Comments CLH proposal Cadmium carbonate

GENERAL COMMENTS:

The International Cadmium association (ICdA) welcomes the opportunity to provide its contribution to the public consultation on the proposed re-classification of cadmium carbonate as

- a Category 1B toxic for carcinogenicity
- a Category 1B toxic for germ cell mutagenicity
- a Category 1 toxic for specific target organ toxicity, repeated

About the ICdA:
ICdA is a non-profit organisation based in Belgium. The mission of ICdA is to represent the interests of a large number of industrial companies which, in the course of their operations, extract, smelt, refine, process, use and recycle cadmium, cadmium compounds, and their products.

As secretariat to the Cadmium REACH Consortium, the international Zinc Association IZA (the mother association of the International Cadmium Association) is acting on behalf of the Lead Registrants for several cadmium substances including cadmium carbonate (CAS 513-78-0).
These comments represent the view of member companies.

We do not believe that the dossier presented by Sweden provides an adequate justification for the proposed classification (notably on mutagenicity) of cadmium carbonate.

For detailed comments on the classification per specific endpoint, see description in the **specific comments.**

The Annex XV cites on p 9 'There is no harmonised classification for cadmium carbonate other than the harmonised classification justified by the Annex VI group entry with index number 048-001-00-5, i.e. Acute Tox. 4* (H302, H312, H332), Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410). However, specific harmonised classification exists for other cadmium compounds (see the Classification & Labelling Inventory (ECHA, 2015a)).'

We would like to emphasize on the latter that there is specific harmonized classification according to Annex VI to CLP (Classification, Labelling and Packaging of substances and mixtures) for different cadmium compounds.

It is generally considered that systemic toxicity of cadmium compounds is attributed to the cadmium ion (European Union Risk Assessment Report – Volume 74 cadmium metal, Part II Human Health (EU RAR) (JRC, 2007)) and therefore the degree of toxicity of a given cadmium compound is expected to depend on its solubility in water or biological fluids.

Several cadmium compounds have harmonised classifications for carcinogenicity, mutagenicity, reproductive toxicity and STOT RE (Annex VI to CLP). When comparing the classifications across the cadmium compounds within the same water-solubility range group (Table A), it can be seen that they have the same classification for mutagenicity, reproductive toxicity. Regarding STOT RE and carcinogenicity, all compounds have been classified in category 1 and category 1B, respectively.

Table A: Cadmium compounds with harmonised classification for selected endpoints.

Ranking of solubility	Cadmium compound	Water solubility (mg/L)[2]	Harmonized classification[1]		
			Carcino-genicity	Muta-genicity	STOT RE
Very soluble	Cadmium sulphate	540 x 10^3	1B; H350	1B; H340	1; H372
	Cadmium nitrate	507 x 10^3			
	Cadmium chloride	457 x 10^3	1B; H350	1B; H340	1; H372
	Cadmium fluoride	35 x 10^3	1B; H350	1B; H340	1; H372
Slightly soluble	Cadmium hydroxide	69.5			
	Cadmium carbonate	3.2			
	Cadmium metal	2.3	1B; H350	2; H341	1; H372
	Cadmium oxide	2.1	1B; H350	2; H341	1; H372
Insoluble	Cadmium sulphide	6.10^{-7}	1B; H350	2; H341	1; H372

[1] Only harmonised classifications for carcinogenicity, mutagenicity and STOT RE are presented, since that is within the scope of the present CLH report. However, there is also harmonised classification for acute toxicity, reproductive toxicity, acute and chronic aquatic toxicity (ECHA, 2015).

[2] Solubility data as presented in the CSR part of the REACH registration (2015), except for cadmium fluoride where solubility data was from ECB (1997).

The approach taken by the Cadmium REACH Consortium (cfr REACH registration) has been to identify the water solubility of cadmium carbonate and the water-solubility range group that cadmium carbonate would belong to. Cadmium carbonate was then classified according to the previous harmonised classification for cadmium compounds belonging to that water-solubility range group.

In conclusion, within the scope of the present CLH report, ICdA and the Cadmium REACH Consortium (cfr REACH registration) stress that cadmium carbonate should be classified as Carc. 1B; H350, Muta 2; H341, and STOT RE 1 (bone and kidney); H372.

ICdA and the Cadmium REACH Consortium supports the proposed classification for cadmium carbonate as Carc. 1B and STOT RE1 (bone and kidney) but does not agree with the proposed Muta 1B based on the read across principles as outlined above.

The harmonized classification according to Annex VI to CLP (Classification, Labelling and Packaging of substances and mixtures) shows a difference in Mutagenicity for the very soluble cadmium compounds versus the slightly soluble cadmium compounds, namely Muta 1B versus Muta 2. The basis for this difference are explained in detail under Specific comments (Mutagenicity)

The Annex XV gives on page 11 under 2.4.1 Current self-classification and labelling based on the CLP Regulation criteria, an overview table of the self classification according to the Classification and Labelling inventory of January 23, 2015. From this overview, we can conclude that most of the

notifiers follow the same classification as coming from the lead dossier of the REACH registration joint submission (self- classification: Acute Tox. 2; H330, Muta. 2 ; H341, Carc. 1B; H350, Repr. 2; H361, STOT RE 1; H372, Aquatic Acute 1; H400, Aquatic Chronic 1; H410). This is not supporting the proposed harmonized classification as reported in the Annex XV on page 5 (table 2): Carc. 1B; H350, Muta. 1B; H340, STOT RE 1; H372 (bone, kidney), Acute Tox. 4*; H302, Acute Tox. 4*; H312, Acute Tox. 4*; H332, Aquatic Acute 1; H400, Aquatic Chronic 1; H410.
The proposed harmonized classification is the result of the Annex VI group entry with index number 048-001-00-5, i.e. Acute Tox. 4* (H302, H312, H332), Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) and the harmonized classification proposed for consideration by RAC. However, for this proposed harmonized classification (as future entry in Annex VI, CLP regulation), the hazard classes coming from the group classification are not re-assessed in this Annex XV dossier but taken over as such.

On page 9, the labelling is describing only the hazards of the proposed harmonized classification and not of the hazard classes coming from the group classification being not assessed in this Annex XV dossier.

SPECIFIC COMMENTS:

Mutagenicity:

ICdA and the Cadmium REACH Consortium do not support the in Annex XV proposed classification for cadmium carbonate as Muta 1B.

Cadmium oxide is listed as Index number 048-002-00-0 in Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as mutagen, Muta 2 (H341: Suspected of causing genetic defects).

Cadmium carbonate belongs as cadmium oxide to the water-solubility range group “slightly soluble” (see Table A) and for consistency it is therefore reasonable that it should be classified in a similar way as other members of this group (i.e cadmium oxide, cadmium metal); therefore, a classification in Muta. 2; H341 is warranted.

The harmonized classification according to Annex VI to CLP (Classification, Labelling and Packaging of substances and mixtures) shows a difference for Mutagenicity classification for the very soluble cadmium compounds versus the slightly soluble cadmium compounds, namely Muta 1B versus Muta 2. The basis for this difference refers back to the meetings of the Commission Working Group on the Classification and Labelling of Dangerous Substances and classification proposals.

For Cadmium chloride, the Commission Working Group ECB concluded on a classification as Muta Cat 2: R46 (may cause heritable genetic damage) based on the fact that most studies on aneuploidy in oocytes (and spermatocytes) and sperm head morphology are positive. This classification was adopted in Annex I of Directive 67/548/EC. The corresponding GHS-CLP classification is Mutagenic category 1B; H340. This is conform the criteria in the CLP regulation, Annex I: 3.5.2.2 : Classification in Category 1B is for substances for which there are positive results from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations in germ cells. This is in agreement with the Annex XV on pag 43 summarising that there is sufficient evidence to conclude that cadmium chloride induces structural chromosome aberrations and micronuclei in somatic cells in vivo, and numerical and structural chromosome aberrations in germ cells in vivo.

For Cadmium oxide, the Commission Working Group ECB concluded on a classification as Muta Cat 3: R68 (possible risk of irreversible effects) (corresponding GHS-CLP classification is Mutagenic category 2; H341) and not on a Muta Cat 2 (corresponding GHS-CLP classification is Mutagenic category 1B; H340 based on the fact there was no positive evidence for cadmium oxide itself.

The criteria in the CLP regulation, Annex I: 3.5.2.2 : Classification in Category 2 is for substances for which there is positive evidence obtained from experiments in mammals and/or in some cases from *in vitro* experiments, obtained from somatic cell mutagenicity tests *in vivo* in mammals; or other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays.

Bacterial in vitro tests with cadmium oxide yielded negative results. Only one in vivo study using cadmium oxide by inhalation was located. Inhalation exposure for 13 weeks to cadmium oxide did not result in increased frequency of micronucleated erythrocytes in peripheral blood of male or female B6C3F1 mice (Dunnick, 1995). However, this result should be interpreted with caution due to the absence of sufficient bioavailability to the bone marrow and the fact that the most relevant target cells (lung) were not examined.
Several experiments using cadmium water-soluble compounds were identified and summarized by IARC (1993). Results were judged conflicting (ECB, 2007). More recently, Fahmy and Aly (2000) found induction of micronuclei, increased sister chromatid exchange in bone marrow and chromosomal aberration after a single intraperitoneal treatment with cadmium chloride.
The Commission Working Group ECB concluded that in vivo somatic cell mutagenicity studies were negative with respect of cadmium oxide while the positive results leading to the category 3 (corresponding GHS-CLP classification is Mutagenic category 2; H341) proposal were based on the positive results of in vivo somatic cell mutagenicity studies for other cadmium compounds.

Carcinogenicity:

ICdA and the Cadmium REACH Consortium agree with the proposed Carc Cat 1B classification for cadmium carbonate since there is sufficient evidence to demonstrate animal carcinogenicity. ICdA and the Cadmium REACH Consortium follow the justification that classification in Carc Cat 1A is not warranted since evidence from human epidemiological studies is not available.

Cadmium oxide is listed as Index number 048-002-00-0 in Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as carcinogen, Carc. 1B (H350: May cause cancer). Cadmium sulphate, cadmium chloride and cadmium metal have been granted the same classification, based on weight of evidence and read-across.

Cadmium carbonate belongs to the water solubility range group “slightly soluble” (see Table A) and for consistency it is therefore reasonable that it should be classified in a similar way as other members of this group (i.e cadmium oxide and cadmium metal); therefore, a classification in Carc. 1B; H350 is warranted.

Specific Target Organ toxicity, repeated:

ICdA and the Cadmium REACH Consortium agree with the proposed STOT RE1 classification for cadmium carbonate since significant toxicity in humans was demonstrated in kidney and bone.

Cadmium oxide, cadmium metal, cadmium sulphate and cadmium chloride are listed respectively as Index number 048-002-00-0, 048-002-00-0, 048-009-00-9, 048-008-00-3 in Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as Specific target organ toxicity - repeated:, STOT RE1 (H372: Causes damage to organs).

Cadmium carbonate belongs to the water solubility range group “slightly soluble” (see Table A) and for consistency it is therefore reasonable that it should be classified in a similar way as other members of this group (i.e cadmium oxide and cadmium metal); therefore, a classification in STOT RE1; H372 is warranted.

References:

Dunnick JK (1995). NTP technical report on toxicity studies of cadmium oxide administrated by inhalation to F344/N rats and B6C3F1 mice. NIH Publication 95-3388. Report no.: 39.

ECHA (2015) Classification & Labelling Inventory

European Union Risk Assessment Report – Volume 74 cadmium metal, Part II Human Health (EU RAR) (ECB-JRC, 2007))

Fahmy MA and Aly FA (2000). In vivo and in vitro studies on the genotoxicity of cadmium chloride in mice. J Appl Toxicol 20:231-238

International Agency for Research on Cancer (IARC) (1993). Cadmium and cadmium compounds. Beryllium, cadmium, mercury and exposure in the glass manufacturing industry 58:119-237.