

## ***New Classifications for Cobalt Dioxide***

### **Industry Actions for Responsible Assessment and Classification of Cobalt Compounds**

The members of the Cobalt Institute (CI) and the Cobalt REACH Consortium (CoRC) have taken the decision to **self-classify** the substance cobalt dihydroxide (EC number 244-166-4; CAS number 21041-93-0)<sup>1</sup> under the UN Globally Harmonized System for Classification and Labelling of Chemicals (UN GHS) as acutely toxic by inhalation category 1 (**Acute Tox. 1; H330**) and carcinogenic by inhalation category 1B (**Carc. 1B; H350i**), with the following comments:

- Under UN GHS mixture rules, all mixtures will carry a classification for acute inhalation toxicity when containing  $\geq 0.1\%$  cobalt dihydroxide<sup>2</sup> (if it is the only component of the mixture that is acutely toxic by inhalation).
- Under the UN GHS mixture rules, all mixtures will carry the carcinogenicity category 1B (H350i) classification when containing  $\geq 0.1\%$  cobalt dihydroxide.
- 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**

### ***Acute Toxicity***

Cobalt dihydroxide was tested for acute inhalation toxicity following OECD guideline 436 in rats by using a single four-hour exposure at concentrations of 5, 0.5 and 0.05 mg/L. As agreed by the Cobalt REACH Consortium, the finest (smallest particle size distribution) and most representative material on the market was tested. At all concentrations tested, all animals died prematurely (before the end of the 14-day recovery period). Based on the acute toxicity test data for cobalt dihydroxide, this compound has an LC<sub>50</sub> (lethal concentration causing death of 50% of the test animals) below 0.05 mg/L, and therefore meets the criteria for classification in Category 1.

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<sup>1</sup>Co dihydroxide existing self-classifications: Eye Irrit. 2; Skin Sens. 1; Resp. Sens. 1B;

Acute Tox. (oral) 4; Aquatic Acute 1 (M=10); and Aquatic Chronic 2.

<sup>2</sup> Mixture classifications based on Co(OH)<sub>2</sub> concentrations:

<b>Concentration of Co(OH)<sub>2</sub></b>	<b>Mixture classification</b>
0.1% $\leq$ C < 0.5%	Acute Tox. 4
0.5% $\leq$ C < 1.0%	Acute Tox. 3
1.0% $\leq$ C < 10%	Acute Tox. 2
C $\geq$ 10%	Acute Tox. 1

As an LC<sub>50</sub> for cobalt dihydroxide is not available (100% lethality at the lowest exposure level) for use as an acute toxicity estimate (ATE) in mixture classification, the Classification, Labelling and Packaging (CLP) Regulation was used to convert an acute toxicity range value into an ATE. The default ATE that should be used to calculate mixture classifications with cobalt dihydroxide is 0.005 mg/L.

## **Carcinogenicity**

Based on a lifetime inhalation carcinogenicity study by the US NTP<sup>3</sup> (Technical Report (TR) 471), cobalt sulphate 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 CLP Regulation for cobalt sulphate as Carc. 1B; H350i. In Europe, this classification was extended to other soluble cobalt compounds<sup>4</sup> based on their similar physicochemical 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 CI 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).

Considering the carcinogenicity of two cobalt substances in inhalation testing, the CI and CoRC have set up a research programme with the aim of predicting chronic inhalation effects 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 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<sup>5</sup>.

Cobalt dihydroxide has undergone the complete set of lower tier tests, and has been shown to behave similarly to Co metal powder and/or Co sulphate in these tests. In addition, Co dihydroxide was negative for *in vitro* genotoxicity in an HPRT mutation test<sup>6</sup>. The findings support the hypothesis that cobalt dihydroxide acts similarly to Co metal powder and Co sulphate by a thresholded, non-genotoxic

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<sup>3</sup> United States National Toxicology Program

<sup>4</sup> Cobalt dichloride, cobalt dinitrate, cobalt acetate, cobalt carbonate

<sup>5</sup> See, e.g. NTP Report on Carcinogens 14<sup>th</sup> 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 79:74-82. Inhalation cancer risk assessment of cobalt metal.

<sup>6</sup> Kirkland et al, 2015 (as cited above).

mode of action. The available data indicate that cobalt dihydroxide 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 dihydroxide is predicted to resemble cobalt sulphate or cobalt metal powder with respect to its chronic inhalation toxicity. As a result, the members of the CI and CoRC have taken the decision to self-classify cobalt dihydroxide under UN GHS as **Carc. 1B; H350i**.

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