Draft Report on Carcinogens (RoC) Concept: Cobalt

1 Background and rationale

1.1 Background

Cobalt metal (CAS No. 7440-48-4) is a naturally occurring shiny brittle silver-gray metallic element with ferromagnetic properties, which is used in a variety of industrial applications. It was nominated for review for possible listing in the Report on Carcinogens because of the potential for human exposure and the availability of a 2-year inhalation study in rodents (NTP, 2013). In September 2013, the National Toxicology Program solicited information on cobalt metal and other nominated substances (78FR57868, *http://ntp.niehs.nih.gov/go/rocnom*) and received one public comment that provided relevant information on production and human exposure to cobalt, cited recent publications, and noted some scientific issues pertinent to its assessment for carcinogenicity.

Information related to carcinogenicity is available on several other cobalt-containing compounds. Two cobalt compounds, 'cobalt sulfate' and 'cobalt-tungsten carbide: powders and hard metals', are listed in the RoC as *reasonably anticipated to be human carcinogens* (NTP, 2011). The International Agency for Research on Cancer (IARC) has reviewed other cobalt-containing substances and classified 'cobalt metal without tungsten carbide' and 'cobalt sulfate and other soluble cobalt (II) salts' as *possibly carcinogenic to humans* (Group 2B) and classified 'cobalt metal with tungsten carbide' as *probably carcinogenic to humans* (Group 2A) (IARC, 2006). Mechanistic data described in these reviews and additional research studies on cobalt and cobalt compounds support common carcinogenic mechanism(s) of action due to solubilized cobalt or released cobalt ion (See Section 3.3).

Cobalt can be both harmful and beneficial to human health. While some cobalt compounds have been shown to be toxic or carcinogenic, cobalt is also an essential trace dietary mineral (vitamin B12) and cobalt plays vital bodily roles in cell division, metabolism, and nervous system function for all animals (ATSDR, 2004).

1.2 Rationale and scope of the topic

Cobalt has been selected as a topic for review for the RoC because of its potential for substantial human exposure in the United States, due to its use in several industrial processes and as an herbal remedy, and because there is an adequate database by which to evaluate its potential carcinogenicity.

Although the recent NTP cancer study of cobalt metal in experimental animals provided the initial focus, mechanistic or cancer studies on other cobalt compounds, some of which have not been evaluated for the RoC, are available. In addition, mechanistic data suggests that the observed carcinogenic effects of cobalt compounds may occur via the same mechanism, thus it may be possible to group different cobalt compounds as a class. Therefore the first step in this review will be to define the scope of the candidate substance(s)[1] – e.g., cobalt

[1] If selected as a candidate substance, the scientific evaluation of cobalt will be captured in a draft RoC monograph (for more details, see *http://ntp.niehs.nih.gov/go/rocprocess*). The proposed approach, delineated in this concept document, for preparing the draft monograph, is tailored to the nature, extent, and complexity of the scientific information on cobalt. This concept document also discusses information supporting the rationale and the proposed approach for reviewing the substance, including data on human exposure, an overview of the nature and extent of the scientific information for evaluating carcinogenicity in humans and/or animals, and

metal, cobalt and cobalt compounds as a class, inorganic cobalt compounds – for possible listing in the RoC. The review would not include cobalt alloys or radioactive cobalt because of potential confounders from the other compounds in the alloy (which are often metals) or radioactivity. The proposed ORoC approach for reviewing cobalt is described below in Section 5 and the approach for conducting the preliminary literature search strategy is outlined in Appendix A.

2 Overview of data related to human exposure

According to the National Institute for Occupational Safety and Health, more than a million workers in the United States are potentially exposed to cobalt (NIOSH, 2013). Exposure to cobalt metal or cobalt-containing compounds in the United States occurs in occupational settings through the production of alloys and manufacture of cobalt salts, including those used as pigment for coloring glass, ceramics, and paint, as well as by some new applications of cobalt for producing "green" technologies such as electric car batteries and solar panels. In factory workers, the greatest exposure occurs by inhalation of cobalt dust in industries that process cobalt alloys, e.g., in the production of cemented carbide hard metals (e.g., tungsten carbide) for grinding and cutting tools, and as an alloy in the manufacture of superalloys, permanent magnets, and in chemical and metallic applications. The greatest exposure occurs in industries using cemented tungsten-carbide, cobalt powder, or producing cobalt alloys.

Although cobalt has not been mined in the Untied States for more than 30 years (ASTDR, 2004), a new mine and mill are currently being established in Idaho that anticipate production of more than 1,500 tonnes of high-purity cobalt metal annually (Idaho Cobalt Project, 2013). Cobalt mining and new uses such as those for green technology may increase the potential for human exposure in the United States.

Cobalt is distributed through the environment from natural sources or human activity. Exposure to cobalt metal or cobalt-containing compounds occurs in the general population primarily by dietary ingestion, which has been estimated to range between 5 to 40 μg per day, and in the environment in the air, drinking water, and through skin contact. Cobalt is the active center of cobalamin (vitamin B12), which is an essential trace element. Ingestion of excess vitamin (e.g., B12) supplements containing cobalt, prescribed cobalt therapies, and use of cobalt-containing prosthetics can all result in elevated exposure.

Radioactive cobalt (^{60}Co and ^{57}Co) is utilized in cancer therapy, sterilizing medical equipment and in other scientific and commercial applications. Exposure can be industrial, occurring in the process of handling the substance, or to patients receiving treatment with radiolabelled compound.

3 Overview of the carcinogenicity data

3.1 Human cancer studies

Based on a preliminary search of the literature, the database of human cancer studies with potential exposure to cobalt consists of the following:

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scientific issues and questions relevant to the evaluation of carcinogenicity of cobalt. It also includes the proposed approach for conducting the scientific evaluation, including literature search strategy, scope and focus of the monograph, and approaches for obtaining scientific and public input to address the key scientific questions and issues.

- four historical cohort mortality studies, some on overlapping populations (Hogstedt and Alexandersson, 1990; Lasfargues *et al.*, 1994; Moulin *et al.*, 1998; Wild *et al.*, 2000) of cobalt-tungsten carbide hard metal workers
- one historical cohort study (reported in two updates) of cobalt production workers (Mur *et al.*, 1987; Moulin *et al.*, 1993)
- one cohort study of Danish porcelain workers exposed to cobalt-aluminate spinel and/or cobalt silicate (Tüchsen *et al.*, 1996)
- a population-based case-control study of cancers of the upper aerodigestive tract which assessed exposure to cobalt and other metals via levels in toenails (Rogers *et al.*, 1993)

Both IARC and NTP concluded that there was limited evidence of the carcinogenicity of cobalt-tungsten carbide from studies in humans. These studies have limited utility for evaluating the carcinogenicity of cobalt itself because toxicological studies have found that cobalt-tungsten carbide is more toxic and genotoxic than cobalt itself; however, some studies report risk estimates for exposure to cobalt without co-exposure to tungsten carbide (NTP 2009). In its evaluation of cobalt metal and cobalt compounds, IARC concluded that there was inadequate evidence of carcinogenicity in humans of cobalt metal without tungsten carbide.

3.2 Cancer studies in experimental animals

Inhalation exposure to cobalt sulfate in an earlier NTP study resulted in tumors of the lung and adrenal medulla (NTP 1998), which was the basis of its listing in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen.*

Studies in experimental animals are also available for other cobalt compounds that have not been evaluated for possible listing in the RoC. Cobalt metal was tested for carcinogenicity in a 2-year inhalation study conducted by the NTP in both sexes of F344/NTac rats and $B6C3F_1$/N mice (NTP 2013). Increased incidences of neoplasms were reported at several tissue sites (some of which are similar to cobalt sulfate), including lung, adrenal medulla, and islet cells of the pancreas, in male and female rats and mice treated with cobalt metal. In general, the database of cancer studies in experimental animals for other cobalt compounds is limited to either one study of a specific cobalt compound or multiple studies via parenteral exposure (e.g., intramuscular, intraperitoneal, subcutaneous injection). The few available inhalation studies are limited in design (e.g., less sensitive species, or short exposure duration). Both soluble (cobalt chloride, cobalt naphthenate cobalt (III) acetate) and insoluble (cobalt oxide (II), cobalt (II) sulfide, cobalt dust) compounds have been tested and the most common tumors observed were injection site or lung tumors (reviewed by NTP 2008).

3.3 Mechanistic information

Tissue body burden data from the inhalation study of cobalt metal found that cobalt can be solubilized, absorbed, and systemically distributed to several tissues in the body (NTP 2013). The proposed mechanism by which solubilized cobalt ions may cause cancer involves interaction with hydrogen peroxide to produce reactive oxygen species (ROS), resulting in increased oxidative stress and damage to DNA. In addition, inhibition of DNA repair and disruption of the normal function of biochemical pathways (i.e., cell signaling, gene regulation, apoptosis) may be involved and there is evidence that cobalt causes cytotoxic, toxic, and genotoxic effects. The combination of the direct effects from cobalt ions

and the indirect oxidative stress response from ROS production provide plausible modes of action for the carcinogenicity of cobalt.

4 Issues and key scientific questions relevant for the cancer evaluation

The key questions and issues for the review of cobalt concern the evaluation of cancer studies in humans and experimental animals, and mechanistic data.

- What is the level of evidence (inadequate, limited, sufficient) for the carcinogenicity of cobalt from the studies in humans?
  - What are the cancer sites?
- What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of cobalt from the studies in experimental animals?
  - If sufficient, what are the target tissue sites?
- What are the potential mechanisms by which cobalt may cause cancer?
  - What is the quality of the mechanistic and other related data?
- Is there evidence to support biological plausibility for cancers of the lung in experimental animals and humans?

5 Proposed approach for conducting the cancer evaluation

A key consideration for the cobalt concept is defining the scope of the review. Therefore, the proposed approach is to first seek external input to identify the candidate substance(s); the substance(s) and rationale for their review will be provided in a protocol, as described below.

5.1 Establishment of a RoC monograph planning team

The ORoC will consult with appropriate technical advisors (external or internal to government) who will become part of the RoC monograph team for cobalt; these advisors will also include ORoC staff (government and contractor) as well as key NTP personnel. Sources for identifying these advisors include, but are not limited to, peer-reviewed literature databases and recommendations from the scientific community and the public. Chemists, experts in metabolism and mechanisms of metal carcinogenicity, and experts with specific and relevant expertise on cobalt or metals will be consulted to advise the ORoC on the assessments of these substances.

The first task for the RoC monograph team will be to define the scope of the candidate substance(s) to be evaluated, i.e., to identify the specific candidate substance(s), or class of substances. The monograph team will be provided with background materials, including all available pertinent epidemiological, experimental animal, and mechanistic information on cobalt and cobalt compounds. Based on this information, the team will identify the review candidate substances to be included, such as cobalt metal, cobalt compounds as a class, a subcategory of cobalt compounds, or some combination of these.

5.2 Protocol development

The next step will be for the RoC monograph team to develop a written protocol that clearly defines the candidate substance and provides the rationale for its review, as well as to outline the methods for preparing the monograph. The protocol will include the literature search strategy, the methods for evaluating the quality of the cancer studies in humans and experimental animals, guidelines for integrating this information to reach a listing

recommendation, and a preliminary outline for the monograph. The protocol will be made publicly available on the RoC website and the public will be able to provide input on the protocol via an input box on the candidate substance webpage.

The ORoC will create a webpage for cobalt, after approval for review, which will include (1) RoC documents related to the review of the substance (e.g., concept document, protocol for the review, draft RoC monograph), (2) public comments, (3) an input box for the public to provide information (such as new literature) or comment (such as the identification of additional scientific issues), and (4) information on public meetings or listening sessions. The NTP will communicate when new information is added or updated (such as updated literature searches) to the website via the NTP listserv. Additional scientific issues may be identified during the preparation of the monograph.

In addition to the input box on the candidate substance webpage, other opportunities for public comments during the review process include a request for information on the nomination, for comment on the draft concept when it has been approved, and for comment on the recommended protocol for achieving the review of cobalt. The ORoC will consider the information suggested by the public[2] in drafting the cancer evaluation component of the draft monograph. Future forums, such as a listening session, for receiving public comment on any additional scientific issues may be considered depending on public interest; these would be announced via the *Federal Register* notice and NTP listserv[3] and posted on the RoC website.

5.3 Development and peer review of the draft RoC monographs

The draft RoC monograph reviews, assesses, and integrates the scientific literature, issues, and relevant evidence, applying the listing criteria to reach a preliminary RoC listing recommendation.[4] The Report on Carcinogens Background Document on Cobalt-Tungsten Carbide: Powders and Hard Metals will be used as a resource starting point for some of the information, such as the mechanistic section of the review (NTP 2009). Details on the methods for writing the draft RoC monograph and topics typically covered in the monograph are outlined in the NTP process for the preparation of the RoC (*http://ntp.niehs.nih.gov/go/rocprocess*).

The NTP will convene a peer-review panel[5] of scientific experts to review the draft RoC monograph on cobalt in a public meeting. The NTP Office of Liaison, Policy and Review will manage the NTP expert panel peer review. Members of the panel will be from the public and private sectors with expertise in disciplines related to the cancer evaluations of cobalt, particularly those with relevant knowledge of human exposure to cobalt compounds, metal compounds, animal carcinogenesis, pathology (particularly lung and adrenal medulla tumors), chemistry, toxicology, genotoxicity and mechanisms of carcinogenesis. The NTP

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[2] Federal Register notice and public comments are available at *http://ntp.niehs.nih.gov/go/rocnom*.
[3] Persons can subscribe to the NTP listserv free-of-charge at *http://ntp.niehs.nih.gov/go/getnews.*
[4] A listing recommendation can be not to list, to list as *reasonably anticipated to be a human carcinogen*, or to list as *known to be a human carcinogen*.
[5] NTP panels are federally chartered technical and scientific advisory groups convened as needed to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with Federal Advisory Committee Act and HHS implementing guidelines; *http://ntp.niehs.nih.gov/go/166*.

will set aside time at the peer-review meeting for a discussion of specific scientific issues raised in the public comments.

6 References

ATSDR. 2004. *Toxicological profile for cobalt.* Atlanta, GA: Agency for Toxic Substances and Disease Registry. 88 pp. http://www.atsdr.cdc.gov/toxprofiles/tp33.pdf.

Hogstedt C, Alexandersson R. 1990. Dödsorsaker hos Hardmetallarbetare. *Arbete och Hälsa* 21: 1-26. ("Causes of Death Among Hard Metal Workers" - English translation prepared by Global Translation Systems; Chapel Hill, NC.)

IARC. 2006. *Cobalt in Hard-metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Lyon, France: International Agency for Research on Cancer. 330 pp.

Idaho Cobalt Project. 2013. http://www.idahocobalt.com/s/Home.asp.

Lasfargues G, Wild P, Moulin JJ, Hammon B, Rosmorduc B, Rondeau du Noyer C, Lavandier M, Moline J. 1994. Lung cancer mortality in a French cohort of hard-metal workers. *Am J Ind Med* 26(5): 585-595.

Moulin JJ, Wild P, Mur JM, Fournier-Betz M, Mercier-Gallay M. 1993. A mortality study of cobalt production workers: an extension of the follow-up. *Am J Ind Med* 23(2): 281-288.

Moulin JJ, Wild P, Romazini S, Lasfargues G, Peltier A, Bozec C, Deguerry P, Pellet F, Perdrix A. 1998. Lung cancer risk in hard-metal workers. *Am J Epidemiol* 148(3): 241-248.

Mur JM, Moulin JJ, Charruyer-Seinerra MP, Lafitte J. 1987. A cohort mortality study among cobalt and sodium workers in an electrochemical plant. *Am J Ind Med* 11(1): 75-81.

NIOSH. 2013. http://www.cdc.gov/niosh/topics/cobalt/. 4 pp.

NTP. 1998. *Toxicology and Carcinogenesis Studies of Cobalt Sulfate Heptahydrate in F344/N Rats and B6C3F1 Mice*. Technical Report Series No. 471. NIH Publication No. 98-3961. Research Triangle Park, NC: National Toxicology Program. 268 pp. http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr471.pdf.

NTP. 2002. *Report on Carcinogens Background Document for Cobalt Sulfate.* National Toxicology Program. http://ntp.niehs.nih.gov/ntp/newhomeroc/roc11/CoSO4Pub_no_appendices_508.pdf.

NTP. 2009. *Report on Carcinogens Background Document for Cobalt-Tungsten Carbide: Powders and Hard Metals.* National Toxicology Program. http://ntp.niehs.nih.gov/NTP/roc/twelfth/2010/FinalBDs/HardMetalsBD20100408_508.pdf.

NTP. 2011. *Report on Carcinogens, Twelfth Edition.* Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. 499 pp. http://ntp.niehs.nih.gov/go/roc12.

NTP. 2013. *DRAFT Toxicology Studies of Cobalt Metal (CAS NO. 7440-48-4) in F344/N Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Cobalt Metal in F344/NTac Rats and B6C3F1/N Mice (Inhalation Studies).* Technical Report Series No. 581. NIH Publication No. 14-5923. Research Triangle Park, NC: National Toxicology Program. 354 pp. http://ntp.niehs.nih.gov/NTP/About_NTP/TRPanel/2013/October/DRAFT_TR-581.pdf#search=cobalt%20metal.

Rogers M, Thomas DB, Davis S, Vaughan TL, Nevissi AE. 1993. A case-control study of element levels and cancer of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* 2:305-312.

Tüchsen F, Jensen MV, Villadsen E, Lynge E. 1996. Incidence of lung cancer among cobalt-exposed women. *Scand J Work Environ Health* 22(6): 444-450.

Wild P, Perdrix A, Romazini S, Moulin JJ, Pellet F. 2000. Lung cancer mortality in a site producing hard metals. *Occup Environ Med* 57(8): 568-573.

Appendix A: Preliminary Literature Search Strategies

This document summarizes the approach for identifying literature for the draft Report on Carcinogens (RoC) monograph on cobalt. If this topic is selected to move forward, a more detailed strategy for identifying and reviewing citations will be described in the protocol that is posted on the ORoC website. The goal of the literature search strategy is to identify information on environmental exposures associated with cobalt for the broad range of subjects covered by a RoC monograph, as listed below.

- Properties and Human Exposure (focusing on the U.S. population)
- Disposition (ADME) and Toxicokinetics
- Human Cancer Studies (if available)
- Studies of Cancer in Experimental Animals
- Mechanisms and Other Relevant Effects

In general, literature will be identified from the following sources or methods:

1. **General and exposure-related data search:** This search covers a broad range of general data sources such as authoritative reviews (e.g., IARC monographs, U.S. federal and state, and international evaluations) and sources for general exposure information (e.g., Bureau of Labor Statistics, or other sources of data on occupational exposure or information on cobalt).
2. **Database searches in PubMed, Scopus, and Web of Science:** The majority of the primary literature will be identified from these three databases using search strategies that combine terms for the exposure (such as cobalt or cobalt synonyms) with terms for the monograph subject (such as metabolism, genotoxicity). Additional biomedical literature database (such as Embase) may also be searched. Technical advisors will be consulted regarding occupational setting with potential exposure to cobalt, which will be used to identify human epidemiologic studies. Search terms for each monograph topic will be developed in consultation with an information specialist.
3. **QUOSA library:** A number of QUOSA libraries will be (or have been) created including libraries of occupational case-control studies and cohort studies of occupations associated with cobalt use. Full-text searches of the libraries will be conducted using search terms related to cobalt. The advantage of using this approach is to identify relevant studies that would not be picked up in the database searches if cobalt (or other key search terms) were not mentioned in the abstract or key words.
4. **Special topic-focused searches:** Searches will be made on special topics or specific issues identified in the monograph development.
5. **Secondary sources:** Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science "Cited Reference Search," will be added.

Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature are conducted, with initial screening based of titles and abstracts only, followed by full-text screening. Searches will be updated by creating monthly search alerts in the relevant databases (such as PubMed, Scopus, and Web of Science).