Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Cadmium hydroxide

EC Number: 244-168-5
CAS Number: 21041-95-2

CLH-O-0000001412-86-80/F

Adopted

4 December 2015

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.
All attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: **Cadmium hydroxide**
EC number: **244-168-5**
CAS number: **21041-95-2**
Dossier submitter: **Sweden**

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2015	Belgium	International Cadmium Association	BehalfOfAnOrganisation	1

Comment received

Comments CLH proposal Cadmium hydroxide:
Tables and references to these comments can be found in the uploaded attachment.

The International Cadmium association (ICdA) welcomes the opportunity to provide its contribution to the public consultation on the proposed re-classification of cadmium hydroxide 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 hydroxide (CAS 21041-95-2).
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 hydroxide.

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 hydroxide 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.

The approach taken by the Cadmium REACH Consortium (cfr REACH registration) has been to identify the water solubility of cadmium hydroxide and the water-solubility range group that cadmium hydroxide would belong to. Cadmium hydroxide 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 hydroxide 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 hydroxide 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. This is not in accordance with what can be found as of May 7, 2015 (see table B below). From this overview table B, 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.

Table B: Self-classification according to the Classification and Labelling inventory as of May 7, 2015.

ECHA's comment: The following attachment was provided by the International Cadmium Association: Comments CLH proposal Cadmium hydroxide

Dossier Submitter's Response

Thank you for supporting the proposed classifications Carc. 1B, H350; STOT RE 1, H372 (bone, kidney).

You do not support the proposed classification Muta. 1B, H340, since you do not believe that we have provided an adequate justification for this proposal. For our respons to this, please refer to our response to comment 10.

Thank you for drawing attention to the fact that the labelling is describing only the hazards of the proposed harmonized classification and not of the hazard classes coming from the group classification not assessed in this Annex XV dossier. The complete labelling would, of course, comprise also the hazards covered by the Annex VI group entry.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2015	France		MemberState	3

Comment received

MS FR agrees with the classification proposal for STOT RE 1, H372 (kidney, bone) and Muta. 1B, H340.

Dossier Submitter's Response

Thank you for supporting the proposed classifications Muta. 1B, H340; STOT RE 1, H372. (bone, kidney).

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2015	Germany		MemberState	4

Comment received

The view that the Cd 2+ ion is considered as the toxic species of Cadmium hydroxide is shared by DE, accordingly Cadmium hydroxide should be considered to have the same

intrinsic toxic properties as other Cadmium compounds which already have a harmonized classification and labelling.

As different Cadmium compounds have different solubilities (e.g. in water and body fluids) and as liberation of the Cd 2+ ion by dissolution processes is supposed to play a crucial role in toxicity the issue "solubility and bioavailability of Cd 2+ is extensively discussed in section 4 "Equivalence between Cadmium salts in mammalian toxicity".

In this context, however, it should also be kept in mind that:
(1) presystemic solubility might not be the only factor contributing to systemic toxic effects of Cadmium compounds and that
(2) in addition, further factors, not only solubility, have to be considered when discussing the bioavailability of Cd 2+ from different Cadmium compounds.

For (1) it has to be taken into account that particulate Cadmium compounds (e.g. CdO) are supposed to enter the lung/lung cells via phagocytosis. With respect to inhalation uptake it has been demonstrated that variation in absorption for a single Cadmium compound was even higher than variation between different Cadmium substances. The study by Glaser et al. (1990) demonstrated that tumor incidences obtained with different Cadmium compounds did not correlate with water solubilities [1].
For (2) there is information available from the literature that Zinc and ion status of a mammalian organism has an influence on Cadmium bioavailability.

Thus, many different factors can contribute to bioavailability of Cadmium compounds and the extent of availability of Cd 2+ ions after exposure to different salts may vary not only based on solubility but due to the sum of influencing factors. This can lead to quantitative differences of toxic species after exposure to comparable doses of different Cadmium compounds. This issue should be discussed in more details in section "Equivalence between Cadmium salts in mammalian toxicity" because equivalence may hold true for qualitative but not for quantitative grounds.

As discussion on toxicity in section 4 is based on the toxicity of Cadmium in general which might be taken up by different pathways, the most probable exposure routes for Cadmium hydroxide should be briefly mentioned.

[1] AGS, 2014 (Ausschuss für Gefahrstoffe, Begründung zu ERB Cadmium in TRGS 910, available at http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/Begruendungen-910.html)

Substance identity:
In IUCLID section 1.2 „composition" the reference substance is not given as a constituent. At the same time the degree of purity is >80- <100 %. Even though Cadmium hydroxide is a mono-constituent substance IUCLID section 1.2 should be filled in completely, including the reference substance as constituent and further impurities or additives if appropriate.

Dossier Submitter's Response

In the case there is variation in absorption for a single cadmium compound after inhalation exposure due to particulate properties affecting uptake via phagocytosis, this would be considered to demonstrate differences in potency rather than influencing the hazard. Certainly, various factors might influence the bioavailability of a particular cadmium compound, leading to differences in the uptake of the toxic species Cd^{2+} between different cadmium compounds after exposure to comparable doses. However, even for cadmium compounds with lower bioavailability, cadmium will accumulate in an organism following chronic exposure, resulting in increasing probability for a hazardous poperty to be

manifested over time. Thus, all bioavailable cadmium compounds should be considered to have a potential for the hazardous effects of the Cd^{2+} ion.

There is information in the scientific literature suggesting that dietary deficiency in iron may lead to increased absorption of cadmium following oral exposure. It has also been argued that zinc transporters may play a role for cadmium uptake, and that zinc supplementation might be protective towards cadmium uptake. However, the evidence for this is less clear (see pp 15-16 in Åkesson and Vahter, 2011, http://ec.europa.eu/enterprise/sectors/chemicals/files/reports/sweden_health_effects_cadmium_jan2011_en.pdf). Please also note that following cadmium exposure, no indication of higher tumour incidence was observed in rats given a marginally zinc-deficient diet as compared to rats given a zinc-adequate diet in the study by Waalkes and Rehm (1992) included in the CLH report.

The most probable routes of exposure are oral and inhalation.

We agree that IUCLID section 1.2 should be filled in completely and that the information should be in agreement with the information given in the CLH report.

RAC's response

We concur with the response provided by the DS.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2015	Belgium	International Cadmium Association	BehalfOfAnOrganisation	6

Comment received

Carcinogenicity:
ICdA and the Cadmium REACH Consortium agree with the proposed Carc Cat 1B classification for cadmium hydroxide 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 hydroxide 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.

Dossier Submitter's Response

Thank you for supporting the proposed classification Carc. 1B, H350.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2015	France		MemberState	7
Comment received				
Harmonised classification and labelling proposal, page 5 Cadmium chloride is classified into annex VI of regulation (EC) 1272/2008, carc cat 1B, H350 with a specified concentration limit for carcinogenicity at 0.01%. Could you please justified why no SCL has been proposed for cadmium hydroxide? Comparison with criteria, page 54 The classification of cadmium hydroxide in Category 1B for carcinogenicity need to be discussed. In fact, in 2012, IARC has considered that sufficient evidence were available in humans for the carcinogenicity of cadmium compounds. Therefore, category 1A may be more appropriate. Nevertheless, the shortcomings limiting the causal relationship between exposure to cadmium and cancer in humans need to be more detailed.				
Dossier Submitter's Response				
When there are good reasons for extrapolation of a hazardous property from one or more substances to another (in this case because of indications of bioavailability of the Cd^{2+} ion), the expected potency of the substances may vary, making it difficult or impossible to evaluate the potency of the substance of interest. For that reason we have not proposed a specific concentration limit for cadmium hydroxide. This is analogous to the message conveyed in section 3.7.2.5.2. of the Guidance on the Application of the CLP Criteria (ECHA 2013) regarding substances causing reproductive toxicity, and in section 2.5 of the Guidelines for Setting Specific Concentration Limits for Carcinogens in Annex I of Directive 67/548/EEC, Inclusion of Potency Considerations (Commission Working Group on the Classification and Labelling of Dangerous Substances) regarding carcinogens. Regarding the issue whether it would be more appropriate to classify cadmium hydroxide in Carc. 1A than in Carc. 1B, we think this calls for careful consideration, since IARC (2012) considered that there is sufficient evidence in humans for the carcinogenicity of cadmium compounds, but also considered that the assessment of human studies was constrained by various flaws or that results of different studies are inconsistent. For further details on shortcomings of studies in humans we refer to the EU RAR: cadmium metal Part II - human health (2007), particularly the conclusions presented on pages 489-493. This information may serve as a background for discussions in RAC on whether there is evidence in humans for a causal relationship between exposure to cadmium and the development of cancer (known human carcinogen), justifying classification of cadmium hydroxide in Carc. 1A.				
RAC's response				
The setting of a SCL is discretionary and therefore the position of the DS is noted. The RAC assessment for this endpoint is based on information provided by the DS. Like those who have commented in the PC, we find this sufficient for a Carc. 1B classification.				

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2015	Germany		MemberState	8
Comment received				
For all animal studies described it should be mentioned whether the study was performed in accordance with an OECD or EU test guideline.				

Dossier Submitter's Response
We agree and indicate our consideration on this below for each study. Mutagenicity Mukherjee et al. (1988): chromosome aberrations, OECD 475 with deviations; micronuclei OECD 474 with deviations, sister chromatid exchanges, no guideline. Fahmy and Aly (2000): chromosome aberrations, OECD 475 with deviations; micronuclei OECD 474 with deviations, sister chromatid exchanges, no guideline; spermatogonial chromosome aberrations, OECD 483 with deviations. Jagetia and Adiga (1994): OECD 475 with deviations. Kašuba et al. (2002): micronuclei OECD 474 with deviations; comet assay, OECD 489 with deviations. Valverde et al. (2000): OECD 489 with deviations. Devi et al. (2001): OECD 489 with deviations. Watanabe et al. (1979): no guideline. Watanabe and Endo (1982): no guideline. Mailhes et al. (1988): no guideline. Miller and Adler (1992): similarity to OECD 483, which, however, is not designed to measure numerical aberrations and is not routinely used for this purpose. Epstein et al. (1972): OECD 478 with deviations. Gilliavod and Léonard (1975): dominant lethal test, OECD 478 with deviations; heritable translocation test, OECD 485 with deviations. Suter (1975): OECD 478 with deviations, females treated. Sutou et al. (1980a, 1980b): OECD 478 with deviations. Carcinogenicity Waalkes and Rehm (1992): OECD 451 with deviations. Takenaka et al. (1983): OECD 451 with deviations. Glaser et al. (1990): OECD 451 with deviations. Heinrich et al. (1989): OECD 451 with deviations.
RAC's response
Thank you for this clarification.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2015	Belgium	International Cadmium Association	BehalfOfAnOrganisation	10

Comment received

Mutagenicity:
ICdA and the Cadmium REACH Consortium do not support the in Annex XV proposed classification for cadmium hydroxide 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 hydroxide 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.

Dossier Submitter's Response

You do not support the proposed classification Muta. 1B, H340, since you do not believe that we have provided an adequate justification for this proposal. Instead, you stress that the classification for germ cell mutagenicity should be Muta. 2, H341, according to the approach taken by the Cadmium REACH Consortium as presented in the REACH registration. This approach is based on the water solubility of cadmium hydroxide and the water-solubility range group (as defined in the REACH registration) that cadmium hydroxide would belong to, and that cadmium hydroxide should be classified for germ cell mutagenicity according to the previous harmonised classification for cadmium compounds belonging that water-solubility range group. However, we do not agree with this approach, since available data support that the toxic species Cd^{2+} of a cadmium salt is bioavailable also from cadmium salts with low water solubility (see Section 4 of the CLH report). Consequently, cadmium chloride (very soluble) is an appropriate analogue for cadmium hydroxide (slightly soluble). In conclusion, the hazardous properties of the Cd^{2+} ion would exist for a cadmium salt whatever its water solubility may be. Since data from studies with cadmium chloride support that the hazardous properties of the Cd^{2+} ion involve mutagenicity in germ cells, we propose that cadmium hydroxide should be classified in Muta. 1B, H340.

RAC's response

We concur with the response provided by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2015	Germany		MemberState	11

Comment received

Table 12 (p. 37) and text description on p.41: For the Kašuba et al. (2002) study, differences between the two different administration routes should be briefly discussed.

Table 12 (p. 38): for the Devi study, tissues (apparently leucocytes) investigated should be mentioned in the table.

Page 42: description of the Valverde study: it should be mentioned that no DNA damage was observed in kidney, liver and lung cells when extracts of the cells were exposed to Cadmium chloride at 0.1 µM in the presence of proteinase K.

Section 4.8.1.2 Human information

A more recent human study could be taken up: Ketelslegers, H.B.; Gottschalk, R.W.; Koppen, G.; Schoeters, G.; Baeyens, W.F.; van Larebeke, N.A.; van Delft, J.H.; Kleinjans, J.C. (2008): Multiplex genotyping as a biomarker for susceptibility to carcinogenic exposure in the FLEHS biomonitoring study. Cancer Epidemiology, Biomarkers and Prevention, 17, 1902-1912.

Dossier Submitter's Response

The study by Kašuba et al. (2002) revealed that the mutagenic and genotoxic effects of the Cd^{2+} ion were similar after oral and subcutaneous administration of cadmium chloride, i.e. similar increases in the mean number of micronuclei and in comet tail length were observed for both routes of administration.

We agree that the tissue investigated in the study by Devi et al. (2001) should be mentioned in Table 12.

We assume that the comment on the description of the study by Valverde et al. (2000), saying that resuts from treatment with cadmium chloride in the presence of proteinase K should be mentioned, is a mistake caused by confusing a study by Valverde et al. (2001, Mutagenesis 16: 265-270) with the study by Valverde et al. (2000) described in the CLH report. In contrast to the 2000 study, the 2001 study did not measure DNA damage in vivo, but examined DNA damage in an acellular assay, in which lysed cells from lung, liver and kidney of mice were treated with cadmium chloride (i.e. this is not even an in vitro study in intact cells). Cells were lysed either in the absence or presence of proteinase K. When cells had been lysed in the presence of proteinase K, the subsequent treatment with cadmium chloride did not induce an increase in DNA damage. Since this study did not measure DNA damage in vivo, it is not a critical study for concluding on classification and was therefore not included in the CLH dossier.

The primary aim of the study by Ketelslegers et al. (2008) was to investigate if interindividual differences in relationships between carcinogen exposure and genotoxic effect in humans can be explained by genotypic differences, enabling the identification of more susceptible subgroups for environmental cancer risks. Individuals from the general population were studied. No statistically significant correlation between the internal dose of cadmium and DNA damage in white blood cells as measured by the comet assay or the frequency of micronuclei in whole blood cultures was established. The design of the study involves that the results cannot be considered informative enough for assessing the mutagenic hazard of cadmium.

RAC's response

RAC concurs with the response provided by the DS regarding studies by Valverde et al. (2000) and Ketelslegers et al. (2008).

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2015	France		MemberState	12

Comment received

Acute toxicity, page 20
Acute toxicity studies have not been evaluated in the CLH report. However, the registrant proposed to classify cadmium hydroxide acute tox. 2, H330, based on the acute toxicity studies available on CdO in mice and rats instead of acute tox 4*, H332 set in annex VI of

the CLP regulation. This endpoint need thus to be discussed in the CLH report.
Dossier Submitter's Response
It is not possible to include acute toxicity in the proposal at this late stage of the process, because no data were provided on this endpoint in the CLH report submitted for public consultation.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.05.2015	Belgium	International Cadmium Association	BehalfOfAnOrganisation	14
Comment received				
Specific Target Organ toxicity, repeated: ICdA and the Cadmium REACH Consortium agree with the proposed STOT RE1 classification for cadmium hydroxide 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 hydroxide 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.				
Dossier Submitter's Response				
Thank you for supporting the proposed classification STOT RE 1, H372 (bone, kidney).				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2015	France		MemberState	15
Comment received				
STOT RE, page 36 Cadmium chloride is classified into annex VI of regulation (EC) 1272/2008, STOT RE 1, H372 with a specified concentration limit at 7%. Could you please justify why no SCL has been proposed for cadmium hydroxide?				
Dossier Submitter's Response				
Please refer to our response to comment 7 on this issue.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2015	Germany		MemberState	16
Comment received				
Section 4.7.2.1 (pp 21 ff) At the beginning of the section, an overview of the biomarkers of effects for kidney toxicity should be given and their significance should be discussed. There is some language in this respect at the beginning of section 4.7.2.1.2 (p. 28f), which could be extended a bit and shifted to the beginning of section 4.7.2.1. A newer study should be taken up for effects on kidneys: Navas-Acien, A.; Tellez-Plaza, M.; Guallar, E.; Muntner, P.; Silbergeld, E.; Jaar, B.; Weaver, V. (2009): Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. American Journal of Epidemiology, 170, 1156-1164 Section 4.7.6 (p. 36): The conclusions are supported				
Dossier Submitter's Response				
We agree that including a more detailed overview of biomarkers for kidney effects could be helpful to the reader. For further information on this matter we refer to the section Kidney physiology on pages 326-329 in the EU RAR: cadmium metal Part II - human health (2007). Thank you for drawing our attention to the study by Navas-Acien et al. (2009) on the impact of low-level cadmium exposure on clinical renal outcomes, which is relevant to consider when assessing the effects of cadmium on kidney after repeated exposure. Thank you for supporting the proposed classification STOT RE 1, H372 (bone, kidney).				
RAC's response				
RAC agrees that the information suggested by Germany would have been helpful to include in the CLH Report. Our assessment is based on information provided in the CLH Report but the response is noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2015	Germany		MemberState	17
Comment received				
proposed harmonised classification M-factors (p. 7): This classification proposal deals not with environmental effects as there is the existing classification Aquatic Acute 1; H400 and Aquatic Chronic 1; H410. We would like to comment that there is no M-factor indicated, but we think that it is necessary. For Cadmium hydroxide we would suggest 10 for both (acute and chronic).				
Dossier Submitter's Response				
It is not possible to include environmental effects in the proposal at this late stage of the process, because no data were provided on these endpoints in the CLH report submitted for				

public consultation.
RAC's response
Noted.

ATTACHMENTS:

1. **Comments CLH proposal Cadmium hydroxide** – submitted by the International Cadmium Association on 8 May 2015