Cobalt Institute: Response Document to ATSDR Toxicological Profile for Cobalt

Submitted along with the following attachments:

Attachment 1. Stantec Cobalt ATSDR Profile Report

Comments on the draft ATSDR ToxProfile for Cobalt

Submitted by Cobalt Institute

Docket ID: **ATSDR-2022-0006**

Document ID: **CI Response to ATSDR 2023-05-10 with Attachment 1 – Stantec Cobalt ATSDR Profile Report**

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The Cobalt Institute (CI) is a trade association composed of producers, users, recyclers, and traders of cobalt. We promote the sustainable and responsible production and use of cobalt in all its forms. The CI aims to protect and grow the market for cobalt and compounds by promoting a proportionate regulatory environment. The CI has invested in high quality, guideline compliant studies to address human health hazard characterization and accompanying risk assessment for different global jurisdictions. We welcome any additional requests or clarifications from ATSDR 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 substances.

The CI supports the ATSDR statement on leading effects of cobalt exposure via the inhalation route as respiratory impairment and the oral route as increase in red blood cells/polycythemia. The CI submits the following comments with regards to the draft ATSDR ToxProfile for cobalt, alongside Attachment 1 – Stantec Cobalt ATSDR Profile Report

1. **Acknowledgement of the essentiality of cobalt for human health in the form of vitamin B12**

- The CI noted the ATSDR's statement on the essential role of cobalt in vitamin B12.
- The CI further states that this means that the level of cobalt in human tissues will never, and should never, be zero.

2. Incorporation of CI mode-of-action testing approach and genotoxicity publications

- The CI mode-of-action (MOA) tiered read-across and grouping approach was published in a series of papers in Regulatory Toxicology and Pharmacology in 2022. The tiered testing approach uses MOA data to predict longer-term toxicity of Co substances. The cobalt ion (as Co^{2+}) is the toxic unit of interest and the driver of toxicity associated with cobalt and cobalt substances – *at and above* certain exposure levels (i.e thresholds). The release of the Co^{2+} ion above these levels leads to hypoxia, oxidative stress, cytotoxicity and if sustained, chronic inflammation. In order to determine if <u>all</u> cobalt substances are able to induce these key events associated with lung toxicity and carcinogenicity, testing was performed in 'tiers', with high quality in vivo and in vitro data generated and published (van den Brule et al. 2022, Derr et al. 2022, Viegas et al. 2022, Burzlaff et al. 2022). The CI MOA approach has identified there are *at least* two groups of cobalt substances – Group 1 'reactive' cobalt substances that lead to lung carcinogenicity (i.e. Co sulphate and Co metal powder) and other hazards associated with cobalt (i.e. respiratory impairment) and Group 2 'poorly reactive' cobalt substances that may have a different mode-of-action similar to poorly soluble low toxicity particles (PSLTs).
- The genotoxicity database for Co and Co substances excludes direct genotoxicity as a MOA for cobalt-induced carcinogenicity. Mutagenic responses <u>have not</u> 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, and is not considered as a marker of cancer in the cobalt read across approach 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]. Based on the points above, cobalt has an indirect genotoxic mode-of-action which supports a threshold for carcinogenicity.

3. Consideration that at least two groups of cobalt substances exist – 'reactive' cobalt substances and 'poorly reactive' substances; with difference in effects and/or exposure levels at which these effects are 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.

- For Group 1, both cobalt sulphate (a very soluble cobalt salt) and cobalt metal powder were tested in the US National Toxicology Program (NTP TR 471 and NTP TR 581) for carcinogenicity and were found to induce lung tumours in both rats and mice at all experimental exposure levels tested[4]. As the reactive group of Co substances has two positive cancer studies in rodents, but no positive human epidemiology data, the substances are classified as 'presumed human carcinogens'.
- The substances in the poorly reactive group (e.g. tricobalt tetraoxide, cobalt sulphide) showed a difference in toxicity to the reactive substances. For the inhalation route, these substances do not have a classification for cancer and show a similarity to poorly soluble low toxicity particles. The CI has submitted a formal request in the EU and will conduct a sub-chronic (90d) study to demonstrate if the substances show the PSLT mode-of-action in a longer duration study. The modes of action for both groups are summarised in Danzeisen et al. 2022. For the oral route, as published in Danzeisen et al. 2020, cobalt dichloride hexahydrate and tricobalt tetraoxide differed by a factor of 310 in their RDT lowest observed effect levels.
- In 2022, a scientific re-evaluation of cobalt and cobalt compounds was performed by the International Agency for Research on Cancer (IARC) and recently published in IARC Monograph 131[5]. Cobalt metal and soluble cobalt (II) salts were classified as 'probably carcinogenic to humans' (Group 2A); cobalt (II) oxide was classified as 'possibly carcinogenic to humans' (Group 2B) and cobalt (II, III) oxide/tricobalt tetraoxide, cobalt sulphide and other cobalt (II) compounds were evaluated as 'not classifiable as to its carcinogenicity in humans' (Group 3). The IARC conclusions serve as further justification to separate tricobalt tetraoxide, Co sulfide and other Co (II) substances from Group 2A or 2B Co substances (e.g. Co metal, 5 soluble Co salts[6], Co monoxide and other 'reactive' Co substances).

4. Derivation of an acute and intermediate MRL to protect against an increase in polycythemia using the Davis and Fields 1958 study should take into account the reversibility of this effect

- As explained further in Stantec Attachment 1, the increase in polycythemia due to cobalt exposure has been found to be reversible (i.e. potentially non-adverse) and this was

[4] Co sulphate: 70, 200, 700 µg Co/m^3 and Co metal powder: 1,250, 2,500 and 5,000 µg Co/m^3
[5] https://www.iarc.who.int/faq/iarc-monographs-evaluate-the-carcinogenicity-of-cobalt-antimony-compounds-and-weapons-grade-tungsten-alloy/
[6] Co dichloride, Co sulphate, Co dinitrate, Co carbonate and Co diacetate

reported in the literature and in Danzeisen et al. 2020. An additional discussion on the effect in terms of adaptability and adversity would be welcomed.

5. Derivation of a chronic MRL to protect against reduced spirometry parameter values using the Nemery et al. 1992 study should take into account other studies of high quality in a weight-of-evidence approach

- There are several relevant and high-quality studies for cobalt and cobalt compounds, investigating respiratory impairment with significant follow-up (Roto et al. 1980, Swennen et al. 1993, Linna et al. 2003, Verougstraete et al. 2004, and Sauni et al. 2010). The CI uses these studies in a weight of evidence, and one key study (i.e. Sauni et al. 2010, chemicals department workplace) to derive a limit value, where a relatively large cohort from a cobalt plant in Finland (cobalt metallurgical plant in Kokkola that started operations in 1966) was studied by several authors through 3 decades.
- See below and the Stantec Attachment 1 for a summary outlining the limitations that should be taken into consideration when using the Nemery et al. 1992 study:
    - Restrictive versus obstructive lung effects
    - Co-exposure to diamond polishing dust and other abrasion materials from polishing wheel
    - Cross-sectional study where exposure in previous years is not known versus longitudinal or cohort studies
    - The control group was examined approximately one year later than the exposure groups
    - Correlation between exposure to Co and reduction in FEV were only observed at group level; Individuals with elevated Co exposure (by urine measurement) were not identical to those displaying decreased lung function (FEV1).

6. References

Burzlaff et al. (2022). “A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 4: Effects from a 28-day inhalation toxicity study with tricobalt tetraoxide in rats.” Regul Toxicol Pharmacol. https://doi.org/10.1016/j.yrtph.2022.105129

Danzeisen et al. (2020). “Bioelution, bioavailability, and toxicity of cobalt compounds correlate.” Toxicol. Sci. 174 (2), 311–325.

Danzeisen et al. (2022). “The underlying mode of action for lung tumors in a tiered approach to the assessment of inhaled cobalt compounds.” Regul Toxicol Pharmacol 130: 105127. https://doi.org/10.1016/j.yrtph.2022.105140

Derr et al. (2022). “A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 2 b: Reactive cobalt substances induce oxidative stress in ToxTracker and activate hypoxia target genes.” Regul Toxicol Pharmacol. https://doi.org/10.1016/j.yrtph.2022.105120

Linna et al. (2003). “Respiratory health of cobalt production workers.” Am. J. Ind. Med. 44: 124-132.

NTP (1998). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Cobalt Sulphate Heptahydrate (CAS No 10026-24-1) in F344/N rats and B6C3F1 mice (inhalation studies). NTP TR 471. NIH Publication No. 98-3961.

OECD (2014). "SIDS Initial Assessment Profile Soluble Co salts CoCAM 6."

Roto (1980). “Asthma, symptoms of chronic bronchitis and ventilatory capacity among cobalt and zinc production workers.” Scand. J. Work Environ. Health 6**:** 1-49.

Sauni et al. (2010). “Cobalt asthma – a case series from a cobalt plant.” Occup. Med (Lond). 60(40: 301-306.

Sauni et al. (2017). "Cancer incidence among Finnish male cobalt production workers in 1969-2013: a cohort study." BMC Cancer 17(1): 340.

Swennen et al. (1993). “Epidemiological survey of workers exposed to cobalt oxides, cobalt salts, and cobalt metal.” Br. J. Ind. Med 50: 835-842.

van den Brule et al. (2022). “A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 2 a: Grouping cobalt compounds based on their capacity to stabilize HIF-1α in human alveolar epithelial cells in vitro.” Regul Toxicol Pharmacol https://doi.org/10.1016/j.yrtph.2022.105121

Verougstraete et al. (2004). “Lung function changes in workers exposed to cobalt compounds: A 13-year follow-up.” Am J Respir Crit Care Med 170(2):162-166.

Verougstraete et al. (2022). “A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 1: Bioaccessibility testing.” Regul Toxicol Pharmacol. https://doi.org/10.1016/j.yrtph.2022.105124

Viegas et al. (2022). “A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 3: Inflammatory response following acute inhalation exposure correlates with lower tier data.” Regul Toxicol Pharmacol 130: 105127. https://doi.org/10.1016/j.yrtph.2022.105127