Comments on the RoC Monograph on Cobalt and Certain Cobalt Compounds

July 22nd, 2015
RoC Monograph peer-review meeting

Ruth Danzeisen, PhD, DABT
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 *in vitro*, probably due to reactive oxygen. The absence of chromosome damage in robust GLP studies *in vivo* suggests that effective protective processes are sufficient to prevent oxidative DNA damage in whole mammals.

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

Presence of lung phagocytes throughout pathway to cancer

In vitro markers (ROS, HIF)

CDI data

Appearance of neutrophils in lung, acute inflammation

CDI data

Adaptive/reparative hyperplasia, chronic inflammation

Inflammation, “histiocytic infiltration”, epithelial necrosis

NTP 2-week study

NTP 13-week study

NTP 2-year cancer study

Cancer

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

Co oxides / Co oxides
Co metal and carbonate
Co salts
Co carboxylates
spinel pigments

Group of cobalt substance

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
Distal-site neoplasms, treatment related

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

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

% incidence of MCL after 105 wk inhalation exposure
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