

Report on Carcinogens Cobalt Concept Review

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Background: Cobalt Metal

Cobalt is a naturally occurring element, present in different forms.

Pure cobalt metal is a shiny brittle silver-gray metallic element with ferromagnetic properties.

The NTP inhalation bioassay provided the initial focus for the nomination of cobalt metal.

One public comment in response to FR notice (September 20, 2013).

We are proposing cobalt as a topic for review by the RoC because there is information on other important cobalt compounds.

Other Cobalt Compounds

Some cobalt compounds with authoritative reviews and listings:

- International Agency for Research on Cancer (IARC 2006)
 - ‘Cobalt metal without tungsten carbide’ and ‘cobalt sulfate and other soluble cobalt’ as *possibly carcinogenic to humans* (Group 2B)
 - ‘Cobalt with tungsten carbide’ as *probably carcinogenic to humans* (Group 2A)
- Report on Carcinogens (RoC)
 - Cobalt sulfate (2002) and cobalt-tungsten carbide (2009)
 - Both listed in the 12th RoC as *reasonably anticipated to be human carcinogens*

NTP bioassays on cobalt sulfate (TR, NTP 1998) and cobalt metal (draft TR, NTP 2013).

Studies are available on other cobalt compounds which have not been reviewed for carcinogenesis.

Common mechanism of action through cobalt ion.

How are people exposed to cobalt in the United States?

Occupational exposure

- Uses in production of alloys, manufacture of salts, colorant; primarily by inhalation
- NIOSH estimates that a million workers are exposed to cobalt or cobalt-containing compounds
- Mining – proposed new mine in Idaho
- “Green technology” – emerging clean technology applications

General population exposure

- Cobalt is listed as a contaminant on EPA’s National Priorities Superfund Sites
- Lower levels in diet (food or water) and to a lesser extent from air
- Cobalt is a trace essential dietary mineral (vitamin B12)



Rationale

Significant exposure in the United States

- Primarily from occupational uses but also from the environment

Adequate database

- NTP bioassay on cobalt metal
- Cancer and mechanistic studies on several other cobalt compounds



Scope

First step is to define the candidate for review

- Cobalt metal, cobalt compounds as a class, inorganic cobalt compounds, other cobalt compound(s)? or some combination
- Not include cobalt alloys or radioactive cobalt
 - May have confounding issues, such as the alloy and/or its components or the radioactive nature of the compound



Cancer Studies in Humans

Four historical cohort mortality studies, some on overlapping populations of cobalt-tungsten carbide hard metal workers

Historical cohort study (reported in two updates) of cobalt production workers

Cohort study of Danish porcelain workers exposed to cobalt-aluminate spinel and/or cobalt silicate

Population-based case-control study of cancers of upper aerodigestive tract, assessed exposure to cobalt and other metals via levels in toenails

NTP Cancer Studies in Experimental Animals

Neoplastic effects due to inhalation exposure in the 2-year bioassay

	Rat (F344/NTac or /N)		Mouse (B6C3F1)	
	Male	Female	Male	Female
Cobalt metal TR 581, 2013	Lung Adrenal medulla Pancreatic islet cells	Lung Adrenal medulla Mononuclear cell leukemia	Lung	Lung
Cobalt sulfate* TR 471, 1998	Lung	Lung Adrenal medulla	Lung	Lung

*Listed in the RoC as *reasonably anticipated to be a human carcinogen*

Cancer Studies in Experimental Animals

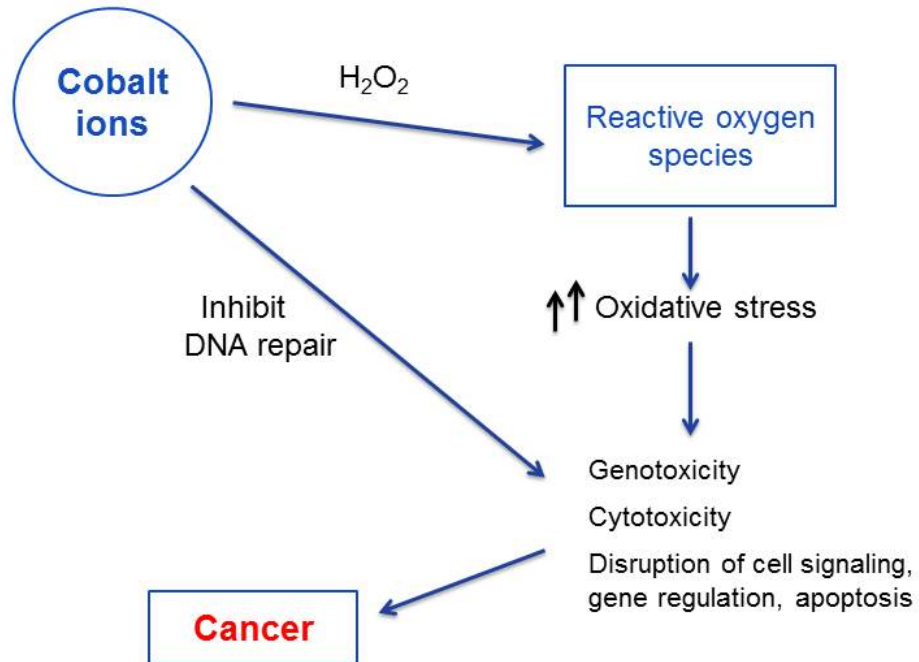
Cobalt and other cobalt compounds

- Cobalt chloride, cobalt naphthenate, cobalt acetate, cobalt oxide, cobalt sulfide, cobalt powder/dust

Database

- Limited number of studies on each compound
- Routes of exposure for some compounds may be less relevant
 - Inhalation, intrapleural, intratracheal
 - s.c., i.m., i.v., i.p., intrahepatic, intrarenal, intrathoracic
- Target tissue sites for tumors
 - Lung, adrenal, implant- or injection-site

Potential Mechanisms for Cobalt Carcinogenesis



Key Scientific Questions and Issues

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?

Proposed Approach: Scientific Input

Monograph planning team

- NTP staff and technical experts
- Technical advisors
 - Chemists, metal experts, relevant expertise on human exposure and uses
- Help identify relevant literature and review protocol and key sections of draft monograph
- First task: define scope of the review
 - Provided with background materials on cobalt and cobalt compounds
 - Identify candidate substance(s) for review

Protocol

- Team will develop written protocol to clearly define the candidate substance(s) and the rationale for review
 - Literature search strategy (exclusion/inclusion criteria)
 - Approach for evaluation of study quality
 - Guidelines for integrating information to reach a listing recommendation



Proposed Approach: Public Input

Webpage

- RoC documents (concept, protocol, monograph) related to the review of the substance
- Input box
- Information on public meetings
- Public comments

Public input

- Multiple opportunities for comment
- Solicited throughout review process
 - Nomination, concept, monograph
 - Announced via FR notice, NTP listserv, posted on ORoC website



BSC Review Questions

1. Comment on whether there appears to be evidence of past and/or current exposure to people living in the U.S.
2. Comment on whether the extent and nature of the scientific database appears to be adequate to support a RoC evaluation.
3. Advise as to whether the relevant scientific issues are identified. Are you aware of any other scientific issues that need to be considered during the evaluation?
4. Comment on the proposed approach for obtaining scientific and public input in development of the evaluation.
5. Rate the overall significance and public health impact of this evaluation as low, moderate, or high. NTP will use this rating in assessing the relative priority of evaluations of RoC candidate substances.
6. Provide any other comments you feel staff should consider in developing this evaluation.



Cancer studies in experimental animals

NTP identified treatment-related effects (tumor sites), due to inhalation of cobalt compounds, in the 2-year bioassay:

	Rat (F344/NTac or /N)		Mouse (B6C3F1)	
	Male	Female	Male	Female
Cobalt metal (inhalation) TR 581, 2013	Lung Adrenal medulla Pancreatic islet cells Kidney*	Lung Adrenal medulla Pancreatic islet cells* Mononuclear cell leukemia	Lung	Lung
	(clear evidence)	(clear evidence)	(clear evidence)	(clear evidence)
Cobalt sulfate (inhalation) TR 471, 1998	Lung Adrenal medulla*	Lung Adrenal medulla	Lung	Lung
	(some evidence)	(clear evidence)	(clear evidence)	(clear evidence)

* Findings equivocal