



April 15, 2002

Dr. Scott Masten, PhD
Environmental Toxicology Program
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Dear Dr. Masten:

The U.S. Occupational Safety and Health Administration (OSHA) supports the Cobalt Development Institute nomination of cobalt metal powder for a chronic inhalation study in experimental animals. A substantial amount of cobalt in the US is used in the production of metal alloys found in machinery, cutting tools, high-strength steels, and engine parts. Worker exposure to cobalt metal dust often occurs during grinding, cutting, and welding operations. Cobalt exposure in the workplace has been found in over 400 personal air samples reported in OSHA's Integrated Management Information System since 1995. For the above reasons, OSHA believes there may be widespread worker exposure to cobalt-containing dusts.

It has been well documented in epidemiological studies that inhalation of cobalt metal dust, particularly when combined with tungsten carbide, can cause an interstitial pneumoconiosis of the lung, termed hard metal disease. Respiratory tract exposure to cobalt metal and alloy dusts also leads to lung damage in experimental animals. NTP previously reported that long-term inhalation of the divalent cobalt salt, cobalt sulfate heptahydrate, resulted in alveolar/bronchiolar neoplasms as well as a spectrum of inflammatory and fibrotic lesions in the respiratory tract of rats and mice. However, it is not clear whether the chronic bioassay conditions using a water-soluble cobalt salt adequately predicts the ability of inhaled cobalt metal particulates to cause cancer. A chronic inhalation bioassay of the metal powder would clarify this issue. OSHA also suggests that NTP consider inhalation studies of the disposition, metabolism, and carcinogenic determinants of cobalt metal, cobalt-tungsten carbide, and cobalt sulfate in the lung. These would provide an improved understanding of the fate of the major cobalt forms in lung tissue.

A short brief that summarizes the existing data on use, exposure, and toxicology of cobalt dust along with a rationale for the suggested studies is attached. More thorough reviews of cobalt have been prepared by the Agency for Toxic Substances and Disease Registry, the International Agency for Research on Cancer, and in the published literature. Please feel free to contact me or Dr. Val Schaeffer (301-693-2279) on my staff if you have further questions.

Sincerely,



Steven F. Witt
Director of Health Standards Programs

Enclosure

SUPPORT DOCUMENT FOR TOXICITY TESTING OF COBALT DUST BY THE NATIONAL TOXICOLOGY PROGRAM (NTP)

Properties, Production, Use, and Worker Exposure

Cobalt is a transition metal that exists in several chemical forms. The pure metal is shiny, hard, practically insoluble in water and relatively unreactive. Cobalt also exists as divalent and trivalent oxides and salts that vary in terms of solubility and physicochemical properties. About 70 percent of the cobalt processed in the US is used in the production of special alloys. The most well studied are the hard metal alloys made up of approximately 80 percent tungsten carbide and 20 percent cobalt used in metal-tipped tools for grinding and cutting (e.g. saws, drills, etc.). Other cobalt alloys are used in gas turbines, jet engines, telecommunications equipment, and surgical/dental implants. Cobalt oxides and salts are used as catalysts, drying agents in paints, and glass decolorizer. Several hundred thousand workers could be potentially exposed to cobalt in the production, processing, and utilization of the metal and the various cobalt containing alloys and salts. The majority of worker exposure is believed to occur by inhalation of cobalt metal and alloy dust during grinding, cutting, and welding operations. Out of 2343 personal air samples examined for cobalt in OSHA's IMIS [Integrated Management Information System] database between 1995 and 2000, 448 had detectable levels of the metal. About 7 percent of the samples with measurable cobalt were above the OSHA PEL (0.1 mg/m³). More than 10 percent were above the ACGIH TLV (0.02 mg/m³).

Toxicology and Adverse Health Effects

Inhalation of cobalt particulates predominantly affects the respiratory tract. A number of case reports and cross-sectional studies of workers in the hard metal and other industries involving inhalation of cobalt metal dust have reported an increased prevalence of interstitial pneumoconiosis termed hard metal disease (Kelleher et al., 2000). This collection of disorders is characterized by persistent cough, exertional dyspnea, and acute pneumonitis eventually leading to functional signs of restrictive lung disease and radiographic evidence of interstitial fibrosis. The exposures that caused these effects have not been extensively documented but are reported to occur in the range of 0.007 to 0.893 mg cobalt/m³ over 2 to 17 years depending on the study (ATSDR, 1992). Experimental animals administered either cobalt metal, cobalt-tungsten carbide or divalent cobalt salts by inhalation or by intratracheal instillation suffer lung inflammation and damage to the alveolar epithelium (Lasfargues et al., 1992 & 1995; Bucher et al., 1999). However, the cobalt-tungsten carbide hard metal causes more persistent and serious lung damage than either cobalt metal alone or cobalt ion. While the tungsten carbide itself is not biologically active, there is experimental evidence that it enhances the toxicity of cobalt by promoting the release of bioactive cobalt at the cellular target and/or by catalyzing cobalt-supported reactive oxygen generation at the target cell surface (Fubini, 1997; Rosems et al., 2000). Although not as well studied as lung parenchymal disease, worker exposure to cobalt [all forms] can also cause bronchial hyperreactivity and the development of occupational asthma (Lison, 1996).

Some studies report increased lung cancer mortality among workers exposed to cobalt dust but there has been no adequately controlled study on which to reliably conclude the cancer was a result of the inhaled cobalt (IARC, 1991). There was clear evidence of alveolar/bronchiolar neoplasms in rats and mice exposed to cobalt sulfate [soluble divalent cobalt ion] by inhalation in a two year NTP bioassay at exposure levels that also caused lung inflammation and fibrosis (NTP, 1998). Cobalt oxide produced a few lung tumors in rats, but not hamsters, following intratracheal administration (IARC, 1991). Several cobalt oxides and salts cause DNA damage and cellular transformation in assays using mammalian cells (Beyersman and Hartwig, 1992). Cobalt tungsten carbide produced greater DNA damage than cobalt metal or cobalt salt in human leukocytes using the in vitro alkaline comet elution assays (Anard et al., 1997; De Boeck et al., 1998). The cobalt metal forms have not undergone long-term inhalation testing in experimental animals.

Recommended Studies and Rationale

Cobalt dust is recommended for further study because it is uncertain whether the chronic bioassay using cobalt sulfate aerosol adequately predicts the ability of inhaled cobalt metal or alloy particulates to cause cancer. A potentially large number of workers are exposed to these other cobalt forms. Despite their differences in physicochemical properties and ability to cause lung inflammation, there has not been systematic study comparing the toxicokinetics of inhaled cobalt metal, cobalt - tungsten carbide, and ionic cobalt. The ability of different cobalt forms to undergo oxidation/reduction within the lung and initiate carcinogenesis has also not been adequately investigated. NTP study of cobalt was originally nominated by the United Auto Workers and a chronic inhalation bioassay of cobalt metal powder is being nominated by the Cobalt Development Institute.

It is recommended that NTP consider a study program to determine whether inhalation of cobalt metal and cobalt-tungsten carbide are similar to cobalt sulfate with respect to carcinogenic determinants such as deposition/retention in the lung, oxidation/reduction in target cells, damage to the cellular DNA, and alteration in proliferative state of the cells. This research would result in an improved understanding of the disposition and fate of cobalt in lung tissue following animal inhalation of the major cobalt forms. It should include in vitro studies, as necessary to better understand effects at the cellular level. Biomarkers related to the carcinogenic process, such as DNA damage, mitogenesis, and oncogene activation, should be measured in order to better understand mode of action. It is recommended that NTP investigate whether lung inflammation/fibrosis influences the potential of the various cobalt species to cause tumors. If these studies suggest that the carcinogenic potential of cobalt metal or cobalt-tungsten carbide differ from that of cobalt sulfate then a chronic inhalation bioassay with these other cobalt particulates is warranted.

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