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 $CoSO_4$; classified by read-across $CoCl_2$, $Co(NO_3)_2$, $CoCO_3$, Co di(acetate)

3 areas of comment

- Genotoxicity and cancer mode of action
- Grouping of cobalt substances
- Interpretation of non-portal of entry neoplasms

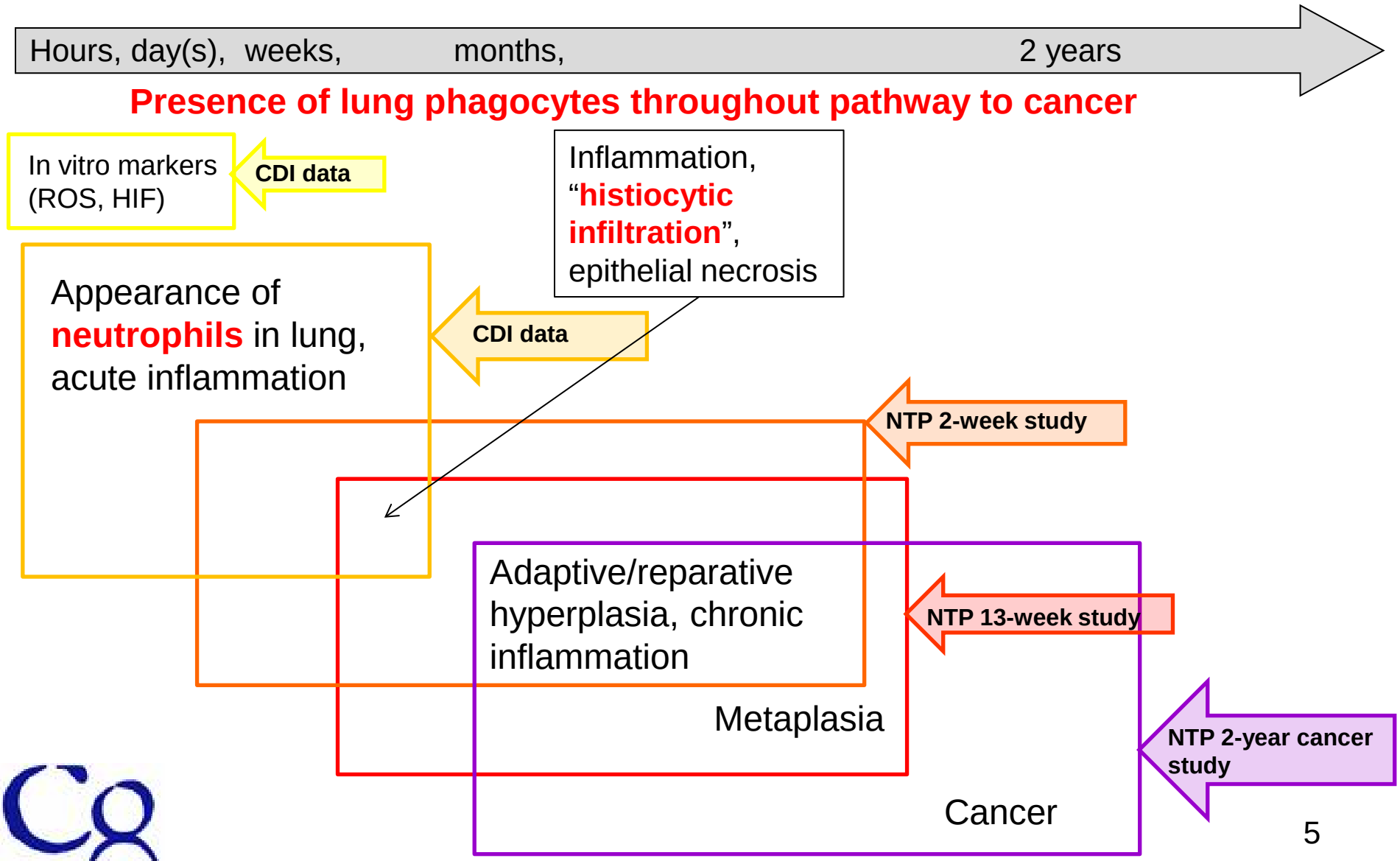
Genotoxicity and cancer MoA

- 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

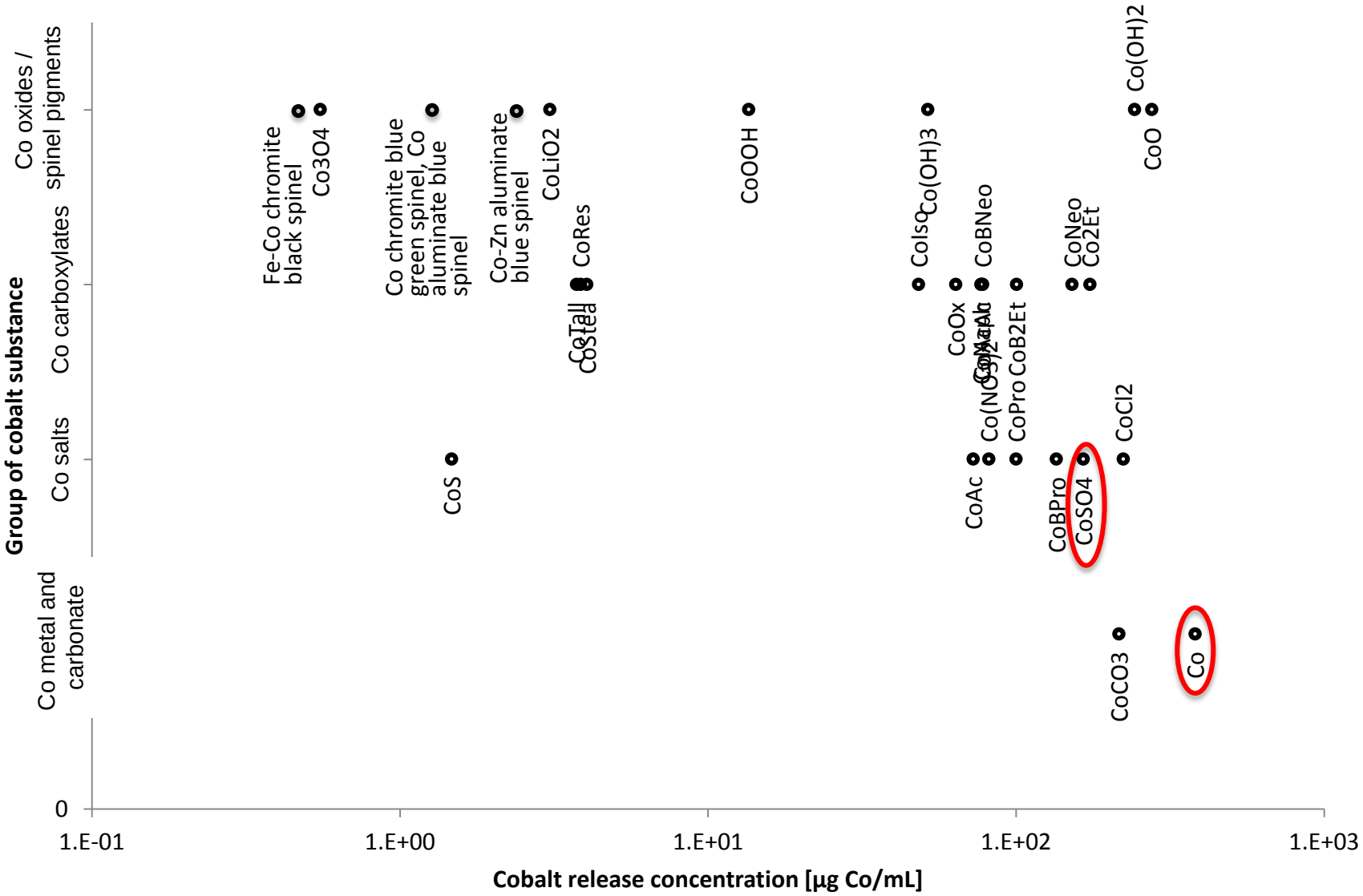


Grouping of cobalt substances

- 1st group: 5 inorganic soluble salts – soluble in pH neutral fluids
- 2nd group: Co metal powder – poorly soluble at neutral pH, soluble in acidic fluids (lysosomes)
- 3rd group: insoluble in neutral AND in acidic fluids (Co_3O_4, inorganic pigments, other)

- Evidence for this from *in vitro* and *in vivo* data

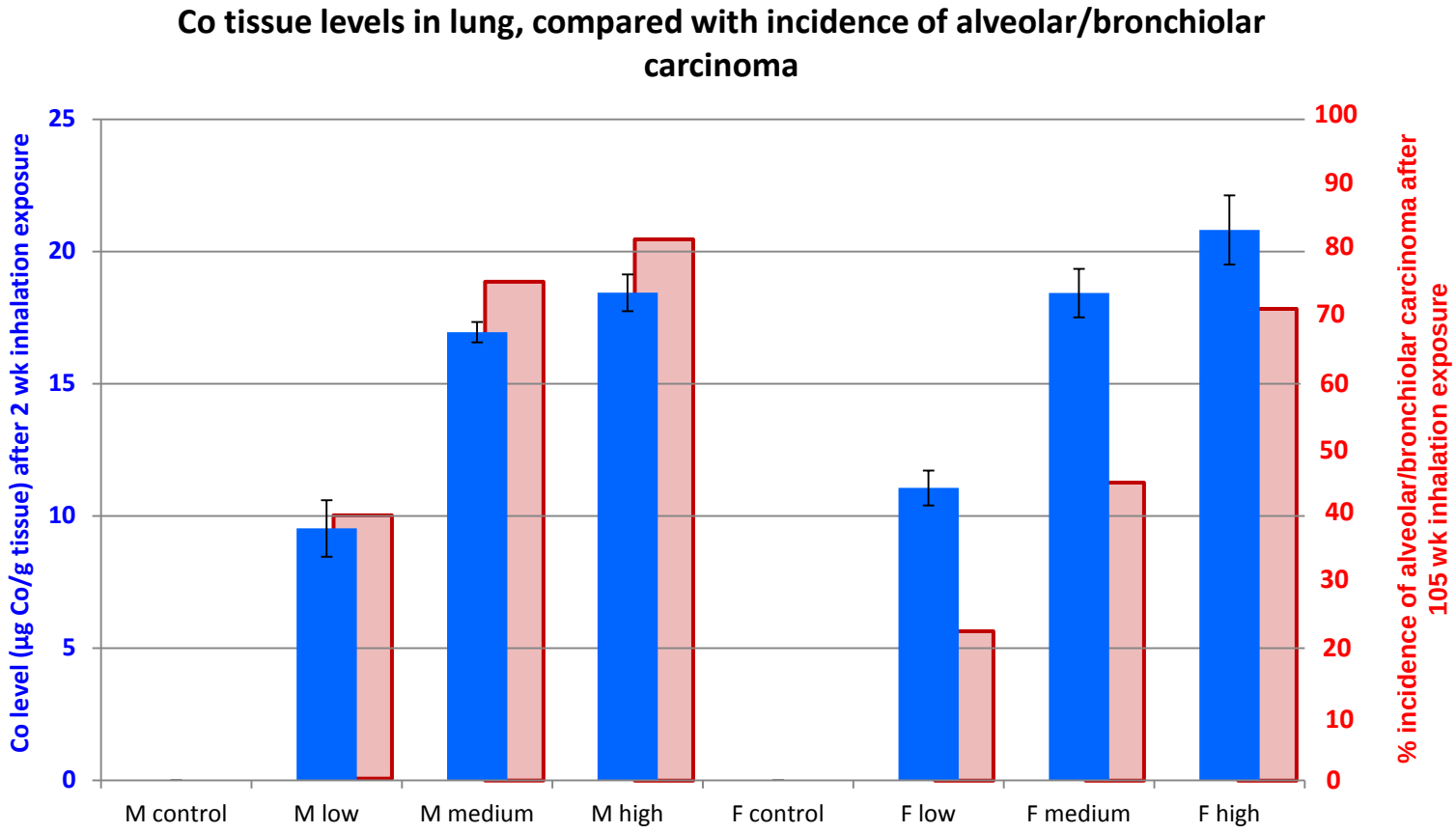
Co release in lysosomal fluid



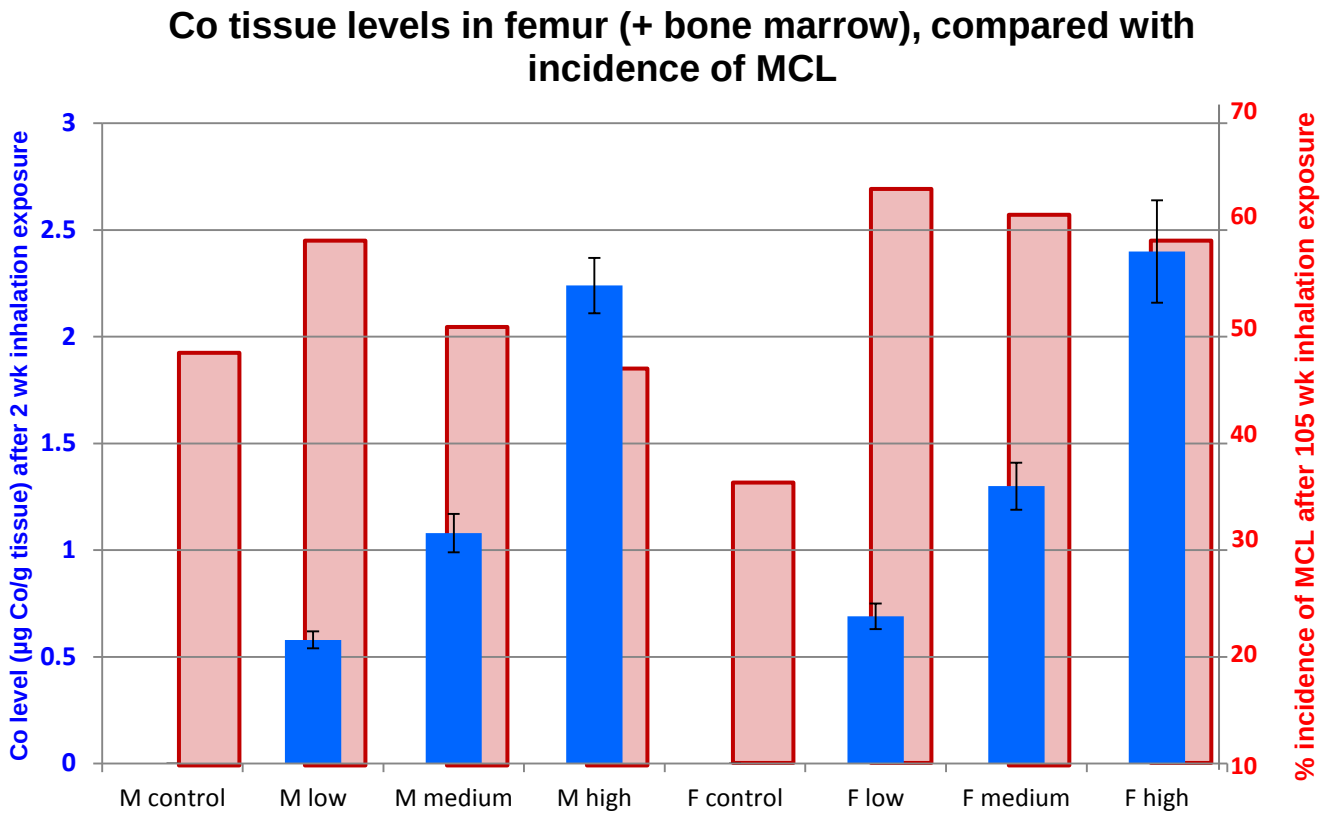
Distal-site neoplasms

- 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



Distal-site neoplasms, treatment related



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