the Cobalt Development Institute

c/o NIPERA • Suite 200
2605 Meridian Parkway
Durham, NC 27713 (USA)
Tel: +1 919-544-7722
Fax: +1 919-544-7724
e-mail: tbrock@asciences.com

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Via E-Mail

RECEIVED
SEP 24 2001

Dr. C.W. Jameson
National Toxicology Program
Report On Carcinogens
79 Alexander Drive
Building 4401, Room 3118
PO Box 12233
Research Triangle Park, NC 27709

Re: National Toxicology Program: Call for Public Comments on 16 Substances, Mixtures, and Exposures Circumstances Proposed for Listing in the Report on Carcinogens, Eleventh Edition: 66 Fed. Reg. 38430 (July 24, 2001)

Dear Dr. Jameson:

The Cobalt Development Institute (CDI) submits the appended comments in response to the National Toxicology Program's call for comments on the proposal to list cobalt sulfate heptahydrate (CAS No. 10026-24-1) in the Eleventh Edition of the *Report on Carcinogens* (ROC). The members of CDI include producers and users of cobalt and cobalt compounds.

Sincerely Yours,

Thomas O. Brock, PhD DABT
Manager of Health and Environmental Sciences
The Cobalt Development Institute

Attachments
Cc: Mr. Scott Grove
Dr. Michael Hawkins
Dr. Bert Swennen

Head Office: 167 High Street • Guildford, Surrey GU1 3AJ UK
Tel: +44 (0)1483 578877 • e-mail: 101637.2106@compuserve.com • Fax: +44 (0)1483 573873

Comments on the Proposed Addition of Cobalt Sulfate Heptahydrate to the National Toxicology Program 11th Report on Carcinogens
Provided by
The Cobalt Development Institute

The National Toxicology Program (NTP) has recommended that cobalt sulfate heptahydrate (CAS No:10026-24-1) be placed on the 11th Report on Carcinogens (11th ROC). The Cobalt Development Institute (CDI) would like to provide to the NTP the information it has regarding the number of businesses producing or using cobalt sulfate heptahydrate, the number of people exposed and the available information on the conditions and duration of exposures. In addition, the CDI would like to provide a synopsis of the scientific information it has obtained from searches in the scientific literature regarding cancer and human /animal exposures to water-soluble cobalt salts including cobalt sulfate heptahydrate.

The Number of Businesses Producing/Using Cobalt Sulfate Heptahydrate

The CDI received information from two (2) companies who identified themselves as domestic producers of cobalt sulfate heptahydrate. Twenty-five (25) users of cobalt sulfate heptahydrate also provided information The CDI are not able to verify the percent this number represents of all current producers and users.

The Number of People Exposed to Cobalt Sulfate Heptahydrate

The total number of people reported exposed to cobalt sulfate heptahydrate in these businesses was twenty-nine (29).

Conditions and Duration of Exposure to Cobalt Sulfate Heptahydrate

The major cobalt sulfate uses were reported as: electrowinning-mining, chemical intermediates, magnetic media, water-treatment, petrochemical. Other reported uses were driers (paints, ink, varnishes), coloring agents for ceramics, micronutrients (animal food supplements). In the major uses, twenty-seven (27) people were exposed to cobalt sulfate heptahydrate for 2 hours or less per day. Two (2) were exposed up to 4 hours per day. Of the 29 people, all but 3 were exposed to cobalt sulfate heptahydrate for 30 days or less per year. (1 for 90-120 days per year and 2 for 120-240 days per year.) The major operations and uses occur in occupational settings which require a provision of safe environment via engineering controls, use of personal protective equipment, etc.. In addition, it is estimated that over half of the cobalt sulfate heptahydrate used is in the form of a solution which reduces overall dust inhalation exposure.

The Evidence for Cancer from the Inhalation of Cobalt Sulfate Heptahydrate

A 2-year inhalation study was conducted in adult mice and rats by the NTP using cobalt sulfate heptahydrate (NTP 1998). The study found that inhaled doses of 100% respirable cobalt sulfate (dose range-0.063-0.63mg/m3 Co; particle size- 2-3 um diameter) were associated with bronchiolar/alveolar tumors in both sexes

of mice and in female rats. Cobalt sulfate heptahydrate is a water-soluble cobalt salt and thus, the likely species of cobalt is the bioavailable cobalt (II) ion.

The most likely scenario for human exposure to cobalt compounds is in occupational settings (ATSDR 1992, IARC 1991). To the knowledge of CDI, a single occupational study on the exposure of workers to water-soluble (and some insoluble) cobalt compounds has been conducted (Mur *et al,* 1987). The initial study found increased risk for mortality due to lung cancer in exposed workers, however the follow-up study (Moulin *et al*, 1993) found no increased risk in the same cohort. The proper re-classification of 1 lung cancer death was a major factor in the finding of the second study as was the finding of no new deaths from lung cancer reported in the 7 year follow-up . The equivocal results do not provide adequate data for the assessment of the risk of lung cancer in occupational settings. The CDI believes that the findings by the NTP support aims to conduct further studies on inhalation exposure to cobalt compounds and the possible relationship to lung cancer in humans.

The CDI is currently developing a risk assessment program to collect data to ascertain the health risks to humans from exposure to cobalt compounds.

Experience with Oral Human Exposure to Water-Soluble Cobalt Salts

The evidence that human exposure to water-soluble cobalt salts is related to cancer by routes of exposure other than by inhalation (e.g. oral and dermal) is lacking (IARC1991, IARC 1999, Lison 2001). Bioavailable cobalt (e.g. the cobalt (II) ion) in the form of cobalt chloride hexahydrate (a water-soluble cobalt salt) has been used clinically to treat intractable forms of anemia for time periods up to several years. Dose levels as high as 7.5 mg/kg body weight have been reported, although average doses were in the range of 0.16 to 1.0 mg Co/kg bw (ATSDR 1992, Veien 1987, Taylor 1978, Manifold 1978,Bowie 1975, Davis 1958, Holly 1955, Gross 1955, Kriss 1955). Based on case studies, pregnant women treated did not have adverse reproductive outcomes nor were their offspring affected (ASTDR 1992, Jacobziner et al 1961). The studies found that long-term exposure to bioavailable cobalt was associated with polycythemia and hyperthyroid (goiter) however no reports of cancer associated with these treatments has been found. Studies of municipal water supplies have not shown any correlation between oral exposure to cobalt in drinking water and cancer mortality in humans (Berg, 1972).

Under certain conditions cobalt salts (e.g. the cobalt (II) ion) can be toxic to humans at low doses. Cobalt sulfate or cobalt chloride (Co:1-1.5 parts per million) were added to a specific brand of beer during the mid-1960's in several regions of Europe and North America (Alexander 1972; Grice 1981). Many people who ingested large amounts (in excess of 6 pints per day) of the beer developed a serious and often fatal cardiomyopathy. The average dose levels of cobalt in cobalt-beer cardiomyopathy cases were in the range of 0.014 and 0.14 mg/kg body weight. Higher clinical doses of oral bioavailable cobalt (0.1 to 1.0 mg/kg bw) over longer durations of exposure have not been associated with cardiomyopathy. Studies of the epidemic have pointed to an interaction with diet and alcohol consumption along with cobalt as causative factors of disease (Kesteloot 1966,1968 , Grice 1981). To the knowledge of CDI, there is no information on the association of cobalt with cancer among the exposed individuals who have survived.

Experience with the Agricultural/Veterinary Use of Water-Soluble Cobalt Salts

Bioavailable cobalt is a standard feed supplement for ruminating animals usually in the form of cobalt sulfate or cobalt carbonate. Generally recommended dosages are in the range of 0.01 to 0.1 mg/kg/bw as dietary supplements to prevent a range of veterinary illnesses (Ysart 1999, Kennedy et al 1996, ATSDR 1992,Robinson 1996, Ferrando 1972; c.f. review: Cobalt Development Institute 1986). Larger doses have been administered

for experimental and medical reasons. A 15 week study by Corrier et al (1986; c. f. also 1985) found that oral cobalt levels of 15 mg/kg did not cause testicular changes in adult rams. A 250 mg single oral cobalt dose given monthly to lambs as an antihelminthic produced no toxicity (McPherson et al 1987). A similar study in lambs found benefit to administration of 38mg cobalt in 3 doses over a 10 week period (Bremmer et al 1988). Veterinary and agricultural uses of cobalt salts have not been associated with cancers in ruminants to the knowledge of CDI.

Summary

The current evidence for carcinogenicity of cobalt sulfate heptahydrate is based entirely on the 2-year NTP animal inhalation study. A single occupational epidemiology study with follow-up was equivocal. The NTP study underscores the need for further study of occupational inhalation exposure to cobalt compounds and the relationship if any with lung cancer. It is important to take into account, that clinical, veterinary, and agricultural experiences with oral exposures to water- soluble cobalt salts including cobalt sulfate heptahydrate have not been associated with cancer. The data do show that oral human and animal exposures have beneficial levels and toxic levels that are not related to cancer.

Classification as "Known to be a Human Carcinogen": The CDI believes that the current evidence regarding the carcinogenicity of cobalt sulfate heptahydrate does not provide a strong scientific basis for it's classification as a human carcinogen. In addition, it should be pointed out that the only route of exposure to cobalt sulfate heptahydrate known to be associated with cancer is by inhalation .

Classification as " Reasonably anticipated to be a Human Carcinogen": The most likely human exposures to cobalt sulfate heptahydrate are by occupational inhalation and thus it might be expected that if significant numbers of personal exposures are found they would be found in occupational settings. In many of these settings, exposure controls are in place and cobalt sulfate heptahydrate is often in liquid form. The industry production and use data provided by the CDI are insufficient by themselves for determining accurately whether a significant number of persons are exposed to cobalt sulfate heptahydrate in the US. Listing on the 11th ROC as "Reasonably anticipated to be…" depends (in part) on the number of people exposed. The current information may be helpful in contributing to a more accurate determination of the true number of persons exposed to cobalt sulfate heptahydrate.

Submitted on behalf of The Cobalt Development Institute by:

Tom Brock, PhD, DABT
Manager of Health and Environmental Sciences
The Cobalt Development Institute
2605 Meridian Parkway, Suite 200
Durham, NC 27713 USA
Tel: (919) 544-7722
Email: tbrock@asciences.com

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