Cobalt Institute's Comments On The HAWPr Tool

Cobalt Institute (CI) has provided this attachment to supplement the Mining Association of Canada (MAC)'s response on Health Canada's HAWPr tool.

Cobalt Institute is the global knowledge center for cobalt and cobalt compounds and has prioritized addressing critical scientific data gaps in the cobalt dataset. CI has used a multi-tier testing and assessment approach in order to apply a read-across of data to and from toxicologically-relevant cobalt substances. CI has a read-across approach specific for each route of exposure (i.e. inhalation, oral and dermal). These approaches require several tiers of information, starting with a basis of in vitro and release data and building on this with higher tier in vivo studies, to demonstrate similarities between the source and target substances. Applying read-across has led to a reduction in animal testing and application of a weight-of-evidence approach.

At present, a large multi-year comprehensive testing program is on-going in Europe to address data gaps for carcinogenicity (i.e. OECD 453 combined chronic/carcinogenicity study), genotoxicity (i.e. OECD 488 and 489 in vivo transgenic rodent and comet studies), repeated-dose toxicity (i.e. 14-day, 28-day and OECD 413 90-day inhalation studies), reproductive toxicity (i.e. OECD 443 extended one-generation reproductive toxicity study) and endocrine disruption endpoints. Cobalt Institute holds legal datasets under EU REACH for the following substances involved in the testing program:

- **Cobalt metal**
- **Cobalt salts with inorganic ligands and cobalt oxides**: Co dichloride, Co sulphate, Co dinitrate, Co carbonate, Co monoxide, Co dihydroxide, tricobalt tetraoxide, Co sulphide, Co lithium dioxide and Co hydroxide oxide
- **Cobalt salts with organic ligands**: Co diacetate, Co acetyl acetonate, Co oxalate, Co propionate, Co borate propionate, Co bis(2-ethylhexanoate), Co borate 2-ethylhexanoate, Co neodecanoate, Co borate neodecanoate, Co resinate, Co stearate.

Cobalt Institute would appreciate further clarifications from Health Canada regarding the cobalt substances listed in the HAWPr tool database, particularly for the following points:

- Further detail regarding the data sources used per endpoint, particularly when rapid read-across is applied from one substance to another.

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- Further information regarding the basis behind the indication of positive carcinogenicity for many cobalt substances in the database. As a comparison, read-across and grouping approaches have been applied in the EU. Based on data generated and assessed, there are cobalt substances that show differences in the upregulation of key events leading to carcinogenicity (i.e. lack of upregulation and potentially different effects). Further testing is on-going for three groups, namely the bioavailable cobalt substances, poorly reactive cobalt substances and cobalt substances with organic ligands.
- Further information regarding the basis behind the indication of positive genotoxicity for many cobalt substances in the database. There should be a definition provided on the term genotoxicity, and if direct, indirect and secondary genotoxicity definitions have been defined. Mutagenic responses have not been detected in any cobalt guideline-compliant studies – this is including studies that are positive for cancer by inhalation exposure in rodent studies. Mutagenicity/direct genotoxicity was excluded as a relevant driver of cobalt-related carcinogenicity on the basis of: (1) data generated under the EU REACH Regulation for the endpoint mutagenicity, including state-of-the-science ToxTracker® data[1], (2) a recent OECD CoCAM conclusion on four soluble Co salts[2] and (3) an extensive Co-related genotoxicity database publication by D. Kirkland (2015)[3].
- Further information regarding the basis behind the indication of positive reproductive toxicity (fertility and developmental) for many cobalt substances in the database. As a comparison, a read-across and grouping approach has been applied in the EU. Based on the data generated, there are three distinct groups leading to different outcomes for reproductive toxicity (i.e. groups that do not demonstrate reproductive toxicity effects). Further testing is on-going for the poorly bioavailable substances and cobalt salts with long-chain organic ligands.
- Further information regarding the basis behind the indication of positive repeated dose toxicity for many cobalt substances in the database. Adversity, adaptability and secondary effects should be considered when providing detail on the type of repeated dose toxicity effect observed.

[1] The ToxTracker assay (Toxys) is a stem cell-based reporter assay that provides mechanistic insights into the genotoxic properties of chemicals, contributing to a mechanism-based, animal-free, cancer hazard and risk assessment of chemicals. It is currently undergoing review to become an OECD guideline testing method.
[2] OECD (2014). "SIDS Initial Assessment Profile Soluble Co salts CoCAM 6. http://webnet.oecd.org/hpv/ui/handler.axd?id=e5e60085-1f3f-4df5-92f6-8f32c26c3082;
[3] Kirkland, D., T. Brock, H. Haddouk, V. Hargeaves, M. Lloyd, S. M. Garry, R. Proudlock, S. Sarlang, K. Sewald, G. Sire, A. Sokolowski and C. Ziemann (2015). "New investigations into the genotoxicity of cobalt compounds and their impact on overall assessment of genotoxic risk." Regul Toxicol Pharmacol **73**(1): 311–338.

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- Further information regarding the basis behind the indication of positive ER and AR pathways. There is currently an assessment on-going for ED in the EU, with consideration of the available guidance and testing strategies that are applicable to metals and metal compounds. The assessment for cobalt has not been concluded, due in part to the need to consider OECD- and guideline-compliant data which will be generated in the upcoming years. QSARs are not widely used for metal and metal compounds.
- Clarification on the use of measured (or modelled) exposure data within the HAWPr tool.

The CI promotes the responsible and sustainable production and use of cobalt in all its forms and applications. The Institute aims to protect and grow the market for cobalt and compounds by promoting a proportionate regulatory environment. We welcome any additional requests or clarifications from Health Canada regarding the current submission and would appreciate the opportunity for cooperation and communication to lead to the appropriate risk management measures and limit values applied to cobalt and cobalt compounds.

Please contact Dr. Vanessa Viegas (vviegas@cobaltinstitute.org) for further information regarding this response.

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