$ cells (µg/mL) (0.01, 0.05, 0.1, 0.2 µmol/$10^6$ cells) cobalt or 12, 50, 59, 100, 118, and 200 µg/$10^6$ cells (µg/mL) WC-Co for 18 or 24 h | For cobalt powder, a dose-dependent increase in glucose uptake by mouse peritoneal macrophages in culture was observed. For WC-Co, the glucose uptake was initially stimulated at low concentrations (190 µg glucose/$10^6$ cells/24 h at 59 µg/$10^6$ cells) but then was eliminated with increasing concentrations (~140 µg glucose/$10^6$ cells/24 h at 118 µg/$10^6$ cells). At a concentration of 12 µg/$10^6$ cells, cobalt inhibited glucose-6-phosphate dehydrogenase activity by >50%; WC-Co showed similar results. WC-Co decreased superoxide anion production by alveolar macrophages; at 100 µg/mL, production was already reduced by ~50%. Cobalt had no effect. In peritoneal macrophages, cobalt and WC-Co produced a significant reduction in plasminogen activator activity at all doses. In rat alveolar macrophages, both powders produced a moderate reduction at the highest dose. | Lison and Lauwerys (1991) |
| Mouse peritoneal macrophages | extra fine cobalt metal powder, 99.7% pure; WC-Co containing 6.3% cobalt, purity n.p. | incubation with 3, 9, and 20 µg/mL (0.05, 0.15, 0.34 mM) cobalt or 50 and 150 µg/mL WC-Co for up to 24 h; uptake measured after 2, 4, and 6 h of exposure | At 150 µg WC-Co/mL, LDH activity was significantly increased after 6 h of exposure compared to controls and reached a plateau after 16 h. At both doses, maximal intracellular levels of cobalt were reached after 2 h; the high dose produced about 2x greater levels than that of the low dose. With cobalt metal alone (3 and 9 µg/mL), metal uptake was maximal after 2 h, but the levels were 3x lower than those found with WC-Co. No increase in LDH release was observed with cobalt at any dose. | Lison and Lauwerys (1994) |
| Alveolar macrophages from Sprague-Dawley rats | extra fine cobalt metal powder, 99.87% pure; WC-Co containing 6.3% cobalt, purity n.p. | incubation with 3 µg/mL (0.05 mM) cobalt or 50 µg/mL (corresponding to 3 µg Co/mL) WC-Co for 12 or 24 h | In the presence and absence of LPS, cobalt and WC-Co had no effect on TNF-α release. Without LPS, no IL-1 activity was detected. After LPS stimulation, a "modest but inconsistent increase" occurred with cobalt only. Both cobalt and WC-Co had no effect on fibronectin release, with and without LPS stimulation. | Huaux et al. (1995) |

## Table 4. Cytotoxicity Studies of Cobalt Dust (Continued)

| Test System or Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, and Duration | Results/Comments | Reference |
|---|---|---|---|---|
| ***In Vivo* Assays** | | | | |
| Rats, Sprague-Dawley, 3F/group | extra fine cobalt metal powder, 99.87% pure; WC-Co containing 6.3% cobalt, purity n.p. | i.t.; 0.06 mg/100 g (0.01 µmol/g) bw saline suspension of cobalt or 1 mg/100 g bw (corresponding to 0.06 mg Co/100 g bw) suspension of WC-Co; broncho-alveolar lavage performed 24 h later | Cobalt had no significant effects on LDH activity, TP, and albumin content of BALF. Compared to the controls (saline) and rats given cobalt alone, WC-Co significantly increased the mean levels of these parameters. Cobalt did not affect the cellularity of BALF, whereas WC-Co significantly increased total cell number, macrophages, and neutrophils compared to controls and rats given cobalt only.<br>BALF phagocytes were isolated from the lung. In unstimulated cells, no effects on TNF-α production occurred with cobalt or WC-Co. After addition of LPS, an insignificant increase occurred with cobalt. Cobalt and WC-Co both significantly stimulated cystatin-c production; however, no effects on IL-1 activity, with or without LPS, and on fibronectin release were observed. | Huaux et al. (1995) |

Abbreviations: BALF = bronchoalveolar lavage fluid; bw = body weight; F = female(s); h = hour(s); inh = inhalation; IL-1 = interleukin-1; LDH = lactate dehydrogenase; LPS = lipopolysaccharide; M = male(s); n.p. = not provided; TNF-α = tumor necrosis factor-α; TP = total proteins; WC-Co = tungsten carbide-cobalt mixture; wk = week(s)

powder and WC-Co (both at 3 µg Co/mL [0.05 mM]) did not stimulate the production of interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), or fibronectin by rat alveolar macrophages (Huaux et al., 1995).

In an *in vivo* assay with rats, WC-Co (0.06 mg Co/100 g [0.01 µmol/g] body weight) showed greater toxicity than cobalt alone (same dose). Significant increases in bronchoalveolar lavage fluid (BALF) parameters (e.g., LDH activity) and the cellularity of BALF (e.g., increased number of macrophages) occurred with WC-Co. In lung phagocytes, WC-Co and cobalt both significantly stimulated cystatin-c production (Huaux et al., 1995).

In chick primary cultures and rodent fibroblast cell lines, cobalt released from cobalt metal, alloys or dissolved salts was cytotoxic at concentrations >7.5 µg/mL (0.13 mM); cell death, growth inhibition, and mitotic aberrations were observed (study details were not provided in review) (Heath, 1954b; Daniel et al., 1963; Bearden, 1976; Bearden and Cooke, 1980; Takahashi and Koshi, 1981; all cited by IARC, 1991).

## 9.2 Reproductive and Teratological Effects

In test animals (species not provided) exposed to cobalt by inhalation (dose and exposure duration not provided), adverse effects included testicular atrophy, decreased sperm motility, and an increased length of the estrus cycle. Oral exposure to the metal at levels causing maternal toxicity produced stunted growth and decreased survival of newborn pups (Cal-ARB, 1997).

## 9.3 Carcinogenicity

The details of the following studies are presented in **Table 5**.

In rats, single or repeated intramuscular or intrathoracic injections of cobalt metal powder (28 mg [0.48 mmol]) produced tumors at the injection site, mostly rhabdomyosarcomas (Heath, 1954, 1956; Heath and Daniel, 1962 [all cited by Jensen and Tüchsen, 1990 and IARC, 1991]). One male rat had leukocyte infiltration, muscle fiber necrosis and regeneration, and a tumor nodule (Heath, 1960; cited by IARC, 1991). In rats, rabbits, and miniature swine, no tumors were observed for exposure via inhalation (up to 1.5 mg/m$^3$ [0.62 ppm] in rabbits and swine; 200 mg/m$^3$ [83.0 ppm] in rats) and i.t. (2.5-50 mg [0.042-0.85 mmol]) and intrarenal (5 mg [0.08 mmol]) injections; observation periods were up to one year (Kaplun, 1957; Delahant, 1955; Schepers, 1955b; Stokinger and Wagner, 1958 [all cited by Herndon et al., 1981]; Jasmin and Riopelle, 1976 [cited by IARC, 1991]; Kerfoot, 1973).

In rats, cobalt metal powder has also produced tumors in the thyroid gland, as well as the injection site (Weaver et al., 1956; cited by Léonard and Lauwerys, 1990). In rabbits, injection of cobalt dust produced transplantable liposarcomas and hyperplasia of adipose tissue (Thomas and Thiery, 1953; cited by Léonard and Lauwerys, 1990). [Study details were not provided.]

## 9.4 Initiation/Promotion Studies

No data were available.

## 9.5 Anticarcinogenicity

No data were available.

## Table 5. Carcinogenicity Studies of Cobalt Dust

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| Rats | cobalt dust, purity n.p. | inh; 200 mg/m$^3$ (83.0 ppm) for 12 h every other day for 4 mo; observation period ≥4 mo | No tumors were observed. | Kaplun (1957; cited by Herndon et al., 1981) |
| Rats | cobalt metal, purity n.p. | i.t.; 3-10 mg (0.05-0.17 mmol) in saline for ≥8 mo; observation period ≥8 mo | No tumors were observed. | Kaplun (1957; cited by Herndon et al., 1981) |
| Rats, hooded, 2- to 3-mo-old, 10F and 10M | cobalt metal powder, spectro-graphically pure | intramuscular (i.m.); single injection of 28 mg (0.48 mmol) in 0.4 mL fowl serum into the thigh; observed for 7.5 mo | At 5 mo, 2 M rats developed malignant rhabdomyosarcomas at the injection site; one contained a definite lymph node metastasis. At 7.5 mo, 3 M and 2 F had fibrosarcomas. | Heath (1954; cited by Jensen and Tüchsen, 1990 and IARC, 1991) |
| Rats, hooded, 2- to 3-mo-old, 10M and 20F | cobalt metal powder, spectro-graphically pure | i.m.; single injection of 28 mg (0.48 mmol) in 0.4 mL fowl serum into the thigh; observed for 5 to 12 mo<br>All F rats then received a single i.m. injection of 28 mg (0.48 mmol) cobalt metal powder, while 5M received 28 mg zinc powder and 5M received 28 mg tungsten powder. | Average survival times were 71 wk in M and 61 wk in F (survival in controls not specified). At the injection site, 4/10 M and 5/10 F developed sarcomas, mostly rhabdomyosarcomas (controls: 0).<br>After the second administration, average survival time was 43 wk for F treated rats. At the injection site, sarcomas, mostly rhabdomyosarcomas, were seen in 8/10 F (treated M: 0). | Heath (1956; cited by Jensen and Tüchsen, 1990 and IARC, 1991) |
| Rats, hooded, 2- to 3-mo-old, 30M | cobalt metal powder, spectro-graphically pure | i.m.; single injection of 28 mg (0.48 mmol) in 0.4 mL fowl serum into the right thigh; observed for >20 wk | One rat had leukocyte infiltration, muscle fiber necrosis and regeneration, and a tumor nodule. | Heath (1960; cited by IARC, 1991) |
| Rats, hooded, 2- to 3-mo-old, 10F/group | cobalt metal powder, spectro-graphically pure | intrathoracic; injections of 28 mg (0.48 mmol) in serum through the right dome of the diaphragm (group 1) or the fourth left intercostal space (group 2); observed for up to 28 mo | Within 3 days of treatment, 6/10 and 2/10 rats in groups 1 and 2, respectively, died. Survival times for the remaining rats were 11-28 and 7.5-17.5 mo, respectively. Four rats had intrathoracic sarcomas (3 of mixed origin and one rhabdomyosarcoma in the intercostal muscles) in or near the heart. | Heath and Daniel (1962; cited by Jensen and Tüchsen, 1990 and IARC, 1991) |
| Rats, Sprague-Dawley, 18F | metallic cobalt powder, purity n.p. | intrarenal; single injection of 5 mg (0.08 mmol) suspended in 0.05 mL glycerine into each pole of the right kidney; observed up to (i.e., necropsied after) 12 mo | No tumors were observed.<br>(IARC Working Group noted the experiment was of short duration and had inadequate reporting.) | Jasmin and Riopelle (1976; cited by IARC, 1991) |

## Table 5. Carcinogenicity Studies of Cobalt Dust (Continued)

| Species, Strain, and Age, Number, and Sex of Animals (If Given) | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|---|---|---|---|
| Guinea pigs (n=6) | 10% cobalt dust, purity n.p. | i.t.; single injection of 25 mg (0.42 mmol) in saline; observed for 360 days | No tumors were observed. | Delahant (1955; cited by Herndon et al., 1981) |
| Guinea pigs (n=6) | cobalt metal dust, purity n.p. | i.t.; 2.5 mg (0.042 mmol) doses in saline injected a wk apart; observed for 360 days | No tumors were observed. | Delahant (1955; cited by Herndon et al., 1981) |
| Guinea pigs | cobalt dust, purity n.p. | i.t.; 5 mg (0.08 mmol) in saline administered two times, 1 wk apart; observed for 1 yr | No tumors were observed. | Schepers (1955b; cited by Herndon et al., 1981) |
| Guinea pigs | cobalt dust, purity n.p. | i.t.; single 25 mg (0.42 mmol) in saline; observed for ≥8 mo | No tumors were observed. | Schepers (1955b; cited by Herndon et al., 1981) |
| Guinea pigs (n=6) | cobalt metal dust, purity n.p. | i.t.; 50 mg (0.85 mmol) in saline; observed for 1 yr | No tumors were observed. | Delahant (1955; cited by Herndon et al., 1981) |
| Guinea pigs | cobalt dust, purity n.p. | i.t.; single 50 mg (0.85 mmol) dose in saline; observed for ≥1 yr | No tumors were observed. | Schepers (1955b; cited by Herndon et al., 1981) |
| Rabbits, albino, 12M | cobalt fumes, purity n.p. | inh; 1.5 mg/m$^3$ (0.62 ppm) for 6 h/day, every third wk for 24 wk; observation period ≥6 mo | No tumors were observed. | Stokinger and Wagner (1958; cited by Herndon et al., 1981) |
| Miniature swine (n=5) | cobalt powder, purity n.p. | inh; 0.1 and 1.0 mg/m$^3$ (0.04 and 0.4 ppm) for 6 h/day 5 days/wk for 3 mo; observation period ≥3 mo | No tumors were observed. | Kerfoot (1973) |

Abbreviations: F = female(s); h = hour(s); i.m. = intramuscular(ly); inh = inhalation; i.t. = intratracheal(ly); M = male(s); mo = month(s); n = number; n.p. = not provided; wk = week(s); yr = year(s)

## 9.6 Genotoxicity

Incubation of human peripheral lymphocytes with cobalt (0.06-6.0 µg/mL [1.0 µM-0.10 mM) or WC-Co (10-100 µg/mL) caused a time- and dose-dependent increase in the production of DNA single strand breaks. On the basis of an equivalent cobalt content, WC-Co had a more significant effect than cobalt alone. Addition of sodium formate (1 M) had a protective effect against the production of the breaks with both powders (Anard et al., 1997).

## 9.7 Cogenotoxicity

No data were available.

## 9.8 Antigenotoxicity

No data were available.

## 9.9 Immunotoxicity

In skin tests, there were no allergic reactions in groups exposed to cobalt. In blood chemistry studies, there was an increase in α-, β-, and γ-globulins over those of controls; a net increase in total protein in groups exposed; and inversion of the albumin/globulin ratio. These changes may be read as early indicators of lung cell damage (Kerfoot et al., 1975).

## 9.10 Other Data

### 9.10.1 Miscellaneous Studies

In rats exposed for four months to metallic cobalt dust (dose not provided), blood pressure was reduced by 20-25%, beginning with the third month of the experiment. In a separate test (study details not provided), significant prolongation of extensor chronaxie and a significant but smaller increase in flexor chronaxie were observed at the second month of exposure in the animals. In addition, the rheobase increased but not significantly. The findings were indicative of changes in the central nervous system. Microscopically, severe hyperemia was found in interalveolar blood vessels, in kidney tubules, and in all internal organs, with dilatation of veins and capillaries. The walls of the small and intermediate blood vessels were swollen and filled with plasma and had hyperplastic endothelium. The liver was severely congested with dilatation of the lobular veins and capillaries (Kaplun, 1967).

In cultured rat myoblasts, cobalt metal powder in horse serum produced cytological changes resembling those found in cobalt-induced rhabdomyosarcomas *in vivo* (Costa, 1979; cited by Herndon et al., 1981).

### 9.10.2 Hard Metal Disease and Cobalt-Tungsten Carbide

Numerous reviews and original studies on cobalt-induced occupational disease (especially hard metal disease) are available. Many of these also included copious epidemiological studies on workers exposed to cobalt-containing dust (e.g., IARC, 1991; ATSDR, 2001 [reviews]; Demedts et al., 1984 [diamond polishers]; Ferdenzi et al., 1994 [powder sintering industry]). Studies on hard metal exposure are especially plentiful (e.g., Chiappino, 1994; Linnainmaa et al., 1996). (See also Section 13.0.)

This section briefly summarizes toxicology data for mixtures containing WC, alone and in combination with cobalt (WC-Co).

Human Data

*Exposure and Pharmacokinetics*: The NIOSH recommended occupational exposure level to dust of cemented WC containing >2% cobalt is 0.1 mg Co/m$^3$ as a TWA for up to a ten-hour shift in a 40-hour week (NIOSH, 1977). Mean cobalt levels in urine were reported as follows: 9.6 µg/L for workers producing presintered WC (Sunday sampling), 11.7 µg/L for those using hard metal (Sunday sampling), and 36-63 µg/L for those producing hard metal (Monday and Friday sampling, respectively). In serum, the following cobalt concentrations were observed: 2.1 µg/L for individuals grinding hard metal, 3.3-18.7 µg/L for producing hard metal tools, and 2.0-18.3 µg/L for producing hard metal (Seiler et al., 1988; cited by HSDB, 2001). Cobalt concentrations ranged from 100 to 1000 µg/kg in two lung tissue samples from hard metal workers with lung disease; a level of 5 µg/kg wet weight was found in controls. In mediastinal lymph nodes, the concentration of cobalt was 3280 µg/kg in exposed workers versus >2 µg/kg in controls (Hillerdal and Hartung, 1983; cited by IARC, 1991). In workers in two plants producing diamond segments and sintered wires for stone cutting, the highest cobalt exposures were found during mixing and granulation of cobalt powders. Environmental cobalt concentrations were ~50 µg/m$^3$ in one plant and as high as 8000 µg Co/m$^3$ in the second plant. Cobalt in urine was found to increase rapidly in the hours after exposure, reaching a peak at about two to four hours after exposure, and then decreased during the following days. The diphasic pattern was independent of the degree of cobalt exposure (Apostoli et al., 1994).

*Toxic Effects*: The major effects in hard metal workers exposed to cobalt-containing dust are pulmonary effects. Interstitial fibrosis (hard-metal pneumoconiosis) and occupational asthma are the two types of lung lesions that occur (Demedts and Ceuppens, 1989; cited by IARC, 1991). Hard-metal pneumoconiosis occurs after several years of exposure to the dust at concentrations of 0.1 to 2 mg/m$^3$ (IARC, 1991). Advanced fibrosis and desquamative interstitial pneumonia of the giant-cell type are common findings (Coates and Watson, 1971; Anttila et al., 1986; both cited by IARC, 1991). Alveolitis progressing to lung fibrosis has been reported in workers exposed to a mixture of cobalt and WC in the hard metal industry (Lasfargues et al., 1992, 1995). Twelve workers involved in the manufacture of or grinding with WC tools developed interstitial lung disease; eight of these died. Serial chest roentgenograms showed gradually progressive densities involving major portions of both lungs. Obstructive lung disease, which usually improves after cessation of exposure, is considered to be an allergic response (Sjögren et al., 1980; cited by IARC, 1991).

Workers in hard-metal plants have been found to possess increased morbidity and mortality from cardiovascular disease (IARC, 1991). A study of cardiac function in workers with hard metal disease (average exposure: 10.4 years; environmental cobalt levels: 0.009-13.6 mg/m$^3$) suggested that cardiomyopathy might have been induced (D'Adda et al., 1994). Dyspnea, heaving breathing, and tightness of the chest were more common in workers exposed to cobalt-containing dusts at concentrations of 0.01-0.06 mg/m$^3$ compared to controls; no pulmonary dysfunction was found (Alexandersson and Atterhög, 1980; cited by IARC, 1991). Among workers (n=3163) exposed to cobalt-containing dusts at levels ranging from 0.001 to 11 mg/m$^3$ for at least one year, those exposed for at least ten years had an excess of deaths from ischemic heart disease (standardized mortality ratio [SMR], 169; 95% confidence interval [CI], 96-275) for at least ten years (Hogstedt and Alexandersson, 1990; cited by IARC, 1991).

A significant amount of conjunctivitis has also been observed in the WC industry; however, workers in the cemented WC industry did not experience eye irritation to cobalt at <1 mg/m$^3$. Cobalt and its compounds can also induce an allergic dermatitis of an erythematous papular type, occurring in skin areas subjected to friction, such as the ankles and sides of the neck (NIOSH, 1978).

*Other Data*: A study of memory functioning found that adult WC workers with hard metal disease had memory deficits related to difficulties in attention and verbal memory (Jordan et al., 1990; cited by Grimsley, 2001). In workers (8 males, 18 females; mean age of 34.2 years) occupationally exposed to cobalt dusts in hard metal manufacturing factories for an average of 3.5 years (median 8-hour TWA air concentration of 83 µg/m$^3$ cobalt dusts), a significant correlation between early markers of kidney dysfunction and the intensity or duration of exposure to cobalt was not seen, suggesting that the kidney is not a target organ during such occupational exposure (Franchini et al., 1994). Hard metal disease has been strongly associated with residue glutamate 69 of the HLA-DPβ chain (Potolicchio et al., 1997).

Animal Studies

*Short-term or Subchronic Studies*: Rats intratracheally administered mixtures (10, 15, 25, and 50 mg) of an 8% cobalt and 92% tungsten ($BK_8$), 15% cobalt and 85% tungsten ($BK_{15}$), and 8% cobalt, 14% titanium, and 78% tungsten ($Ti_{14}K_8$) all died at the high dose of all forms. In the lungs, interalveolar septa were significantly thickened and coalesced in some sectors. Lumina had numerous amounts of secretion and dust. The liver had marked hyperemia and granulonodular degeneration of liver cells. The kidneys had granulomatous degeneration of the cells of the convoluted and descending tubules and stagnation in the glomeruli and tubules. Similar effects were seen at the lower doses (Kaplun and Mezentseva, 1967).

In guinea pigs, repeated inhalation of a mixture of cobalt (25%) and WC (75%) produced acute pneumonitis, which then rapidly led to death (NIOSH, 1978).

*Cytotoxicity*: In rat alveolar epithelial type II cells (AT-II), doses of pure cobalt and WC-Co that induced 50% cell death ($TD_{50}$ values per $10^5$ cells) were 672 and 101 µg, respectively. In comparison, the values were 18 and 5 µg, respectively, in rat alveolar macrophages. In human AT-II, no toxicity was observed. Therefore, rat AT-II were more sensitive to cobalt than macrophages, and human AT-II were less sensitive to cobalt than rat alveolar macrophages. Furthermore, the toxicity of cobalt was increased with WC (Roesems et al., 1997).

In human osteosarcoma (HOS) cells, a pure mixture of tungsten (92%), nickel (5%), and cobalt (3%) particles (r-WNiCo) as well as cobalt powder alone (both at concentrations from 0.75-200 µg/mL) had a dose-dependent decrease in cell survival during a 24-hour incubation period (Miller et al., 2001). (See study also under Genotoxicity.)

*Carcinogenicity*: Rats exposed to repeated inhalation of a cobalt metal blend used by the cemented carbide industry (20 mg/m$^3$ [8.3 ppm] cobalt for three years) had hyperplasia of the bronchial epithelium and focal fibrotic lesions of the lungs with developing granulomata. An experiment in which the animals were exposed daily to cobalt metal fume of cobalt oxide and

cobaltic-cobaltous oxide (almost equal parts) via inhalation produced no such reactions (NIOSH, 1978).

## 10.0 Structure-Activity Relationships

ATSDR (2001) and NTP (1998) reported on the toxicity and/or carcinogenicity of cobalt sulfate heptahydrate, cobalt oxide, cobalt hydrocarbonyl, and cobalt chloride (soluble) in inhalation studies of rats, rabbits, and hamsters.

NTP (1998) evaluated the toxicity and carcinogenicity of cobalt sulfate heptahydrate in two-year inhalation studies using mice and rats. Rats and mice were exposed to aerosols containing 0, 0.3, 1.0, or 3.0 mg/m$^3$ cobalt sulfate heptahydrate six hours per day, five days per week, for 105 weeks. The following conclusions were reached:

> ….[T]here was *some evidence of carcinogenic activity* of cobalt sulfate heptahydrate in male F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms. Marginal increases in incidences of pheochromocytomas of the adrenal medulla may have been related to exposure to cobalt sulfate hepta-hydrate. There was *clear evidence of carcinogenic activity* in female F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms and pheochromocytomas of the adrenal medulla in groups exposed to cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* of cobalt sulfate heptahydrate in male and female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms.
>
> Exposure to cobalt sulfate heptahydrate caused a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice.

Similarly, cobalt oxide inhaled by hamsters (7.9 mg/m$^3$) caused emphysema (Wehner et al., 1977; cited by ATSDR, 2001), and cobalt hydrocarbonyl (9 mg/m$^3$) inhaled by rats caused lung inflammation (Palmes et al., 1959; cited by ATSDR, 2001). Cobalt chloride inhaled by rabbits (0.6 mg/m$^3$) caused histologic alterations in pulmonary tissue and induced pulmonary inflammatory changes (Johansson et al., 1992; cited by ATSDR, 2001).

## 11.0 Online Databases and Secondary References

### 11.1 Online Databases

In-House Databases

CPI Electronic Publishing Federal Databases on CD
Current Contents on Diskette®
The Merck Index, 1996, on CD-ROM

STN International Files

| | | | |
|---|---|---|---|
| AGRICOLA | CANCERLIT | LIFESCI | PROMT |
| BIOSIS | CAPLUS | MEDLINE | Registry |
| CA | EMBASE | NIOSHTIC | RTECS |
| CABA | HSDB | NTIS | TOXLINE |

TOXLINE includes the following subfiles:

| | |
|---|---|
| Toxicity Bibliography | TOXBIB |
| International Labor Office | CIS |
| Hazardous Materials Technical Center | HMTC |
| Environmental Mutagen Information Center File | EMIC |
| Environmental Teratology Information Center File (continued after 1989 by DART) | ETIC |
| Toxicology Document and Data Depository | NTIS |
| Toxicological Research Projects | CRISP |
| NIOSHTIC® | NIOSH |
| Pesticides Abstracts | PESTAB |
| Poisonous Plants Bibliography | PPBIB |
| Aneuploidy | ANEUPL |
| Epidemiology Information System | EPIDEM |
| Toxic Substances Control Act Test Submissions | TSCATS |
| Toxicological Aspects of Environmental Health | BIOSIS |
| International Pharmaceutical Abstracts | IPA |
| Federal Research in Progress | FEDRIP |
| Developmental and Reproductive Toxicology | DART |

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**Units and Abbreviations**
°C = degrees Celsius
μg/L = microgram(s) per liter
μg/m$^3$ = microgram(s) per cubic meter
μg/mL = microgram(s) per milliliter
μM = micromolar
ATSDR = Agency for Toxic Substances and Disease Registry
bw = body weight
CEA = carcinoembryonic antigen
F = female(s)
g = gram(s)

g/mL = gram(s) per milliliter
h = hour(s)
HSDB = Hazardous Substances Data Bank
IARC = International Agency for Research on Cancer
i.m. = intramuscular(ly)
inh = inhalation
i.p. = intraperitoneal(ly)
i.t. = intratracheal(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
$LD_{50}$ = lethal dose for 50% of test animals
LDH = lactate dehydrogenase
M = male(s)
mg/kg = milligram(s) per kilogram
$mg/m^3$ = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
min = minute(s)
mL/kg = milliliter(s) per kilogram
mm = millimeter(s)
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mo = month(s)
mol = mole(s)
mol. wt. = molecular weight
n = number
NAG = *N*-acetyl-β-*D*-glucosaminidase
NIEHS = National Institute of Environmental Health Sciences
NIOSH = National Institute for Occupational Safety and Health
n.p. = not provided
ppb = parts per billion
ppm = parts per million
ppt = parts per trillion
RTECS = Registry of Toxic Effects of Chemical Substances
SCE = sister chromatid exchange
TP = total proteins
TSCA = Toxic Substances Control Act
TWA = time-weighted average
WC = tungsten carbide
WC-Co = tungsten carbide-cobalt mixture
wk = week(s)
yr = year(s)

## Appendix: Literature Search Strategy

An online search of bibliographic databases was performed on STN International on July 2, 2001. The first two columns in the table below shows the distribution of records in all bibliographic databases that contained the term "cobalt?" within six words of "dust?" in either direction. The question mark is used as a truncation symbol. Databases in boldface were searched simultaneously using that strategy (column 3) and by using the search statement "cobalt? within three words of "powd?" (column 4).

| *RECORDS/DATABASE FOR* COBALT? (6A) DUST? IN STN INDEX | | *COBALT?(6A)DUST?* SIMULTANEOUS SEARCHES *(After Duplicate Removal)* | *COBALT (3A) POWD?* SIMULTANEOUS SEARCHES *(After Duplicate Removal)* |
|---|---|---|---|
| 1 | FILE AEROSPACE | | |
| 2 | FILE ANABSTR | | |
| 10 | FILE BIOBUSINESS | | |
| **60** | **FILE BIOSIS** | **12** | **2** |
| **4** | **FILE BIOTECHNO** | **0** | **0** |
| **2** | **FILE CABA** | **1** | **2** |
| 12 | FILE CANCERLIT | 0 | 0 |
| 238 | FILE CAPLUS | | |
| 2 | FILE CBNB | | |
| 4 | FILE CEABA-VTB | | |
| 23 | FILE COMPENDEX | | |
| 1 | FILE CONFSCI | | |
| 1 | FILE CORROSION | | |
| 25 | FILE CSNB | | |
| **58** | **FILE EMBASE** | **10** | **5** |
| 1 | FILE ENCOMPLIT2 | | |
| 24 | FILE ENERGY | | |
| 11 | FILE ESBIOBASE | | |
| 6 | FILE EUROPATFULL | | |
| 1 | FILE GEOREF | | |
| 22 | FILE HEALSAFE | | |
| 7 | FILE IFIPAT | | |
| 4 | FILE INPADOC | | |
| 2 | FILE INSPEC | | |
| 1 | FILE ISMEC | | |
| 9 | FILE JICST-EPLUS | | |
| **27** | **FILE LIFESCI** | **0** | **0** |
| 1 | FILE MATBUS | | |
| **63** | **FILE MEDLINE** | **63** | **11** |
| 18 | FILE METADEX | | |
| **102** | **FILE NIOSHTIC** | **78** | **6** |
| 7 | FILE NLDB | | |
| **5** | **FILE NTIS** | **3** | **7** |
| 1 | FILE OCEAN | | |
| **32** | **FILE PASCAL** | **7** | **105 (mostly technology)** |
| 3 | FILE PATOSEP | | |
| 2 | FILE PCTFULL | | |
| 2 | FILE PHIN | | |
| 1 | FILE PIRA | | |
| 12 | FILE POLLUAB | | |
| 10 | FILE PROMT | | |
| 1 | FILE RUSSCI | | |
| 50 | FILE SCISEARCH | | |
| 4 | FILE SIGLE | | |
| 1 | FILE SOLIDSTATE | | |
| 1 | FILE TEXTILETECH | | |
| **148** | **FILE TOXLINE** | **62** | **6** |
| 49 | FILE TOXLIT | | |
| 1 | FILE TRIBO | | |
| 1 | FILE ULIDAT | | |
| 55 | FILE USPATFULL | | |
| 34 | FILE WPIDS | | |

| | *RECORDS/DATABASE FOR* COBALT? (6A) DUST? IN STN INDEX | *COBALT?(6A)DUST?* SIMULTANEOUS SEARCHES *(After Duplicate Removal)* | *COBALT (3A) POWD?* SIMULTANEOUS SEARCHES *(After Duplicate Removal)* |
|---|---|---|---|
| | 34 FILE WPINDEX | | |
| | 4 FILE WSCA | | |
| **Totals** | | **243** | **143** |

## Details of Simultaneous Searches on 02 Jul 2001 in MEDLINE, CANCERLIT, TOXLINE, AGRICOLA, NIOSHTIC, CABA, EMBASE, PASCAL, BIOTECHNO, BIOSIS, LIFESCI, and NTIS

## Preliminary Considerations

The references cited in Herndon et al. (1981), which was written under NIEHS Contract No. N01-ES-8-2153, "Appraisal of Environmental Exposure to Heavy Metals," was assumed to represent a reasonably comprehensive search on the toxicology of cobalt dusts for publications up to about 1979. In 1979, that project's Principal Investigator (current searcher Bonnie L. Carson) selected references for this cobalt physiology chapter from online searches of MEDLINE and TOXLINE (search term cobalt?) and from manual searches of all *Chemical Abstracts Collective Indexes* back to the early 1900s. For the July 2001 STN International searches, the year 1991 was assumed to be a reasonable lower limit because an IARC monograph on cobalt was published in that year. Animal toxicology studies were selected from the search results if unalloyed cobalt metal dusts or powders had been administered by inhalation or by intratracheal (endotracheal) instillation.

## History of STN International Search Session

| Answer *Set* | Records | Search Statement (S = Search) and Comments (Boldface) |
|---|---|---|
| L2 | 513 | S L1 **[L1 = cobalt?(6A)dust?, which was created in the STN Index file.]** |
| | | SET DUPORDER FILE |
| L3 | 243 | DUP REM L2 (270 DUPLICATES REMOVED) **[This command generated data in table column 3.]** |
| L4 | 52 | S L2 AND (REVIEW? OR REVIEW/DT) |
| L5 | 28 | DUP REM L4 (24 DUPLICATES REMOVED) |
| L6 | 28 | SORT L5 1-28 TI **[Printed full records of selected reviews.]** |
| L7 | 461 | S L2 NOT L4 |
| L8 | 25 | S L7 AND (1999-2001)/PY |
| L9 | 11 | DUP REM L8 (14 DUPLICATES REMOVED) |
| L10 | 11 | SORT L9 1-11 TI **[Printed selected full records published 1999-2001.]** |
| L11 | 488 | S L2 NOT L8 |
| L12 | 436 | S L11 NOT L4 |
| L13 | 88 | S L12 AND (1995-1998/PY) |
| L14 | 22 | DUP REM L13 (66 DUPLICATES REMOVED) |
| L15 | 22 | SORT L14 1-22 TI **[Printed selected full records published 1995-1998.]** |
| L16 | 348 | S L2 NOT (L4 OR L8 OR L13) |
| L17 | 126 | S L16 AND (1991-1994/PY) |
| L18 | 44 | DUP REM L17 (82 DUPLICATES REMOVED) |
| L19 | 44 | SORT L18 1-44 TI **[Printed selected full records published 1991-1994.]** |
| L20 | 476 | S COBALT? (3A) POWD? |
| L21 | 409 | S L20 NOT L2 |
| L22 | 196 | S L21 AND (1991-2001)/PY |
| L23 | 143 | DUP REM L22 (53 DUPLICATES REMOVED) **[This command generated data in table column 4.]** |
| L24 | 143 | SORT L23 1-143 TI |

Answer set L24 was saved as 'POWDCOBALT/A' **[All 143 sorted titles were printed for selection offline. Selected and subsequently printed were 21 full records on cobalt powders published between 1991 and 2001.]**

## Other Searches

TOXLINE, GENETOX, and EMIC were browsed on the Internet. More than 500 records were found in TOXLINE on October 1, 2001, that satisfied the search strategy "cobalt* AND (powd* OR dust*)." Results were scanned while online, and about 30 relevant records from older toxicity studies and about 30 records with exposure information were printed. The cobalt chapter from the *Minerals Yearbook* was retrieved from the U.S. Geological Survey web site. Articles from the daily trade newspaper *American Metal Market* were retrieved at findarticles.com. Miscellaneous web searches were conducted using the Google search engine. Three citations that had been inadvertently omitted from the references in the chapter by Herndon et al. (1981) were located in PubMed.