Via e-mail

February 5, 2002

Nominations Faculty
National Toxicology Program
MD B3-10
PO Box 12233
Research Triangle Park, NC, 27709

To the NTP Nominations Faculty:

The Cobalt Development Institute (CDI) would like to take this opportunity to nominate cobalt metal powder to the NTP for a two (2) year animal inhalation carcinogenicity assay. The CDI is composed of members who are involved in the production and use of cobalt compounds including cobalt metal powder. Please find the appended document for cobalt metal powder, including toxicological information, background data on production and uses, and the rationale for the proposed nomination.

Please do not hesitate to contact me if I may be assistance.

Sincerely,

Thomas O. Brock, PhD, DABT
Consulting Toxicologist

Cc: Mr. Scott Grove
    Dr. Michael Hawkins
    Dr. Bert Swennen
I. Chemical Identification

A. Chemical Abstracts Service (CAS) preferred name: Cobalt metal.
B. Common or generic name and synonyms: Cobalt metal, elemental cobalt, cobalt, cobalt-59, CI 77320.
C. CAS Registry Number: 7440-48-4
D. Chemical class and related compounds: Cobalt is a naturally occurring element of Group VIII of the periodic table. There is one stable isotope (Co-59) and 4 principal radioactive isotopes (Co-55, Co-57, Co-58, Co-60).
E. Physical and chemical properties
   1. Physical Description: Steel-gray, shiny, ductile, magnetic metal.
   2. Structural / molecular formula and molecular weight: Co; MW=58.93
   3. Melting and boiling points: MP=1495° c; BP= 2870° c.
   4. Solubility: Cobalt metal is insoluble in water and organic solvents. It is attacked by dilute mineral acids but is stable to dilute alkaline solutions.
   5. Stability and reactivity: Does not oxidize in dry or moist air at normal environmental temperatures. Two common valence states are cobaltous (+2) and cobaltic (+3) in addition to metallic cobalt (0). Valence states of -1, +1, +4, +5 are uncommon. Stable in atmospheric oxygen. Heating produces mixed oxides below 900° c and cobaltous (+2) above 900° c. When heated cobalt combines with carbon, phosphorous, and sulfur but not with hydrogen or nitrogen.
   6. Other relevant information: Cobalt is an essential element for humans and other mammals in the form of vitamin B12 (hydroxycyanocobalamin) which catalyses important synthetic metabolic reactions and thus has important human health and veterinary/agricultural applications. IARC has classified cobalt and cobalt compounds: 2B “Possibly carcinogenic to humans”. Surgical and dental implants of cobalt alloys were classified in Group 3: “Not classifiable as to carcinogenicity in humans”.

F. Commercial product(s) composition: No data
G. References:
   3. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 52. Chlorinated drinking water, chlorination bi-products; some other halogenated compounds; cobalt and cobalt compounds. Lyon, France 1991
II. Production, Use, Occurrence, and Analysis

A. Production

Source and synthesis: Cobalt is found in association with nickel, silver, lead, copper, and iron ores. It is found in mineral form as arsenides, sulfides, and oxides. Sulfide ores are finely ground and sulfides are separated by flotation process. The concentrated product is subjected to sulfatizing roasting and the resulting matte is leached with water. The leachate is precipitated as the hydroxide and dissolved in sulfuric acid. The resulting sulfate is electrolyzed to yield the metal. For cobalt sulfide/arsenides the leaching process is carried out with either ammonia or acid under pressure and increased temperature. The solution is purified to remove iron and is subsequently reduced by hydrogen in the presence of catalyst under elevated temperature and pressure to obtain fine cobalt powder. No cobalt is currently mined or refined in the United States. Except for negligible by-product production, current US production is derived from scrap. Currently, 4 facilities are listed in the US as producing cobalt metal or hard metal (cobalt with tungsten carbide).

B. Use:

The largest use of cobalt metal in the US is in super alloys. It is also used in magnets/magnetic alloys and alloys that require hardness, wear resistance, and corrosion resistance. Cobalt metal powder is used as a binder for tungsten carbide (cemented carbides) cutting tools, in the production of coatings, and in the production of chemicals. A growing use is as an addition to the nickel/cadmium, Ni-metal hydride battery, or as the main component of the lithium ion cell (LiCoO2).

C. Occurrence in the environment:

Cobalt occurs naturally in the earth’s crust and can be found in soil. Low levels occur naturally in sea water, some surface waters, and groundwater. Cobalt is released into the atmosphere from windblown soil, seawater spray, volcanic eruptions, and forest fires. Primary anthropogenic sources include fossil fuel and waste combustion, disposal of cobalt-containing wastes, application of cobalt containing sludge, vehicular and aircraft exhaust, processing of cobalt and cobalt containing alloys, copper and nickel smelting and refining, and the manufacture and use of cobalt chemicals and fertilizers derived from phosphate rocks.

D. Analysis: Human

The preferred samples for in vitro analysis are urine or feces, while tissues including bone and blood can be used on a limited basis. Because contamination of samples from various sources is a problem, blanks should always be run with the test samples. Two single-element instrumental techniques, Graphite furnace atomic absorption spectrometry (GF-AAS) and differential pulse anodic stripping voltammetry (DPAV) are the most
commonly used methods for determining cobalt in biological samples.

Analysis Environmental:
Methods commonly used in the analysis of cobalt are based on instrumental techniques such as atomic absorption spectroscopy (AAS), instrumental neutron activation analysis (INAA), and mass spectroscopy (MS). Sample treatment is important and external contamination must be avoided. Atmospheric cobalt (which is in particulate form) is measured by pumping air through a metal-free filter (usually cellulose nitrate) and quantifying the metal deposited. Wet ashing is the preferred method when sample treatment is necessary. Wet extraction with dilute nitric acid is most suitable for analyzing cobalt in dust samples. Loss of cobalt from aqueous samples due to absorption on to storage containers can be avoided by using polyethylene or similar containers and acidifying the solution to the proper pH. The cited references provide various methodologies for the collection and measurement of environmental cobalt samples.

E. References:
2. ATSDR (US DHHS). Toxicological Profile for Cobalt. TP-91/10 1992

III. Toxicology
A. Human data, case reports, and epidemiological studies:

Inhalation Exposure: Humans are most likely exposed to cobalt metal by inhalation of dusts or aerosols in occupational settings (ATSDR 1992,2001). A single study of workers occupationally exposed to mixed cobalt compounds initially found an elevated risk of mortality due to lung cancer. The eight-year follow-up study did not find further increased mortality due to lung cancer and correctly re-classified one lung cancer death from the original study. Recalculation of the standard mortality ratio following the re-classification of one death in the original study resulted in finding no elevated risk of mortality due to lung cancer. The number of workers studied and the number of cases found were relatively small (n=1,143; deaths =3; Mur 1987, Moulin 1993). The data from these occupational studies are equivocal and are insufficient to establish an association with lung cancer. A study of lung cancer mortality in stainless steel/metal alloy manufacturing did not show any association between mortality due to lung cancer and exposure to cobalt (Moulin 2000). Studies evaluating the
occupational exposure to cobalt metal dust or aerosols in the absence of mixed cobalt compounds have not been found.

Several epidemiologic studies have shown increased mortality rates in worker cohorts due to lung cancer following long-term occupational exposure to cobalt-tungsten carbide (hardmetal) dust however, mixed-metal exposures and smoking cannot be ruled out as being contributory (c.f. Lison 2001 for review). In vitro studies have shown the cytotoxicity of cobalt-tungsten carbide mixtures to be significantly more potent than that of cobalt metal or cobalt compounds alone. Some investigators have proposed that the toxicology of hardmetal exposure be considered as a separate entity for investigation (Lison 2001).

A fibrotic interstitial lung disease (e.g. hardmetal pneumoconioses, or hardmetal disease.) has been associated with long-term occupational exposure to hardmetal (cobalt-tungsten carbide) dust in some hardmetal workers, however the frequency of occurrence of the disease has not been quantified. Some diamond polishers using stainless steel polishing wheels with cobalt-cemented microdiamonds attached have also been reported to contract hardmetal disease. Evidence of hardmetal disease in workers exposed to cobalt compounds in the absence of mixed metal(s) or to cobalt metal dust alone is lacking (ATSDR 1992, 2001; Nemery 1992; Barceloux 1999; Lison 2001)

Occupational asthma can result from industrial cobalt exposures and workers sensitized should be removed from exposure. Workplace exposure to cobalt compounds has also been associated with changes in the ratio of the thyroid hormones T3 and T4. There have been several case reports of cardiomyopathies occurring in industrial cobalt workers, however, these studies did not report the level of exposure to cobalt compounds. The relationship of exposure to cobalt metal itself and cardiomyopathy is unknown (ATSDR 1992,2001; Swennen 1993; Barceloux 1999).

Oral exposure: Humans are orally exposed to cobalt compounds mainly through their diet, without negative health consequences. Cobalt in the form of hydroxocyanocobalamin (Vitamin B12) is biologically essential for humans and other mammals. Studies have shown that for human and veterinary health there are beneficial and harmful levels of oral (bioavailable) cobalt exposure.(ATSDR 1992, 2001; Barceloux, 1999)

Information on the effects of oral exposure to cobalt metal itself on humans has not been found. There are data on the oral exposure to cobalt salts (e.g. cobalt (II) ion) in both consumer and clinical settings. Consumers were exposed to small amounts (1-2 ppm) of cobalt salts (CoCl2, CoSO4) added to beer sold in the parts of the US, Canada, and Europe as a foam stabilizer. People who consumed large quantities (8-25 pints/day; approx 0.014 – 0.14 mg Co/kg bw)) developed an often fatal cardiomyopathy. The cardiomyopathy was probably pluricausal in origin. A background of chronic alcoholism and poor nutrition apparently pre-
conditioned these individuals to the metabolic effects of cobalt ions. (Barceloux 1999, Grice 1981; ATSDR 1992, 2001 for reviews.)

Clinically, cobalt salts (e.g. Roncovite) have been used to treat certain forms of anemia with oral dose levels in the range of 1 mg/kg body weight for periods of up to one year without reported cardiomyopathy (1 reported case of cardiomyopathy during treatment was related to kidney insufficiency and subsequent failure.) The clinical administration of cobalt salts involved dose levels significantly higher than those reported in the cobalt–beer cardiomyopathy cases. (Barceloux ,1999).

Oral exposure to cobalt salts clinically and in cobalt-beer consumers has also been associated with hypothyroid (goiter). The condition resolved when treatment or exposure ceased. (ATSDR 1992, 2001; Barceloux, 1999). It is not known whether exposure to cobalt metal has this effect.

Dermal Exposure: Occupational exposure to cobalt compounds resulting in skin contact can cause an allergic dermatitis or non-allergic skin irritation in sensitive individuals. Health effects other than dermatitis or skin irritation have not been associated with dermal exposure to cobalt compounds. (ATSDR 1992, 2001).

Implants: The International Agency for Research on Cancer (IARC) recently classified cobalt alloy surgical and dental implants in Category 3 (Inadequate evidence of carcinogenicity and not classifiable as to their carcinogenicity to humans). Implanted foreign bodies and smooth film implants made entirely of cobalt metal were classified Category 2 B (limited and sufficient evidence, respectively, of carcinogenicity in animals and possibly carcinogenic to humans; IARC 1999).

A. Experimental Animal Information

Inhalation: Most studies of the toxicity of cobalt have focused on the inhalation of cobalt compounds such as cobalt salts and cobalt oxides rather than on cobalt metal. It should be pointed out that long-term inhalation studies (24 months) conducted on cobalt sulfate heptahydrate (a water-soluble cobalt salt) in rats and mice found an increase in lung tumors. On the other hand a 17-month study on the inhalation of water-insoluble cobalt oxide found fibrotic lung damage in exposed hamsters, but did not find increased lung tumors. (NTP 1998, Wehner 1977).

Several studies have been conducted to evaluate the effects of cobalt metal (powder) on the respiratory system. Inhalation effects have been reported at level of 2.7 mg/m³ in rats from 3 to 5 days including damage to the cellular respiratory mucosa. EKG changes and decreased cellular compliance were reported in miniature swine exposed to 0.1 mg./m³ over a 3 month period. In rats, the intra-
tracheal installation of cobalt metal powder causes local cellular infiltration and inflammation (including the production of cytokines such as tumor necrosis factor-alpha), edema, and cell/tissue destruction (Kerfoot 1975, Kyono 1992, Zhang 2000). Studies that have assessed the effects of the long-term inhalation of cobalt metal (powder or vapors) in experimental animals have not been found.

Oral exposure: Animal studies of oral exposure to cobalt compounds have focused mainly on water-soluble and some water-insoluble cobalt compounds. The oral administration of water-soluble cobalt salts (e.g. the bioavailable cobalt II ion) to test animals (at dose levels higher than humans would be exposed, normally or occupationally) can be related to findings of cardiomyopathy, polycythemia (increased erythropoetin), reproductive toxicity, thyroid and thymic necrosis or atrophy, and proximal tubule degeneration. Studies evaluating the oral exposure of animals to cobalt metal (powder) have not been found. (ATSDR 1992, 2001).

Dermal Exposure: Cobalt compounds including cobalt metal powder are known dermal sensitizers and can induce allergic dermatitis in both experimental animals and humans. The level of exposure associated with the development of dermatitis is not known. In guinea pigs, the development of nickel and cobalt sensitivity may be interrelated. Studies reporting the toxic effects from dermal cobalt exposures other than dermatitis and the related immunological changes have not been found. (ATSDR 1992, 2001).

In Vitro Exposure: Cobalt metal can cause DNA strand breaks in isolated DNA as well as in cultured animal cells and human lymphocytes. A mechanism for cobalt metal itself (in-lieu of the cobalt II ion) to cause genotoxicity (however not tumorogenicity) has been proposed based on in vitro studies. Cobalt metal may also be able to cause DNA repair inhibition by reactions that produce cobalt (II) ions and activated oxygen species. (Lison 2001; ATSDR 2001 for reviews).

Injection studies: Cobalt metal particles have been associated with the formation of tumors adjacent to injection sites in animal tests. In addition, the implantation of pure cobalt metal films in test animals was associated with local tumor formation in some studies. Although IARC found sufficient evidence for tumors in animals, the relevance of these data for humans was questioned based upon the route of exposure. (IARC 1992, 1999).

B. References:
4. Kyono, H; Kusaka, Y; Homma, K. Reversible lung lesions in rats


11. IARC. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 52 Chlorinated drinking water, chlorination bi-products; some other halogenated compounds; cobalt and cobalt compounds. Lyon, France 1992.


IV. Disposition and Structure-activity relationship

A. Disposition (for reviews see ATSDR 1992, 2001; Barceloux 1999).

1. Absorption: In both humans and test animals, oral bioavailability (via gastrointestinal tract) is dependent upon the solubility of the species of cobalt compound (solubilizes yielding cobalt (II) ion). The feeding status (e.g. fasting) of the animal as well as iron levels (low) and age (young) can have an impact to increase gastrointestinal absorption of cobalt. Inhalation studies on the retention of cobalt in the lungs after inhalation of oxide show that considerable variability exists among species. In these studies humans cleared lung burdens of cobalt much slower than rats, however it was pointed out that lower rates may reflect the binding of cobalt to cellular components in the lungs (Bailey 1986; Kreyling 1985, 1986). Dermal exposure of guinea pigs and hamsters found that very insignificant amounts of cobalt (as cobalt chloride) were absorbed through intact skin. Absorption of cobalt was significant through abraded skin. Humans appear able to absorb a significant amount of cobalt through their hands when dermally exposed to hard metal dust containing 15% cobalt metal powder and 85% tungsten carbide powder (Scansetti 1994).

2. Distribution: In humans, cobalt can be identified in all tissues. Cobalt forms a component of vitamin B12 which is essential for humans and other mammals. The oral administration of cobalt chloride or cobalt napthenate to rats resulted in cobalt being found at high levels in the liver and elevated levels in the kidneys, heart, stomach and intestines. Elevated levels were not found in spleen or testes after oral administration of single doses (0.33-33.33 mg/kg) of cobalt napthenate to rats (Ayala-Fiero 1999, Firriolo 1999). Sub-chronic oral exposure to cobalt chloride (8 weeks) resulted in significant increases of cobalt in myocardium, muscle, brain, and testes in rats. (Phersson 1991). Metal smelter workers and coal miners have been found to have elevated lung levels of cobalt, however increases in other tissues were variable and depended on the occupation and exposure characteristics. (Gerhardsson 1984, Hillerdal, 1983). Distribution of cobalt after inhalation of cobalt compounds in test animals is also variable, with lymph nodes, liver, kidney, spleen, heart, bones having increased levels. (Kerfoot 1975, Kreyling 1986, Whener and Craig 1972).

3. Elimination: Cobalt is eliminated by humans after oral exposure primarily by the fecal route. The amount eliminated is variable and depends primarily on the cobalt species, the dose, and the nutritional status of the person (ATSDR 1992, 2001, Barceloux 1999). In experimental animals orally administered cobalt is primarily eliminated by the fecal route. The solubility of the cobalt species (cobalt compound) also effects the elimination route. The more soluble the cobalt species the more probable it will be eliminated in the urine. Iron status of the animal plays a role in the path of cobalt elimination. Iron deficient rats eliminate less cobalt by the fecal route than do normal rats (Rueber, 1994).
Humans exposed to cobalt metal or cobalt oxide (relatively insoluble species) by inhalation appear to follow 3 phases of elimination. The first is believed to represent mucociliary clearance of particles deposited in the tracheobronchial region ($t_1=2-44$ hours) and moved to the gastrointestinal tract where the majority is eliminated by the fecal route (Apostoli 1994, Mosconi, 1994b). The second phase is believed to represent clearance of cobalt from the lungs by macrophages ($t_2=10-78$ days, Beleznay 1994, Mosconi 1994b). The third phase appears to reflect long-term clearance ($t_3=>2$ years, Neleznay 1994, Mosconi, 1994b). Urinary excretion of cobalt increases with time after exposure. The ratio of peak translocation rate to mechanical clearance rate was reported to be about 5 to 1 for humans inhaling cobalt oxide (Bailey 1989; see also ASTDR 1992, 2001; Barceloux 1999 for reviews). Inhalation of cobalt compounds in test animals show that solubility has a major impact on clearance. Soluble compounds are absorbed into the blood and excreted via the urine. The rate of urinary excretion appears to correlate with the rate of cobalt translocation from the lungs to the blood. Fecal clearance seems to correlate with the rate of mechanical clearance of cobalt from the lungs to the gastrointestinal tract (see ASTDR 1992, 2001; Barceloux 1999). Dermal exposure of hamsters to soluble cobalt chloride found that most cobalt was excreted in the urine 48 hours after a single application (Lacy 1996).

B. Structure-Activity Relationships
1. No Data

C. References
7. Scansetti, G; Botta, GC; Spinelli, P; Reviglione, L; Ponzetti, C. Absorption and excretion of cobalt in the hard metal industry. Sci Total Envir 150(1-3):141-144. 1994


A. The CDI is initiating a broad research program designed to assess the risks of exposure to cobalt compounds for humans and the environment. Studies relevant to human health sponsored or co-sponsored by CDI, currently in progress include:

1. The bioavailability of cobalt compounds (species) in surrogate body tissue fluids and serum.

2. Use-specific assessment of cobalt exposures in certain industrial
and consumer applications.

3. Exposure assessment for a proposed cardiomyopathy epidemiological study in Russian cobalt workers.

4. Worker-exposure survey for member companies of the CDI.

The CDI is not aware of any current or proposed long-term studies on the inhalation effects of cobalt metal powder to animals or epidemiological studies of cobalt metal dust/aerosol exposure to humans.

VI. Rationale for Recommendation and Suggested Studies

The Cobalt Development Institute (CDI) nominates cobalt metal powder to the National Toxicology Program for a 2-year animal inhalation carcinogenicity assay based upon the following rationale:

One mission of CDI is to conduct and/or support research to assess the risks created by the production and use of cobalt and cobalt compounds to human health and to the environment. This research focuses on filling gaps in the scientific knowledge of the toxicology, epidemiology, and ecotoxicology of cobalt and its compounds. The CDI supports the position that plans developed to manage human health and environmental risks should be based on a foundation of knowledge created from peer-reviewed scientific studies. The CDI believes that existing studies do not establish or indicate any carcinogenic risks to persons exposed to cobalt metal powder. Critical studies studies to support or refute this presumption are, however, lacking. The CDI believes the proposed study will help to refine future risk assessments for potential exposures to cobalt metal powder.

A specific area where gaps exist is knowledge of long-term effects of the inhalation of cobalt metal particles on humans (c.f. Lison 2001 for review). Long-term animal inhalation assay data on two cobalt species (compounds) have provided conflicting results relative to the formation of lung tumors. Long-term inhalation studies of cobalt sulfate heptahydrate (24 month study, NTP 1998) and cobalt monoxide (17 months study, Whener 1977) have been positive in mice and rats, and negative in hamsters, respectively. These studies are insufficient to provide evidence of the effects of long-term inhalation of cobalt metal particles or their possible carcinogenic potential in experimental animals.

Current epidemiological evidence for increased mortality due to lung cancer in cobalt workers is equivocal (Mur 1987, Moulin 1993). Therefore, the
current epidemiological data on occupational exposure to various cobalt species (i.e. cobalt compounds), in the absence of mixed metal exposures, are insufficient to establish an association with lung cancer. Providing speciated toxicological data on cobalt can assist in the development of a comparative animal data base which will help fill the knowledge gaps on the carcinogenic potential of cobalt species in test animals. A comparative data base on the carcinogenic potential of cobalt species can be useful in the identification of hazard and more importantly in providing guidance for refining assessment of risk in occupational exposure studies of cobalt operations.