New Classification for Cobalt Monoxide

Industry Actions for Responsible Assessment and Classification of Cobalt Compounds

The members of The Cobalt Development Institute (CDI) and the Cobalt REACH Consortium (CoRC) have taken the decision to **self-classify** the substance cobalt monoxide (EC number 215-154-6; CAS number 1307-96-6)[1] under the UN Globally Harmonized System for Classification and Labelling of Chemicals (UN GHS) as carcinogenic by inhalation (**Carc. 1B; H350i),** with the following comments:

- Only inhalable forms of cobalt monoxide may be carcinogenic by inhalation. Under the UN GHS mixture rules, all inhalable mixtures containing ≥ 0.1% cobalt monoxide carry the same classification.
- Companies are responsible for their own self-classification, labelling and communication within their supply chains (e.g. Safety Data Sheets), as appropriate for their products.

BACKGROUND

Based on a lifetime inhalation carcinogenicity study by the US NTP[2] (TR[3] 471), cobalt sulfate heptahydrate (EC number 233-334-2; CAS number 10026-24-1) is carcinogenic by inhalation in rats and mice. The European Union has adopted a harmonised classification under the Classification, Labelling and Packaging (CLP) Regulation for cobalt sulfate heptahydrate as Carc. 1B; H350i (may cause cancer by inhalation). In Europe, this classification was extended to other soluble cobalt compounds[4] based on their similar physiochemical properties (solubility in water).

In 2013, based on the results of a lifetime inhalation carcinogenicity study conducted on cobalt metal powder (NTP TR 581), the members of the CDI and CoRC decided to self-classify cobalt metal (EC number 231-158-0; CAS number 7440-48-4) under UN GHS as a Category 1B carcinogen by inhalation (H350i; May cause cancer by inhalation).

Considering the carcinogenicity of two cobalt substances in inhalation testing, the CDI and CoRC have set up a research programme with the aim of predicting chronic inhalation effects

[1] Co monoxide existing legal classifications: Skin Sens. 1; Acute Tox (Oral) 4; Aquatic Acute 1 (M=10); Aquatic Chronic 1 (M=10); existing self-classification: Resp Sens 1B

2 United States National Toxicology Program

3 Technical Report

4 Cobalt dichloride, cobalt dinitrate, cobalt acetate, cobalt carbonate

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of a range of other cobalt compounds. The prediction is based on *in vitro* studies and short-term *in vivo* data ("lower tiers" of testing). This approach avoids long-term toxicity testing in animals, and is founded on the idea of grouping of substances according to their toxicological properties. Classifications are then read across between substances amongst one group, without the need for further *in vivo* testing.

The CDI and CoRC research programme includes the measurement of a compound's solubility in artificial lung fluids, its toxicological behaviour *in vitro* (lung cell culture), and the detection of the inflammatory response to a compound following *in vivo* acute inhalation exposure. These properties are relevant to the mode of action of cobalt-related carcinogenicity, which is considered to be a non-genotoxic, thresholded mechanism, including cytotoxicity, hypoxia and an inflammatory response[5].

Cobalt monoxide (CoO) has undergone the complete set of lower tier tests, and has been shown to behave very much like Co metal powder and/or Co sulfate in these tests. Co monoxide is neither genotoxic *in vitro* nor *in vivo*[6]. The findings support the hypothesis that cobalt monoxide acts similarly to Co metal powder and Co sulfate by a thresholded, non-genotoxic mode of action. The available data indicate that cobalt monoxide exerts local effects upon inhalation, but no systemic (non-lung) effects.

According to the cobalt industry's inhalation grouping paradigm, and to the hypothesis on the cobalt-related mode of action, cobalt monoxide is predicted to resemble cobalt sulfate or cobalt metal powder with respect to its chronic inhalation toxicity. As a result, the members of the CDI and CoRC have taken the decision to self-classify cobalt monoxide under UN GHS as **Carc. 1B; H350i.**

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[5] See, e.g. NTP Report on Carcinogens 14th Edition (Cobalt Monograph); Kirkland et al, 2015, Regul Toxicol Pharmacol 73:311-338. New investigations into the genotoxicity of cobalt compounds and their impact on overall assessment of genotoxic risk.; Suh et al, 2016, Regul Toxicol Pharmacol. Aug;79:74-82. Inhalation cancer risk assessment of cobalt metal.

[6] Kirkland et al, 2015 (as cited above), Cobalt monoxide (CoO) was negative in an *in vitro* HPRT mutation test. Based on *in vivo* data, CoO has cytotoxic rather than mutagenic or genotoxicity activity.

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