Integrated Risk Information System (IRIS) Program
Public Science Meeting

Draft Agenda

U.S. Environmental Protection Agency
Office of Research and Development
Webinar Meeting

Wednesday January 11, 2023

1:00 pm (ET) **Welcome and Announcements:**
Dr. Kris Thayer, IRIS Program Director, EPA/CPHEA

1:10 pm **Overview of the Cobalt and Cobalt Compounds (Inhalation) IRIS Assessment Plan (IAP) and Protocol**

Dr. Pamela Noyes and Dr. Ravi Subramaniam, EPA/CPHEA, Cobalt and Cobalt Compounds (Inhalation) Assessment Managers

Background: An IRIS Assessment Plan (IAP) communicates to the public the plan for assessing each individual chemical and includes summary information on the IRIS Program's scoping and initial problem formulation; objectives and specific aims for the assessment; the PECO (Populations, Exposures, Comparators, and Outcomes) criteria that outlines the evidence considered most pertinent to the assessment; and identification of key areas of scientific complexity. The PECO provides the framework for developing literature search strategies and inclusion/exclusion criteria, particularly with respect to evidence stream (i.e., human, animal, mechanistic), exposure and outcome measures.

The IRIS assessment protocol describes the methodology for how the assessment will be conducted, including dose-response methods.

1:25 pm *The IRIS Program is seeking a discussion with the public aimed at improving or clarifying the IAP/Protocol. Below are topics to facilitate the discussion:*

Topic 1. Association between lung and adrenal tumor formation

The IRIS program is seeking discussion on a plausible association between lung and adrenal gland tumors associated with exposure to cobalt and cobalt compounds. Background information is provided below.

An analysis of the results of NTP inhalation exposure studies in rats found an apparent association between the occurrence of pulmonary non-neoplastic lesions and the development of pheochromocytomas. This plausible association has been attributed to the adrenal response arising from systemic hypoxemia due to the reduced gas exchange induced by the lung lesions and the accompanying fibrosis and chronic inflammation. Assessment of the dependence of the tumor types impacts upon the method used to estimate composite cancer risk. A combined tumor analysis may not be appropriate if tumors do not form independently.

Topic 2. Cellular Uptake and Tissue Disposition

The IRIS program is seeking discussion on cellular uptake and tissue disposition associated with exposure to cobalt and cobalt compounds. Background information is provided below.

Although cobalt bioavailability and its influence on carcinogenicity are not fully understood, it is known that cellular uptake of free cobalt ion and particles occur via different processes; differences between uptake and distribution of water-soluble and water-insoluble cobalt compounds could lead to differences in pharmacodynamics. Mechanistic information regarding cellular uptake and tissue deposition can inform dosimetric adjustments and modeling approaches.

Topic 3. Cobalt Particle Toxicity

The IRIS program is seeking discussion on particle toxicity associated with exposure to cobalt and cobalt compounds. Background information is provided below.

In addition to potential differences in particle ion uptake and distribution that might influence tissue dosimetry, cobalt is a redox-active transition metal. Cobalt particles may have a greater effect than ions in catalyzing production of reactive oxygen species (ROS). How cobalt ions are released in vivo also differs between water-soluble and water-insoluble cobalt compounds. Updating the mechanistic evidence concerning whether cobalt particles may elicit direct toxicity contributing to carcinogenesis will help inform the choice of the particle lung dose metric used for rodent-to-human extrapolation and dose-response.

Topic 4. Proposed MOA of cobalt carcinogenicity

The IRIS program is seeking discussion on the potential MOA of cobalt and cobalt compounds. Background information is provided below.

There is evidence that cobalt-induced neoplastic development likely involves pathways of genotoxicity, oxidative stress (and generation/scavenging of ROS), and stabilization of hypoxia-inducible factor 1α. Other evidence suggests that cobalt genotoxicity involves primarily clastogenic effects, as well as direct and indirect DNA damage and inhibition of DNA repair. Updating the current evidence in the proposed cobalt cancer MOA, including capturing any new evidence of mechanistic responses beyond those previously described, will help inform the dose-response analyses, pharmacokinetic evaluations, and animal-to-human extrapolation methodologies.

Substances that can release cobalt ions in vivo, both water soluble and insoluble, likely define the domain of applicability for this assessment.

2:30 pm ***Public Comment Period - Comments Specific to the Cobalt IAP/Protocol***

3:00 pm **ADJOURN**