

October 18, 2013

Dr. Ruth Lunn, Director, ORoC, DNTP
NIEHS, P.O. Box 12233, MD K2-14
Research Triangle Park, NC 27709
lunn@niehs.nih.gov

RE: Nominations to the Report on Carcinogens; Request for Information on Cobalt

Dr. Lunn:

It is Cardno-ChemRisk's understanding that the National Toxicology Program (NTP) Office of the Report on Carcinogens is requesting the following information for cobalt (Co): (1) data on current production, use patterns, and human exposure; (2) information about published, ongoing, or planned studies related to evaluating carcinogenicity; (3) scientific issues important for assessing carcinogenicity of the substance; and (4) names of scientists with expertise or knowledge about the substance.

The purpose of our letter is to provide the NTP with some comments regarding the carcinogenic potential of Co. Cardno-ChemRisk has performed extensive research regarding the toxicology of Co (including carcinogenic potential). Attached please find some of our recently published work that you may find useful:

- 1) Paustenbach DJ, Tvermoes BE, Unice KM, Finley BL, Kerger BD. A review of the health hazards posed by Co. *Crit Rev Toxicol* 2013, 43:316-362.
- 2) Finley BL, Monnot AD, Gaffney SH, Paustenbach DJ. Dose-response relationships for blood Co concentrations and health effects: A review of the literature and application of a biokinetic model. *J Toxicol Environ Health B* 2012, 15:493-523.

In addition, please find specific responses to your requests noted below.

Cardno-ChemRisk Comments on Requested Information:

(1) Production, use patterns, and human exposure to Co

Cardno-ChemRisk has published a thorough review on the health hazards associated with Co that discusses the production, use, and human exposure to the metal (Paustenbach et al., 2013). The primary uses of Co metal are: (1) high temperature, corrosion-resistant superalloys (e.g., used in turbine aircraft engines); (2) magnetic alloys with aluminum, copper, nickel (Ni) or titanium; (3) high strength steels; (4) electro-deposited alloys; (5) as a component of lithium ion batteries and Ni/Cd (cadmium) or Ni-metal hydride batteries; and (6) as a binding agent for metal carbides (USGS, 2011). Co compounds are also used as pigments in glass, ceramics, and paints, as catalysts in petroleum refining, as paint driers, and as trace element additives in agriculture and medicine (ATSDR, 2004; Barceloux, 1999; IARC, 2006; USGS, 2011). According to data from 2010, the major uses of Co in the US include: superalloys (49%), chemical applications (29%), metallic applications (15%), and cemented carbides for cutting (7%) (USGS, 2011).

Diet is the main source of Co exposure in the general population, and dietary Co intake in the United States has been estimated to range between 5 and 40 µg/day, with the highest Co concentrations found in fish, green leafy vegetables, and fresh cereals (WHO, 2006; Hokin et al., 2004a, 2004b). Individuals may have elevated Co exposures due to (1) occupational Co exposures, (2) prescribed medical Co therapies, (3) voluntary ingestion of vitamin B12 and other Co-containing supplements, (4) ingestion of Co-contaminated water and other environmental media, or (5) the presence of Co-containing prosthetics and other medical devices.

(2) Information about published, ongoing, or planned studies related to evaluating carcinogenicity

Cardno-ChemRisk and others have published on the carcinogenicity of Co (please see summaries below). There is limited evidence in humans and animals that Co inhalation may increase the risks of developing cancer, further study may be warranted. However, systemic exposure to Co does not appear to be carcinogenic, as we have discussed in our previous publications noted above, as well as in a pending manuscript on this topic. A summary of our findings regarding Co and cancer are provided below.

Inhalation Exposure to Co

Chronic exposure to Co-containing hard metal (dust or fume) can result in a lung disease called "hard metal lung disease," a type of pneumoconiosis (lung fibrosis). The primary pulmonary effects of chronic exposure to hard metal dust include: reversible airway obstruction, subacute alveolitis, and chronic diffuse interstitial pulmonary fibrosis (Barceloux, 1999). This interstitial fibrosis occurs as a result of industrial exposure to hard metal dust consisting of Co and tungsten carbide, and is not seen in workers exposed only to Co. This finding is consistent with *in vitro* results indicating that Co and tungsten carbide particles produce larger amounts of activated oxygen species when compared to Co metal particles alone (Lison et al., 1995).

Several human studies have evaluated the carcinogenic potential of Co resulting from inhalation exposure to Co-containing compounds. For example lung cancer deaths increased in factory workers who refined and processed Co (Mur et al., 1987). A follow up study of the same cohort of workers, however, did not report statistically significant increases in mortality due to respiratory diseases, and there was no increase in the standard mortality ratio (SMR) for lung cancer in the exposed workers compared to controls (Moulin et al., 1993). Studies of hard metal workers have reported significantly increased lung cancer mortality in workers occupationally exposed to Co and tungsten carbide, suggesting that sufficient inhalation exposure of Co could increase the risk of developing lung cancer (Lasfargues et al., 1994; Wild et al., 2000). However, Co and tungsten carbide particles have been shown to be more toxic than Co alone, since tungsten carbide facilitates the transfer of electrons from Co to oxygen generating superoxide. As such, the evaluation of the carcinogenic potential of Co and its compounds should be considered separately.

Systemic or Oral Exposure to Co

Based on Cardno-ChemRisk's review of the literature, there were no studies assessing the carcinogenic potential of Co in animals after oral exposure, and there was only one human study that assessed the carcinogenic potential of Co via oral exposure. Berg and Burbank (1972) reported no correlation between cancer mortality and the level of Co in US water.

Our review of the historical literature reporting on the carcinogenic potential of Co particles and ionic Co (CoCl₂) following intraperitoneal and intrathoracic injections in animals suggests that tumorigenesis may result from Co exposure, but only under non-physiologically relevant conditions. From our analysis, tumor formation resulted at the site of injection in rats upon intramuscular and intrathoracic injection of 93 – 124 mg metal Co particulate/kg-day (Heath et al., 1954, 1956, and 1962), yet intrarenal injection of 38 mg particulate/kg-day did not (Jasmin et al., 1976). In addition, intraperitoneal injection of 18 mg Co(II)/kg-day in rats yielded a tumor incidence of 40% (Shabaan et al., 1977). Although these studies indicate the possibility of carcinogenic potential, the biological relevance is extremely low because most metals can cause carcinogenic effects at high enough concentrations simply because of their reactive nature. Systemic Co exposure at biologically relevant exposure scenarios, then, is therefore not likely to be carcinogenic for the following reasons:

- The available studies that assessed the carcinogenicity of metal Co particles and ionic solutions of Co do not utilize physiologically relevant doses and routes of administration. As mentioned above, exposure to Co occurs primarily via inhalation, ingestion, or endogenous release from Co-containing prosthetic devices, not from intraperitoneal and intrathoracic injections.
- In the studies referenced above, it is not clear that the selected dose(s) was without significant or contributory toxicity (i.e., no parallel toxicology study carried out under identical conditions (same route of administration, feed, rodent strain, etc.) with an accompanying toxicokinetic analysis was presented, as required by current ICH guidelines which are discussed in more detail below) (FDA, 2002).
- It is important to note that the studies assessing the carcinogenicity of metal Co particles and ionic solutions of Co(II) were largely conducted in the mid 1950s – mid 1970s (Heath et al., 1954, 1956, and 1962; Jasmin et al., 1976; Shabaan et al., 1977), prior to the establishment of a standardized testing protocol.

The EPA has not classified Co for its carcinogenicity, since human studies are inconclusive regarding inhalation exposure, and there is only one study that looked at the association between cancer and oral exposure to Co and found no association (Berg and Burbank, 1972; EPA, 2007, ¶1). While it has been noted that certain forms of Co are classified by the International Agency for Research on Cancer (IARC) as “possible,” “probable,” or “known” human carcinogens (IARC, 2006; Polyzois et al., 2012), the evidence reviewed by IARC (2006) pertains primarily to chronic inhalation of fine metal powders (hard metals with tungsten carbide and Co) or Co

pigments at relatively high doses that accumulate in the lungs and induce “portal-of-entry” carcinogenesis in the form of lung cancer, as discussed above. Lung-specific cancer is not unusual, at some dose, for substances that are inhaled that are genotoxic; frequently, such effects are limited to the lung. In short, there has been no indication of an increase in site-specific cancers outside of the respiratory tract, which has been observed for these occupational groups exposed to Co pigments and metal dusts (IARC, 2006).

Risk of Cancer in Patients with Co-containing Hip Prostheses

It is important to note that individuals with Co-containing hip prostheses are systemically exposed to Co at concentrations above those of the general population. Therefore, studies on these cohorts may be a valuable resource to consider when assessing the carcinogenicity of Co. Numerous epidemiology studies investigating total and specific cancer rates in implant patients with Co-containing hip prosthetics do not appear to indicate an increased risk of cancer. Hip implant cohorts in Denmark (Olsen et al., 1999; Visuri et al., 2003, 2006), England and Wales (Smith et al., 2012; Lalmohamed et al., 2013), Finland (Visuri et al., 1991, 1996, 2003, 2006, 2010; Paavolainen et al., 1999a, 1999b), New Zealand (Gillespie et al., 1988) and Sweden (Visuri et al., 2006; Mathiesen et al., 1995; Nyren et al., 1995; Signorello et al., 2001) have been evaluated, and the weight of evidence indicates that metal containing hip implants do not pose a significant cancer risk to patients. For example, in 2010, Visuri et al. updated their initial analysis of 579 first generation McKee Farrar MoM and 1585 first generation MoP hip implant patients (Visuri et al., 1996) and found no increased incidence of any cancer type. The mean follow-up period was approximately 17 years, and no increased cancers were observed in the subgroup with >20 years follow-up. However, that the study noted that “some tumors have a 20-40 year latency period,” and that even longer follow-up periods would therefore be required to evaluate risks in “younger patients who may use their THA for more than 30 years.” (Visuri et al., 2010). Furthermore, there are no case reports that report or associate carcinogenesis with Co exposure from a hip implant. Taken together, available literature suggests that systemic Co exposure in hip implant patients does not increase the risk of developing cancer.

(3) Scientific issues important for assessing carcinogenicity of the substance

Co is not a cumulative toxicant like some other metals (e.g. lead and cadmium) (Paustenbach et al., 2013); as such, chronic systemic exposure to Co would be unlikely to result in an increased risk for developing cancer. There are ICH guideline requirements for assessing the carcinogenicity of a substance that would be applicable to Co. As discussed above, the current literature on Co that reports an increase in carcinogenesis from non-inhalation exposure are not physiologically relevant, and do not adhere to current guideline requirements.

Relevant guideline requirements include:

- A toxicology study report reflecting the same conditions as proposed for the carcinogenicity study (same mode of administration, same diet, same rodent strain). The usual duration of this type of study is 90 days if it is intended to support dose selection

for a standard 2-year carcinogen bioassay. In addition, the basis for dose selection in the study should be provided.

- Metabolic profiles should be provided for a drug/compound in humans and in the species employed for assessment of carcinogenic potential. In cases where in vivo data are unavailable, in vitro data can be used.
- Toxicokinetic data should be provided that are sufficient to estimate steady state $AUC_{(0-24)}$ for the compound and each major human metabolite at doses employed in the range finding study.
- Exposure (steady state $AUC_{(0-24)}$) data should be provided for the parent compound and for the major metabolites from clinical trials conducted at the maximum recommended human dose (MRHD) or other appropriate human reference dose if the MRHD exposure data are unavailable. Where pharmacokinetics differ significantly between genders, data from males and females should be reported separately, as a gender difference can modify the study approach and conclusions.
- A summary of the investigations into the genotoxic potential of the compound should be included.

(4) Names of scientists with expertise or knowledge about the substance

Detmar Beyersmann has published some pertinent articles on Co and metal carcinogenesis. His contact information is provided below:

Detmar Beyersmann
University of Bremen, Bremen, Germany
e-mail: beyers@uni-bremen.de

Closing Thoughts

We hope these comments will be considered during the NTP's assessment of Co's carcinogenicity. We currently have a few on-going studies assessing Co and cancer; once they are published, we will send copies to the NTP.

If you have any questions regarding any of the information provided above, please do not hesitate to call me at 415-618-3477, or contact me by e-mail at andrew.monnot@cardno.com.

Respectfully,

[Redacted]

Andrew D. Monnot, Ph.D.
Health Scientist II
Cardno-ChemRisk
101 Second Street Suite 700
San Francisco, CA
(415) 618-3477 phone
Email: andrew.monnot@cardno.com

References

- ATSDR (Agency for Toxic Substances and Disease Registry). 2004. Toxicological profile for cobalt. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.
- Barceloux D. 1999. Cobalt. *Clin Toxicol*, 37:201–16.
- Berg JW, and Burbank F. 1972. Correlations between carcinogenic trace metals in water supplies and cancer mortality. *Ann NY Acad Sci* 199:249-264.
- EPA (Environmental Protection Agency). 2007. Technology Transfer Network, Air Toxics Web Site: Cobalt Compounds – Hazard Summary-Created in April 1992; Revised in January 2000. Retrieved in November, 2012, from: <http://www.epa.gov/ttnatw01/hlthef/cobalt.html>
- FDA (Food and Drug Administration). 2002. Guidance for industry, carcinogenicity study protocol submissions.
- Finley BL, Monnot AD, Gaffney SH, Paustenbach DJ. 2012. Dose-response relationships for blood cobalt concentrations and health effects: A review of the literature and application of a biokinetic model. *J Tox Environ Health Part B*. 15:493-523.
- Gillespie W, Frampton C, Henderson R, Ryan P. 1988. The incidence of cancer following total hip replacement. *J Bone Joint Surg Br*. 70:539-542.
- Heath JC. 1954. Cobalt as a carcinogen. *Nature* 173(4409): 822-823.
- Heath JC. 1956. The production of malignant tumours by cobalt in the rat. *Br J Cancer* 10(4):668-673.
- Heath JC, Daniel MR. 1962. The production of malignant tumours by cobalt in the rat: intrathoracic tumours. *Br J Cancer* 16(3):473-478.
- Hokin B, Adams M, Ashton J, and Louie H. 2004a. Analysis of the cobalt content in Australian foods. *Asia Pacific J Clin Nutr* 13: 284–288.
- Hokin B, Adams M, Ashton J, and Louie H. 2004b. Comparison of the dietary cobalt intake in three different Australian diets. *Asia Pacific J Clin. Nutr* 13: 289–291.
- IARC (International Agency for Research on Cancer). 2006. Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 86. Lyon, France: World Health Organization.

- Jamsin G, and Riopelle JL. 1976. Renal carcinomas and erythrocytosis in rats following intrarenal injection of nickel subsulfide. *Lab Invest* 35(1):71-78.
- Lalmohamed A, MacGregor AJ, de Vries F, Leufkens HGM, and van Staa TP. 2013. Patterns of risk of cancer in patients with metal-on-metal hip replacements versus other bearing surface types: A record linkage study between a prospective joint registry and general practice electronic health records in England. *PLoS ONE* 8:e65891.
- Lasfargues G, Wild P, Moulin JJ, Hammon B, Rosmorduc B, Rondeau du Noyer C, Lavandier M, and Moline J. 1994. Lung cancer mortality in a French cohort of hard-metal workers. *Am J Ind Med* 26:585-595.
- Lison D, Carbonnelle P, Mollo L, Lauwerys R, Fubini B. 1995. Physicochemical mechanism of the interaction between cobalt metal and carbide particles to generate toxic activated oxygen species. *Chem Res Toxicol* 8: 600-606.
- Mathiesen EB, Ahlbom A, Bermann G, and Lindgren JU. 1995. Total hip replacement and cancer: A cohort study. *J Bone Joint Surg Br* 77:345-350.
- Moulin JJ, Wild P, Mur JM, Fournier-Betz M, and Mercier-Gallay M. 1993. A mortality study of cobalt production workers: An extension of the follow-up. *Am J Ind Med* 23:281-288.
- Mur JM, Moulin JJ, Charruyer-Seinerra MP, and Lafitte J. 1987. A cohort mortality study among cobalt and sodium workers in an electrochemical plant. *Am J Ind Med* 11:75-81.
- Nyren O, McLaughlin JK, Gridley G, Ekbom A, Johnell O, Fraumeni JF, Jr., and Adami HO. et al. 1995. Cancer risk after hip replacement with metal implants: A population-based cohort study in Sweden. *J Natl Cancer Inst* 87:28-33.
- Olsen JH, McLaughlin JK, Nyren O, Mellekjaer L, Lipworth L, Blot WJ, and Fraumeni JF, Jr. 1999. Hip and knee implantations among patients with osteoarthritis and risk of cancer: A record-linkage study from Denmark. *Int J Cancer*. 81:719-722.
- Paavolainen P, Pukkala E, Pulkkinen P, and Visuri T. 1999a. Cancer incidence after total knee arthroplasty: A nationwide Finnish cohort from 1980 to 1996 involving 9,444 patients. *Acta Orthop Scand* 70:609-617.
- Paavolainen P, Pukkala E, Pulkkinen P, and Visuri T. 1999b. Cancer incidence in Finnish hip replacement patients from 1980 to 1995: A nationwide cohort study involving 31,651 patients. *J Arthroplast*. 14:272-280.
- Paustenbach DJ, Tvermoes BE, Unice KM, Finley BL, and Kerger BD. 2013. A review of the health hazards posed by cobalt. *Crit Rev Toxicol* 43:316-362.

- Polyzois I, Nikolopoulos D, Michos I, Patsouris E, and Theocharis S. Local and systemic toxicity of nanoscale debris particles in total hip arthroplasty. *J Appl Toxicol* 32: 255-269.
- Shabaan AA, Marks V, Lancaster MC, and Defeu GN. 1977. Fibrosarcomas induced by cobalt chloride (CoCl₂) in rats. *Lab Anim* 11(1):43-46.
- Signorello LB, Ye W, Fryzek JP, Lipworth L, Fraumeni JF, Blot WJ, McLaughlin JK, and Nyren O. 2001. Nationwide study of cancer risk among hip replacement patients in Sweden. *J Natl Cancer Inst.* 93:1405-1410.
- Smith AJ, Dieppe P, Porter M, and Blom AW. 2012. Risk of cancer in first seven years after metal-on-metal hip replacement compared with other bearings and general population: Linkage study between the National Joint Registry of England and Wales and hospital episode statistics. *BMJ* 344:e2383-e2394.
- USGS (United States Geological Survey). 2011. Mineral commodity summaries 2011. Washington, D.C.: U.S. Geological Survey
- Visuri T, and Koskenvuo M. 1991. Cancer risk after McKee-Farrar total hip replacement. *Orthopedics* 14:137-142.
- Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, and Riska EB. 1996. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clin Orthop* 329 Suppl:S280-S289.
- Visuri T, Pukkala E, Pulkkinen P, and Paavolainen P. 2003. Decreased cancer risk in patients who have been operated on with total hip and knee arthroplasty for primary osteoarthritis: A meta-analysis of 6 Nordic cohorts with 73,000 patients. *Acta Orthop Scand* 74:351-360.
- Visuri TI, Pukkala E, Pulkkinen P, and Paavolainen P. 2006. Cancer incidence and causes of death among total hip replacement patients: A review based on Nordic cohorts with a special emphasis on metal-on-metal bearings. *Proc Inst Mech I Eng Part H J Eng Med* 220:399-407.
- Visuri T, Pulkkinen P, Paavolainen P, and Pukkala E. 2010. Cancer risk is not increased after conventional hip arthroplasty. A nationwide study from the Finnish Arthroplasty Register with follow-up of 24,636 patients for a mean of 13 years. *Acta Orthop* 81:77-81.
- WHO (World Health Organization). 2006. Cobalt and inorganic cobalt compounds. Concise International Chemical Assessment Document: 69. Geneva: World Health Organization.
- Wild P, Perdrix A, Romazini S, Moulin JJ, and Pellet F. 2000. Lung cancer mortality in a site producing hard metals. *Occup Environ Med* 57:568-573.

