Comments on the RoC Monograph on Cobalt and Certain Cobalt Compounds

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RoC Monograph peer-review meeting

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on behalf of the Cobalt Development Institute
Classifications based on NTP data

• 5 soluble inorganic cobalt salts* have a long-standing harmonized classification Carc. 1B (H350i) in the EU

• Cobalt metal has a global industry self-classification Carc. 1B (H350i) since December 2013

• Hazard of carcinogenicity by inhalation is addressed for those cobalt substances with test data, plus 4 substances by read-across

*Test item CoSO₄; classified by read-across CoCl₂, Co(NO₃)₂, CoCO₃, Co di(acetate)
3 areas of comment

• Genotoxicity and cancer mode of action

• Grouping of cobalt substances

• Interpretation of non-portal of entry neoplasms
Genotoxicity and cancer MoA

- Recent conclusion by OECD CoCAM* and by Kirkland et al#:
  - Based on new, guideline-compliant GLP testing
  - “Poorly soluble cobalt compounds are not genotoxic.
  - Soluble compounds do induce some DNA and chromosomal damage \textit{in vitro}, probably due to reactive oxygen. The absence of chromosome damage in robust GLP studies \textit{in vivo} suggests that effective protective processes are sufficient to prevent oxidative DNA damage in whole mammals.

\textbf{Overall, there is no evidence of genetic toxicity with relevance for humans of cobalt substances and cobalt metal.}”

* Cooperative Chemicals Assessment Meeting (October 2014); # = accepted for publication in “Regulatory Toxicology and Pharmacology” (July 2015)
Non-genotoxic MoA proposed by CDI

Hours, day(s), weeks, months, 2 years

Presence of lung phagocytes throughout pathway to cancer

In vitro markers (ROS, HIF)

Appearance of neutrophils in lung, acute inflammation

Inflammation, “histiocytic infiltration”, epithelial necrosis

Adaptive/reparative hyperplasia, chronic inflammation

Metaplasia

Cancer

NTP 13-week study

NTP 2-week study

NTP 2-year cancer study

CDI data

CDI data
Grouping of cobalt substances

• 1\textsuperscript{st} group: 5 inorganic soluble salts – soluble in pH neutral fluids
• 2\textsuperscript{nd} group: Co metal powder – poorly soluble at neutral pH, soluble in acidic fluids (lysosomes)
• 3\textsuperscript{rd} group: insoluble in neutral AND in acidic fluids (Co$_3$O$_4$, inorganic pigments, other)

• Evidence for this from \textit{in vitro} and \textit{in vivo} data
Co release in lysosomal fluid

Group of cobalt substance
- Co oxides / spinel pigments
- Co carboxylates
- Co salts
- Co metal and carbonate

Cobalt release concentration [µg Co/mL]
Distal-site neoplasms

- NTP considers these to be “treatment-related”
- No evidence that they are cobalt related
- A concordance of local rise in cobalt levels and dose-response relationship
  - have been observed in the lung cancers
  - have not been observed in the distal-site cancers
Lung neoplasms, Co related

Co tissue levels in lung, compared with incidence of alveolar/bronchiolar carcinoma

Co level (µg Co/g tissue) after 2 wk inhalation exposure

% incidence of alveolar/bronchiolar carcinoma after 105 wk inhalation exposure

Lung neoplasms, Co related
Distal-site neoplasms, treatment related

Co tissue levels in femur (+ bone marrow), compared with incidence of MCL
In summary...

- **Genotoxicity and cancer mode of action:**
  
  "No evidence of genetic toxicity with relevance for humans of cobalt substances and cobalt metal."

  Evidence for inflammation as predominant element of the MoA

- **Grouping of cobalt substances:**

  3rd group: insoluble at neutral and at low pH

- **Interpretation of non-portal of entry neoplasms:**

  Treatment-related, not Co-related