Committee for Risk Assessment

RAC

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

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

4 December 2015

CLH-O-0000001412-86-80/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemical name: **Cadmium hydroxide**

EC Number: **244-168-5**

CAS Number: **21041-95-2**

The proposal was submitted by **Sweden** and received by RAC on **4 February 2015.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Sweden has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **27 March 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **11 May 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Andrew Smith**

Co-rapporteur, appointed by RAC: **Miguel Angel Sogorb**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonized classification and labelling was reached on **4 December 2015.** The RAC opinion was adopted by **consensus.**

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	048-001-00-5	cadmium compounds, with the exception of cadmium sulphoselenide (xCdS.yCdSe), reaction mass of cadmium sulphide with zinc sulphide (xCdS.yZnS), reaction mass of cadmium sulphide with mercury sulphide (xCdS.yHgS), and those specified elsewhere in this Annex	-	-	Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	H332 H312 H302 H400 H410	GHS07 GHS09 Wng	H332 H312 H302 H410		-	A1
Dossier submitters proposal	TBD	Cadmium hydroxide	244-168-5	21041-95-2	Muta. 1B Carc. 1B STOT RE 1	H340 H350 H372 (kidney, bone)	GHS08	H340 H350 H372 (kidney, bone)		-	A1
RAC opinion	TBD	Cadmium hydroxide	244-168-5	21041-95-2	Muta. 1B Carc. 1B STOT RE 1	H340 H350 H372 (kidney, bone)	GHS08	H340 H350 H372 (kidney, bone)		**-**	A1
Resulting Annex VI entry if agreed by COM	TBD	Cadmium hydroxide	244-168-5	21041-95-2	Muta. 1B Carc. 1B Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H340 H350 H332 H312 H302 H372 (kidney, bone) H400 H410	GHS07 GHS08 GHS09 Dgr	H340 H350 H332 H312 H302 H372 (kidney, bone) H410		-	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Background information in support of the proposal

Cadmium hydroxide is currently among a number of cadmium salts classified in CLP Annex VI under the group entry with Index No. 048-001-00-5. This entry indicates a classification of Acute Tox 4*, H302, Acute Tox 4*; H312, Acute Tox 4*; H332, Aquatic Acute 1; H400 and Aquatic Chronic 1; H410.

The Dossier Submitter (DS) has proposed a new entry specifically for cadmium hydroxide itself. This would carry across without any change the current classification provided in the group entry and then proposes to add classification for repeated dose toxicity (STOT RE 1; H372 – kidney, bone), germ cell mutagenicity (Muta. 1B; H340) and carcinogenicity (Carc. 1B; H350).

The DS has described how the systemic toxicity of inorganic cadmium compounds is commonly regarded to result from the intrinsic properties of the Cd^{2+} ion. Those compounds from which Cd^{2+} is readily bioavailable will therefore share common hazards. As there is no definitive data available on the systemic toxicity of cadmium hydroxide, data on the bioavailability of Cd^{2+} from this compound were used by the DS to predict its toxicity.

For those compounds with high water solubility, a high degree of bioavailability can be assumed. At lower levels of water solubility, bioavailability may also depend on other factors.

As shown in the following table, received from the International Cadmium Association during the Public Consultation, the water solubility of cadmium hydroxide is rather low.

Ranking of solubility	Cadmium compound	Water solubility (mg/L)[2]	Harmonized classification[1]		
			Carcinogenicity	Mutagenicity	STOT RE
Very soluble	Cadmium sulphate	540×10^3	1B; H350	1B; H340	1; H372
	Cadmium nitrate	507×10^3			
	Cadmium chloride	457×10^3	1B; H350	1B; H340	1; H372
	Cadmium fluoride	35×10^3	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, cadmium sulphate, chloride and fluoride also have harmonised classifications 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).

However, the DS also summarised a study showing 87% solubility of cadmium carbonate (94% for cadmium oxide and 5% for cadmium sulphide) in artificial gastric juice (pH = 1.47) during a 2-hour incubation period at 37°C. RAC notes though that the solubility in artificial body fluids depends on many factors, including the loading ratio (how much substance is added to how much solvent), the temperature, solubilisation time, presence of soluble impurities and particle size. However, t can be predicted that Cd^{2+} ions would be evolved in the stomach following oral ingestion of cadmium carbonate and that, in a similar fashion to the systemically toxic, highly

water soluble salts, there will be uptake into the general circulation. For example, the DS commented that Cd^{2+} can be absorbed from the proximal duodenum either by simple diffusion or can be mediated by the metal-ion transporter DMT1. Although there is no data to show that cadmium hydroxide is soluble in gastric juice, RAC considers that the evidence demonstrating that cadmium carbonate is highly soluble in gastric juice can be extrapolated to cadmium hydroxide because both have similarly low water solubilities. This study showed that low solubility in water does not necessarily equate to low solubility *in vivo* i.e. a cadmium compound that is poorly soluble in water may be considerably more soluble in gastric juice and thus the toxic Cd^{2+} ion will be evolved *in vivo* and become systemically available following oral exposure.

The ECHA guidance on the application of the CLP criteria (CLP Guidance) states that, "*Bioavailability of a substance or a mixture is normally assumed if there are in vitro studies available which show the solubility of a substance or mixture in body fluids or artificial simulated body fluids.*"

Cadmium oxide, a substance with similar water solubility to cadmium hydroxide, showed bioavailability following inhalational exposure of rats, evidence by systemic effects on fertility and reproductive organs, as well as general and developmental toxicity. This indicates that the systemic effects of Cd^{2+} ions are likely to occur following inhalational exposure to less water soluble cadmium compounds, including cadmium hydroxide.

RAC therefore agrees with the DS that it is reasonable to consider the systemic hazards of cadmium hydroxide using data from other inorganic cadmium compounds, for which Cd^{2+} bioavailability is apparent, although there is some uncertainty on the extent of solubility in (artificial) body fluids of these slightly water soluble cadmium compounds, and hence on the degree of bioavailability of Cd^{2+} (especially following inhalation exposure).

The DS has proposed a new entry specifically for cadmium hydroxide itself. This would carry across without any change the classification provided in the group entry and add classification for repeated dose toxicity (STOT RE 1; H372 – kidney, bone), germ cell mutagenicity (Muta. 1B; H340) and carcinogenicity (Carc. 1B; H350). However, only repeated dose toxicity, mutagenicity and carcinogenicity were assessed in the CLH report.

The DS has provided an assessment only of repeated dose toxicity, mutagenicity and carcinogenicity in their CLH report.

RAC has not addressed the scientific validity of the proposal from the Dossier Submitter to retain by default the existing classifications for acute toxicity and aquatic toxicity. No data were provided in the CLH report for such an assessment to be made and this was outside the scope of the public consultation. Similarly, although some inorganic cadmium compounds are classified for reproductive toxicity in Annex VI of the CLP Regulation, this endpoint was also not assessed by RAC.

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

The DS proposed the classification of cadmium hydroxide as STOT RE 1 (H372) with bone and kidney as target organs and used the updated Toxicological Profile for Cadmium issued by the Agency for Toxic Substances and Disease Registry (ATSDR) as a data source. In the CLH dossier, the DS assumed that the toxic species of cadmium salts is the cadmium ion and did not differentiate among different cadmium salts. The dossier provided evidence to support classification for STOT RE only from epidemiological studies and did not contain data from studies

in animals on the understanding that these studies would not add any information necessary for the classification.

Effects on kidney

Some 25 different epidemiological studies were used to support the classification of STOT RE 1 for kidney. In these studies it was demonstrated that the prevalence of abnormal values of biomarkers of kidney injury was correlated with cadmium exposure. The biomarkers of renal damage were mainly proteinuria (detection of low molecular weight proteins in urine such as β2-microglobulin, human complex-forming glycoprotein, N-acetyl-β-glucosaminidase and retinol binding protein). Sometimes reductions in glomerular filtration rate were also found to be associated with cadmium exposure. The studied populations included general population residents in more or less cadmium contaminated areas and occupational populations (smelters, workers using cadmium pigments in plastic production or in welding and battery workers). The routes of exposure were oral (for the general population) and inhalation (for occupational populations).

Effects on bone

Twenty different epidemiological studies were used to support the classification of STOT RE 1 for bone. In these studies, two types of populations were studied, general population (environmentally exposed by oral route) and occupational population (cadmium workers exposed by inhalation). Positive correlations were found between urinary cadmium level and reduced bone mineral density (osteoporosis, osteopenia, osteomalacia) and increased risk of bone fractures.

Comments received during public consultation

During Public Consultation the International Cadmium Association (a non-profit organisation acting on behalf the International Zinc Association) supported the proposed classification.

Two MS supported the classification of cadmium hydroxide as STOT RE 1 (H372).

One of the two MS requested to set an SCL but the DS responded that it is impossible to assess the potency of cadmium hydroxide itself since the hazardous property is extrapolated from other substances.

The other MS suggested including an overview about the significance of the biomarkers for kidney damage and in response the DS referred to the information included in the EU RAR for cadmium on this issue. This same MS drew attention to a study by Navas-Acien *et al.* (2009) on the impact of low-level cadmium exposure on clinical renal outcomes. RAC has addressed both comments in the section "Additional key elements" in the Background Document, see Annex 1.

Assessment and comparison with the classification criteria

The DS has used an array of epidemiological studies published in the open scientific literature and previously employed by the Agency for Toxic Substances and Disease Registry (ATSDR) to build its updated toxicological profile for cadmium. It is noted that in all cases the toxicity is attributed to the cadmium cation regardless of the original chemical species (cadmium salt, cadmium oxide or cadmium hydroxide).

Effects on kidney

The relevant findings from available epidemiological studies are summarised in the table below.

Method (inc. type of population)	Results	Remarks	Reference
General population (Belgium); 1699 males, females, 20-80 years old	Significant correlation between U-Cd and effect biomarkers.	When 24-hour U-Cd levels were >3.05, 2.87, 2.74, 4.29, or 1.92 µg the probability of displaying	Buchet *et al*. (1990)

Effect biomarker: β2M, RBP, NAG, amino acids, calcium	Dose-response relationship between U-Cd and prevalence of abnormal effect biomarker levels.	abnormal values of β2-M, RBP, amino acid, and calcium values would be higher than 10%, respectively.	
799 residents in cadmium-polluted area + 222 occupationally exposed subjects (Sweden) Effect biomarker: pHC	Mean U-Cd level: 0.81 µg/g creatinine (M), 0.66 µg/g creatinine (F) Linear relationship between U-Cd and pHC.	Relationship remained significant after removal of occupationally exposed subjects. U-Cd level associated with a 10% increased probability of abnormal pHC values was 2.62 µg/g creatinine for the total population.	Järup *et al*. (2000)
General population (United States); 88 males, 71 females, 6-17 years old; 71 males, 80 females ≥18 years old Effect biomarker: β2M, NAG, AAP, albumin	U-Cd levels: 0.07 µg/g creatinine (M, child), 0.08 µg/g creatinine (F, child), 0.24 µg/g creatinine (M, adult), 0.23 µg/g creatinine (F, adult). Significant association and dose-response relationship (after age and gender adjustment) between U-Cd and NAG and AAP in adults.	No significant associations (after correction for age, sex) between U-Cd and effects biomarkers in children. U-Cd levels in adults were not significantly associated with elevated levels of β2M or albumin.	Noonan *et al*. (2002)
Residents in cadmium-polluted area (Japan);878 males, 972 females. ⩾50 years old Effect biomarker: β2M	Dose-response relationship between cadmium in rice and effect biomarker.	Cadmium levels in rice were considered to be representative of cadmium intake because over 70% of the total cadmium intake has been shown to come from rice.	Nogawa *et al*. (1989)
General population (Japan); 558 males, 743 females, ≥50 years old Effect biomarker: β2M, total protein, NAG	Mean U-Cd level: 1.3 µg/g creatinine (both M and F). Significant correlation between U-Cd and effect biomarkers (NAG was only significant in females). Dose-response relationship between U-Cd and prevalence of abnormal effect biomarker levels	The odds ratios were 6.589, 3.065, and 1.887 for protein, β2M and NAG in males and 17.486, 5.625, and 2.313 for protein, β2M, and NAG in females.	Yamanaka *et al*. (1998)
General population (Japan); 568 males, 742 females, ≥50 years old Effect biomarker: total protein, NAG, β2M	Mean U-Cd level: 2.2-3.4 µg/g creatinine (M), 2.8-3.9 µg/g creatinine (F) Significant correlation (with age adjustment) between U-Cd and effect biomarkers.	-	Oo *et al*. (2000)
General population (Japan); 1105 males, 1648	Mean U-Cd level: 1.8 µg/g creatinine (M), 2.4 µg/g creatinine (F).	Blood cadmium levels were significantly associated with urinary	Suwazono *et al*. (2000)

females, ≥50 years old Effect biomarker: β2M, total protein, NAG	Significant correlation between U-Cd and protein and β2M. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	protein and NAG levels in males and urinary protein, β2M and NAG levels in females.	
Residents in cadmium-polluted area (China); 118 males, 170 females, high exposure group; 80 males, 158 females, moderate exposure group Effect biomarker: β2M, RBP, albumin	Mean U-Cd level: 11.18 (M) and 12.86 (F) µg/g creatinine (high exposure group), 3.55 (M) and 4.45 (F) µg/g creatinine (moderate exposure group) Significant correlation between U-Cd and effect biomarkers.	Dose-response relationship between U-Cd and prevalence of abnormal effect biomarker levels.	Jin *et al*. (2002)
Residents in cadmium-polluted area (China); 118 males, 170 females, high exposure group; 80 males, 158 females, moderate exposure group Effect biomarker: β2M, NAG, NAG-B, RBP, albumin	Dose-response relationship between U-Cd and prevalence of abnormal effect biomarker levels.	-	Jin *et al*. (2004a)
Zinc- cadmium smelter workers (n=87)	Effect: age-related decline in maximal GFR was exacerbated in workers with cadmium-induced microproteinuria. Adverse effect level (U-Cd): 11.1 µg/g creatinine.	-	Roels *et al*. (1991)
Workers using cadmium pigments in plastic production or using cadmium in welding (n=27)	Effect: significant increase in urinary β2M and NAG levels.	Adverse effect level (U-Cd): 5 µg/g creatinine.	Verschoor *et al*. (1987)
Cadmium alloy workers (n=164)	Effect: higher incidence of increased urinary β2M levels (>250 µg/L cut-off) when U-Cd levels exceeded 10 µg/g creatinine on one or more occasions, as compared to workers who never exceeded the 10 µg/g creatinine level.	Adverse effect level (U-Cd): 10 µg/g creatinine.	Toffoletto *et al*. (1992)
Cadmium smelter workers (n=53)	Effect: significant increase in urinary protein and β2M	Adverse effect level (U-Cd): 13.3 µg/g	Shaikh *et al*. (1987)

	levels.	creatinine.	
Non-ferrous smelter workers (n=58)	Effect: significant increase in urinary β2M, RBP protein, pHC, albumin, and transferrin levels.	Adverse effect level (U-Cd): >10 µg/g creatinine.	Bernard *et al*. (1990)
Workers exposed to cadmium pigment dust (n=58)	Significant correlation between U-Cd and NAG levels. Significant correlation with β2M at one of the two time points.	Adverse effect level (U-Cd): 1.1-1.4 µg/g creatinine.	Kawada *et al*. (1989)
Zinc- cadmium smelter workers (n=50)	Significant association between U-Cd levels and urinary levels of NAG, albumin, and transferrin. At higher urinary cadmium levels (10 µg/g creatinine), there were significant associations with RBP and β2M.	Adverse effect level (U-Cd): 4 µg/g creatinine.	Roels *et al*. (1993)
Battery workers (n=561)	10% prevalence of abnormal β2M levels (220 µg/g creatinine cut-off).	Adverse effect level (U-Cd): 1.5 µg/g creatinine for ⩾60 years of age; 5 µg/g creatinine for <60 years of age.	Järup and Elinder (1994)
Alkaline battery factory workers (n=102)	10% prevalence of renal dysfunction (β2M >380 µg/g creatinine; RBP >130 µg/g creatinine).	Adverse effect level (U-Cd): 10-15 µg/g creatinine.	Jakubowski *et al*. (1987)
Workers at a factory using cadmium-containing solders (n=60)	25% prevalence of abnormal β2M levels (300 µg/g creatinine cut-off).	Adverse effect level (U-Cd): 2-5 µg/g creatinine.	Elinder *et al*. (1985a)
Workers at nickel-cadmium battery factory (n=92)	Significant increase in pHC and NAG levels (after adjustment for age, gender, and race).	Adverse effect level (U-Cd): 5-10 µg/g creatinine.	Chia *et al*. (1992)
Cadmium smelter workers (n=85)	Significant increases in β2M and NAG levels and increased prevalence of abnormal levels of these biomarkers.	Adverse effect level (U-Cd): 5-10 µg/g creatinine.	Chen *et al*. (2006a, 2006b)
Alkaline battery factory workers (n=141)	10% prevalence of renal dysfunction (β2M >300 µg/g creatinine; RBP >300 µg/g creatinine).	Adverse effect level (B-Cd): 300 µg-years/L (30 years of 10 µg/L).	Jakubowski *et al*. (1992)
Battery workers (n=440)	Approximately 10% prevalence of abnormal β2M levels (35 µg/mmol creatinine cut-off).	Adverse effect level (B-Cd): 5.6 µg/L; cumulative exposure 691 µg-years/m^3.	Järup *et al*. (1988)
Cadmium recovery plant workers (n=45)	Significant association between cumulative exposure and urinary β2M, RBP, phosphate, and calcium and serum	Adverse effect level: cumulative exposure 300 mg/m^3.	Thun *et al*. (1989)

	creatinine levels.		
Workers exposed to cadmium fumes (n=33)	Increased urinary β2M and protein levels (mean 6375 µg/g creatinine and 246 mg/g creatinine, respectively) in 7 workers (mean in remaining 23 workers 53 µg/g creatinine and 34 mg/g creatinine).	Adverse effect level: cumulative exposure 1137 µg/m3/years.	Falck *et al*. (1983)

Abbreviations: AAP = alanine aminopeptidase; β2M = β2-microglobulin; F = female; M = male; NAG = N-acetyl-β-glucosaminidase; pHC = human complex-forming glycoprotein, also referred to as α1M; RBP = retinol binding protein; U-Cd = urinary cadmium; B-Cd = blood cadmium; GFR = glomerular filtration rate.

Effects on bone

The relevant findings from available epidemiological studies are summarised in the table below.

Method (inc. type of population)	Results	Reference
Women environmentally exposed to cadmium (Sweden)	Mean urinary cadmium level: 0.52 µg/L Negative relationship between blood cadmium levels and bone mineral density.	Åkesson *et al*. (2005)
Residents in cadmium-polluted area (Sweden)	Significant decreases in bone mineral density for >60 years of age with blood cadmium levels of ≥0.56 µg/L.	Alfvén *et al*. (2002)
Subjects, of which approximately 10% were environmentally or occupationally exposed to cadmium (Sweden)	Increased risk of bone fractures for >50 years of age with urinary cadmium levels of >2 µg/g creatinine.	Alfvén *et al*. (2004)
Subjects, of which approximately 10% were environmentally or occupationally exposed to cadmium (Sweden)	Increased risk of osteoporosis among men >60 years of age with urinary cadmium levels of >5 µg/g creatinine. Effect not observed in women.	Alfvén *et al*. (2000)
Residents living near zinc smelters (Belgium)	Decrease in proximal and distal forearm bone density of approximately 0.1 g /cm^2 was associated with a two-fold increase in urinary cadmium level in postmenopausal women.	Staessen *et al*. (1999)
Women living near zinc smelters	Suggestive evidence that cadmium has a direct osteotoxic effect.	Schutte *et al*. (2008)
Residents in cadmium-polluted area (Poland)	Significant decrease in bone mineral density in males with urinary cadmium levels of >2 µg/g creatinine.	Trzcinka-Ochocka *et al*. (2010)
Residents in cadmium-polluted area (China)	Significant increases in prevalence of low forearm bone mineral density in postmenopausal women with urinary cadmium levels of >20 µg/g creatinine. Significant increases in prevalence of low forearm bone mineral density in men, premenopausal	Nordberg *et al*. (2002)

	women, and postmenopausal women with blood cadmium levels of >20 µg/g creatinine.	
Residents in cadmium-polluted area (China)	Increase in bone fractures in males (mean urinary cadmium level 9.20 µg/g creatinine) and females (mean urinary cadmium level 12.86 µg/g creatinine).	Wang *et al*. (2003)
Residents in cadmium-polluted area (China)	Significant dose-response relationship between urinary cadmium levels and the prevalence of osteoporosis.	Jin *et al*. (2004b), Wang *et al*. (2003), Zhu *et al*. (2004)
Residents in areas with moderate or heavy cadmium pollution ten years after the source of rice was switched to commercially available rice from cadmium-non-polluted areas (China)	Significant decreases in forearm bone mineral density in women from the moderately polluted area and in men from the heavily polluted area. Decreases in bone mineral density in women 60-69 or ≥70 years old from both polluted areas, and in men ≥70 years old from the heavily polluted area. Significantly higher prevalence of osteoporosis in women from the polluted areas which increased with urinary cadmium levels.	Chen *et al*. (2009)
Residents in cadmium-polluted area (China)	Higher prevalence of osteoporosis in women with renal dysfunction or tubular damage. Significantly lower bone mineral density levels in women with tubular damage. No significant associations between the prevalence of osteoporosis or bone mineral density and alterations in renal biomarkers in men.	Chen *et al*. (2011)
Residents living near an industrial complex (Korea)	Significant associations between high urinary cadmium levels (≥1.0 µg/g creatinine) and osteopenia. Bone mineral density negatively associated with urinary cadmium levels.	Shin *et al*. (2011)
Health- survey population (Sweden)	Significantly lower urinary cadmium levels bone mineral density in postmenopausal women with elevated urinary cadmium levels (median 1.1 µg/g creatinine) compared to women with low urinary cadmium levels (median 0.36 µg/g creatinine). Significant changes of biomarkers indicative of increased bone resorption in the high urinary cadmium group.	Engström *et al*. (2009)
General population (USA)	Significant association between urinary cadmium levels and osteopenia and osteoporosis in adults with urinary cadmium levels of >1 µg/g creatinine.	Wu *et al*. (2010)
General population (USA)	43% increased risk of osteoporosis in women ≥50 years of age with urinary cadmium levels of 0.50-1.00 µg/g creatinine, as compared to women with urinary cadmium levels of <0.50 µg/g creatinine.	Gallagher *et al*. (2008)
Case study: alkaline battery workers	Osteomalacia observed.	Adams *et al*. (1969)
Case study: battery	Osteomalacia observed.	Blainey *et al*.

plate maker		(1980)
Case study: cadmium workers	Hypercalciuria and osteomalacia observed.	Kazantzis 1979
Case study: cadmium-exposed workers	Hypercalciuria and calcium deficit observed	Scott *et al*. (1980)

A potential issue of concern is a possible link between effects on bone and kidney. However, it is remarkable that in the studies by Schuttle *et al.* (2008) only 1 of 294 women examined displayed evidence of renal dysfunction (increased retinol binding protein). In a recent publication by Åkesson *et al.* (2014) it was concluded that the available data point towards a direct effect of cadmium on bone and therefore there are no links between adverse effects on bone and kidney since tubular proteinuria is associated with Cd exposure at > 4 µg/g creatinine and/or blood concentration > 4 µg/L; while the available information shows that associations with bone effects occur in population strata with Cd urinary levels as low as 0.5–2 µg/g creatinine. RAC agrees that both effects should be independently assessed and classified.

RAC notes that no information was available regarding the chemical species of cadmium to which the assessed populations were exposed. Therefore, there was no experimental evidence that cadmium hydroxide was specificallyable to induce any of the previously reported effects in humans. Bioavailability of cadmium arising from cadmium hydroxide might be another issue of concern, especially taking into consideration that its solubility in water is three orders of magnitude lower than the solubility of cadmium nitrate. These two considerations (absence of empirical information with the hydroxide and doubts about bioavailability) might lead to a different classification than the highly soluble salts.

However, the dossier contains results of an *in vitro* study where it was demonstrated that cadmium oxide (slightly soluble in water), cadmium carbonate (slightly soluble in water) and cadmium sulphide (practically insoluble in water) were dissolved after 2 hours at 37 °C in artificial gastric juice (pH 1.47) to the extent of 94%, 87% and 5%, respectively. The rationale to explain these results is that the acid pH of the stomach is able to solubilize cadmium regardless of the original chemical species. Furthermore, despite again no specific information for cadmium hydroxide having been found, it seems plausible that this mechanism also applies for cadmium hydroxide and according to section 1.3.2.1 of the CLP Guidance, this is enough grounds upon which to assume bioavailability for CLH purposes.

Other experimental studies have also probed that cadmium sulphide (the cadmium salt with the lowest solubility in water) is bioavailable after inhalation (although to a lower extent than other very soluble salts). Studies on absorption of cadmium chloride and cadmium sulphide in rats after inhalation exposure 6 hours per day during 10 days showed that accumulation of cadmium in the kidney at the end of the study was 35% and 1% for cadmium chloride and cadmium sulphide, respectively, indicating bioavailability for both.

Therefore, RAC concludes that cadmium hydroxide has enough solubility in body fluids to release cadmium ions into the blood and cause typicaladverse effects attributable to cadmium ions.

In conclusion, the DS supplied a large body of evidence linking the cadmium exposure (mainly through urinary cadmium excretion) in humans to the following alterations:

1. Excretion of low molecular weight proteins typically considered as biomarkers of kidney injury, such as β_2-microglobulin, human complex forming glycoprotein and retinol binding protein.
2. Excretion of calcium and N-acetyl-β-glucosaminidase (also suggesting kidney alterations).
3. Increases in the prevalence of abnormal levels of the former biomarkers in occupational population and non-occupational population living in areas contaminated with cadmium.

4. Increases in the occurrence of osteomalacia, osteoporosis and bone fractures in environmentally or occupationally exposed population versus control population.

According to the Guidance on the Application of the CLP Criteria (Version 4.0, November 2013) specific target organ toxicity (repeated exposure) means significant health effects that can impair function as consequence of a repeated exposure to a substance. The above described effects on kidney and bone can be considered as qualifying for STOT RE classification because they are toxicologically relevant and have affected the function of the kidney (caused proteinuria and increased calcium excretion) and bone morphology (caused osteoporosis and osteomalacia).

According to the Criteria in the CLP Regulation *"substances that have produced significant toxicity in humans"* are classified in Category 1 on the basis of *"reliable and good quality evidence from human cases or epidemiological studies".*

Thus, taking into consideration all the above stated information, **RAC agrees with the DS that cadmium hydroxide warrants classification as STOT RE 1; H372 (kidney, bone).**

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

The DS proposed a Muta. 1B; H340 classification for cadmium hydroxide.

The DS noted that studies in human somatic cells were generally affected by shortcomings limiting their value as evidence for a causal relationship between exposure to cadmium and mutagenicity. Hence, the data would not be sufficient for the purpose of classification according to CLP and, therefore, the studies were not evaluated in the CLH report.

The mutagenic potential of cadmium has been investigated *in vitro* in bacterial cells and mammalian cells, and *in vivo* in somatic cells of mice and rats and in germ cells of mice, rats and golden hamsters.

In vitro studies showed that cadmium induces chromosome aberrations and gene mutations in cultured mammalian cells, while most studies on the induction of gene mutations in bacteria produced negative results.

Cadmium chloride induced chromosome aberrations in somatic cells *in vivo* after intraperitoneal injection, as demonstrated by positive results from cytogenetic studies in the bone marrow of mice and micronucleus studies in the bone marrow of mice. In rats, a micronucleus study in blood was positive after oral administration of cadmium chloride.

Cadmium chloride induced DNA damage in somatic cells *in vivo* detected by the alkaline comet assay, as demonstrated by positive results from a study in blood of mice after oral administration, and a study in nasal epithelial cells, lung, whole blood, liver, kidney, bone marrow and brain of mice exposed by inhalation. One study in blood of orally exposed mice produced equivocal results.

Cadmium chloride induced numerical and structural chromosome aberrations in germ cells *in vivo*, as demonstrated by positive results from studies in mice exposed by intraperitoneal or subcutaneous injection. One study on numerical chromosome aberrations in germ cells of mice exposed to cadmium chloride by subcutaneous injection was negative.

Cadmium chloride administered by intraperitoneal injection did not induce dominant lethals in germ cells of mice and rats, or heritable translocations in mice.

The DS concluded that there was sufficient evidence that cadmium induces structural chromosome aberrations and micronuclei in somatic cells *in vivo*, and numerical and structural chromosome aberrations in germ cells *in vivo*. The potential of cadmium to induce chromosome

aberrations was not detected in germ cells using the dominant lethal test. However, according to the DS, the dominant lethal test is generally considered to be rather insensitive.

The DS considered the toxicity of cadmium salts to result from the intrinsic properties of the Cd^{2+} ion. As bioavailability of the Cd^{2+} ion could be assumed after oral and inhalation exposure to cadmium hydroxide, the mutagenic effects of other cadmium salts, such as cadmium chloride used in the studies summarised above, were considered relevant for cadmium hydroxide. Accordingly, the DS concluded that cadmium hydroxide is mutagenic in germ cells of experimental animals.

Classification in Category 1A was not considered justified because there are no available studies on the mutagenic potential of cadmium in human germ cells.

Based on the observations that structural chromosome aberrations were induced in somatic cells of mice, that micronuclei were induced in somatic cells of mice and rats, and that numerical and structural chromosome aberrations were induced in the germ cells of mice, the DS considered that there was sufficient evidence to demonstrate that cadmium hydroxide warrants classification as a Category 1B mutagen i.e. there were 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.

Comments received during public consultation

One MS agreed explicitly with the classification proposal for Muta. 1B; H340.

The International Cadmium Association (ICdA) did not consider that there was adequate justification for the proposed Muta. 1B; H340 classification. Based on the read across principles, the ICdA commented that the cadmium hydroxide should be classified according to the previous harmonised classification for cadmium compounds belonging to the same water-solubility range group i.e. cadmium oxide and cadmium metal and, therefore, that cadmium hydroxide should be classified as Muta. 2; H341. The ICdA referred to the fact that cadmium oxide received a Muta. Cat. 3: R68 classification (corresponding to CLP classification Muta 2; H340) rather than Muta. Cat. 2: R46 (corresponding to CLP classification Muta. 1B; H340) because there was no positive evidence for cadmium oxide itself. The positive results of *in vivo* somatic cell mutagenicity studies that led to the Muta. Cat. 3: R68 classification for cadmium oxide under the Dangerous Substances Directive **67/548**/**EEC** (DSD) were from other cadmium compounds.

In response to the comment from the ICdA, the DS stated that they did not agree with the approach taken by industry to classify cadmium hydroxide. The DS stated that available data support that cadmium salts release the toxic species Cd^{2+} which is bioavailable even with cadmium salts of low water solubility. Consequently, cadmium chloride (very soluble) is an appropriate analogue for cadmium hydroxide (slightly soluble). Since data from studies with cadmium chloride provided evidence that the hazardous properties of the Cd^{2+} ion include mutagenicity in germ cells, cadmium hydroxide should be classified in Muta. 1B; H340.

Assessment and comparison with the classification criteria

RAC agrees with the DS that the available data show clearly that highly water soluble cadmium salts, exemplified by cadmium chloride, have mutagenic potential. Cadmium chloride induces chromosome aberrations and gene mutations in cultured mammalian cells and this genotoxicity has been confirmed in somatic cells *in vivo* in several mouse bone marrow or peripheral erythrocyte micronucleus and chromosome aberration tests.

In germ cells, negative results have been reported in three mouse dominant lethal assays, a rat dominant lethal assay and a mouse heritable translocation assay. However, none of these tests were conducted according to the most stringent recommended conditions (e.g. in comparison to the OECD test guidelines) and the negative results cannot be regarded as robust evidence that systemically available Cd^{2+} will lack genotoxic activity in the germ cells.

In contrast, a positive response (increased tail length) was found recently in a comet assay of testicular DNA from mice exposed once and multiple times for 60 min to 0.08 μg/cm^3 cadmium chloride by inhalation (details provided in the CLH report). In this test, positive results were also found in DNA from several somatic tissues, including liver, kidney, bone marrow and brain. This study appears to show that bioavailable Cd^{2+} also has potential to damage germ cell DNA. Further support for this is provided in an unconventional, but well performed test for aneuploidy in the spermatocytes of mice treated once with 1, 3 or 6 mg/kg bw cadmium chloride by intra-peritoneal injection. Statistically significant increases in hyperploidy and hypoploidy were seen in comparisons made with a negative control group.

Additionally, a positive result was reported in an *in vivo* mouse spermatogonial chromosome aberration test, in which mice were administered cadmium chloride intra-peritoneally (0.9, 1.9, 5.7 and 9.5 mg/kg bw). Studies employing non-standard methodology to investigate genetic damage in mice and hamster oocytes in vivo gave inconsistent results; overall they provide limited weight in the analysis of the mutagenic potential of Cd^{2+}.

As concluded by the DS, RAC's opinion is that these data indicate that bioavailable Cd^{2+} has the potential to damage the genetic material in somatic and germ cells. Although some of the studies described above used non-physiological routes of administration, there was clear evidence from studies involving oral and inhalational exposure which are of the greatest relevance for assessing this hazard in humans.

On the basis of these studies, it can be concluded that systemically available Cd^{2+} poses a mutagenic hazard to germ cells in animals. As oral and inhalational exposure to cadmium hydroxide can be expected to yield systemically available Cd^{2+} ions, it can be assumed that cadmium hydroxide will thus possess this hazard. Therefore classification in Category 1B for mutagenicity is justified. In the absence of any data informing on germ cell mutagenicity in humans, Category 1A is inappropriate.

An alternative option would be to take note of the current Category 2 mutagenicity classification of cadmium metal and cadmium oxide in Annex VI of the CLP Regulation. These substances have a very similar water solubility to cadmium hydroxide and might therefore be considered to be better models for the potential bioavailability of Cd^{2+} from this compound than the highly water soluble salts. However, there are very limited data available on the mutagenicity of these less water soluble substances. In addition to negative results in the bacterial mutagenicity tests, a negative result was reported in a peripheral blood erythrocyte micronucleus test in mice exposed for 13-weeks to cadmium oxide by inhalation (Dunnick *et al*, 1995; cited by the International Cadmium Association in their submission during the public consultation). Full details of this micronucleus test were not provided to RAC during public consultation, and it was not included in the CLH report from the DS. However, this test was not performed according to a standard regulatory protocol and the study only addressed inhalational exposure. It cannot be taken as evidence for a lack of Cd^{2+} bioavailability and absence of a mutagenic hazard, especially as in other tests conducted by the same laboratory, inhalation of this substance did cause systemic effects in rats (reproductive toxicity). It seems likely that the sensitivity of the micronucleus test was not optimised.

On the basis that mutagenicity is a hazard that can be caused even by very low concentrations of a genotoxic species (i.e. mutagenicity is regarded routinely for regulatory purposes as a "non-threshold" hazard), RAC's opinion is that even relatively limited bioavailability of Cd^{2+} will present an inherent mutagenic hazard to germ cells. On this basis, RAC concluded that classification in **category 1B for mutagenicit**y was warranted.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

The DS proposed a Carc. 1B; H350 classification for cadmium hydroxide.

Human epidemiological studies were generally affected by shortcomings limiting their value as evidence for a causal relationship between exposure to cadmium and cancer. Hence, the data would not be sufficient for the purpose of classification according to CLP and, therefore, the studies were not evaluated in the CLH report.

The carcinogenic potential of cadmium has been investigated in rats, mice and Syrian hamsters.

In rats, oral exposure to cadmium chloride induced proliferative lesions (hyperplasia and adenoma) in the prostate, leukaemia (large granular lymphocytes) and testicular tumours (interstitial cell tumours). Inhalation exposure to cadmium chloride aerosols induced primary lung carcinomas (mostly adenocarcinomas but also epidermoid carcinomas and mucoepidermoid carcinomas) and adenomatous hyperplasia.

In another rat study, inhalation of cadmium chloride, cadmium sulphate, cadmium sulphide, cadmium oxide dust or cadmium oxide fume induced primary lung tumours (mostly adenomas and adenocarcinomas but bronchioalveolar adenomas and squamous-cell carcinomas were also observed in a few rats) after inhalation exposure.

In mice, cadmium oxide dust and cadmium oxide fume, but not cadmium chloride, cadmium sulphate, cadmium sulphide, induced lung tumours (histopathological types not reported) after inhalation exposure.

In Syrian hamsters, cadmium chloride, cadmium sulphate, cadmium sulphide, cadmium oxide dust and cadmium oxide fume did not induce tumours after inhalation exposure.

In other studies in which cadmium chloride was administered by subcutaneous injection, it induced lymphomas, lung tumours and injection-site sarcomas in mice and testicular and prostate tumours together with injection-site sarcomas in rats.

The DS concluded that these studies demonstrated the carcinogenicity of the Cd^{2+} ion in both rats and mice. As it was apparent that Cd^{2+} would be bioavailable after oral and inhalational exposure to cadmium hydroxide, these data were also considered of relevance to this substance.

Based on the observations that treatment-related tumours were observed in two species (rat and mouse), in three different studies in one species (rat), in both sexes of one species (rat), and that tumours occurred at multiple sites and/or were of different types, the DS concluded that there was sufficient evidence to demonstrate the carcinogenicity of Cd^{2+} in animals, and therefore that cadmium hydroxide meets the criteria for a Category 1B carcinogen.

The DS did not provide a comprehensive assessment of the available epidemiological data relating to the carcinogenicity of cadmium compounds (and thus Cd^{2+}) in humans. Briefly, the DS commented that several occupational cohort studies have reported increases in lung cancer risk for exposed workers but reviews under the EU Existing Substances Regulation and by IARC identified significant shortcomings that prevented definitive conclusions about the cadmium carcinogenicity being made from these studies. The DS presented the conclusion about epidemiological studies that had assessed links between cadmium exposure and cancer of the prostate, kidney, bladder, breast and endometrium.

Although the DS acknowledged that IARC (2012) had concluded there is sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds, the DS concluded that the available studies in humans did not provide sufficient evidence for a Cat. 1A classification under CLP. The justification for this position was that the criteria require human evidence from studies establishing a causal relationship between human exposure to a substance and the development of cancer. The DS was not able to rule out with reasonable confidence that the positive association between exposure to cadmium and cancer observed in some of the studies was a result of chance, bias or confounding factors.

Comments received during public consultation

The International Cadmium Association supports the proposed classification for cadmium hydroxide as Carc. 1B; H350.

One MS has suggested that Carc. 1A may be a more appropriate classification for cadmium hydroxide based on the fact that in 2012, IARC considered that there was sufficient evidence available in humans to demonstrate carcinogenicity of cadmium compounds.

In response to the comment from the MS, the DS explained that the IARC also considered that the assessment of human studies was constrained by various flaws or that results of different studies are inconsistent.

One MS also asked why the DS had not proposed a specific concentration limit for the carcinogenicity classification of cadmium hydroxide, given that a limit of 0.01% was in place for cadmium chloride. The DS explained that they considered it inappropriate to extrapolate estimates of potency from one substance to another, even when they may have a comparable inherent hazard.

Assessment and comparison with the classification criteria

RAC acknowledges that the highly water soluble salts cadmium chloride, cadmium sulphate and cadmium fluoride are all classified as category 1B carcinogens in Annex VI of the CLP Regulation on the basis that they possess common hazards related to the ready bioavailability of the Cd^{2+} ion. Notably, evidence that cadmium chloride induces cancer in rats following oral and inhalational exposure, together with the mutagenicity of this substance in somatic tissues, justified this classification.

On re-assessment of the available information, RAC observed that there were only increased lung tumours in rats following inhalation exposure to inorganic cadmium compounds. Exposure to the more highly soluble chloride and sulphate salts might be expected to have led to higher uptake of Cd^{2+} ions, but there was no evidence of an increased tumour response when compared to rats exposed to the less soluble cadmium compounds. However, the increased lung tumours seen with all these compounds strongly supports their classification in category 1B for carcinogenicity. Although it has not been tested, RAC considers that cadmium hydroxide would also present a lung cancer hazard if inhaled by rats. The mixed findings in cancer studies with mice and hamsters do not detract from this conclusion. Although not described in any detail by the DS, IARC noted that poor study design (e.g. lack of complete histopathological examinations) and reporting inadequacies limited the conclusions that could be made for these animal species. The mechanisms by which the various different inorganic compounds induce lung cancer have not been elucidated, although a direct genotoxic activity cannot be ruled out.

Only very limited information is available about the carcinogenicity of the inorganic cadmium compounds to animals exposed orally. In male rats fed 0, 25, 50, 100 or 200 ppm cadmium chloride for 77 weeks, there were statistically significant increases in leukemia at 50 and 100 ppm. Evidently general toxicity may have prevented an increase being seen in the top dose group. The relatively short exposure period may have limited the sensitivity of this carcinogenicity test. Increased focal atypical hyperplasia and adenomas were seen in the ventral prostate but a clear dose-response was lacking and no similar lesions were seen in the dorso-lateral prostate. No carcinomas were seen in the prostate of these animals. There was an increased incidence of interstitial cell tumours of the testes in the highest dose group. Subsequent studies (reviewed by IARC but not by the DS) have shown that cadmium perturbs the hypothalamic-pituitary-testes axis in rats and that the increased testicular tumours were likely related to cadmium-induced testicular function and reduced circulating testosterone levels.

Given the increased lung cancer incidences seen in rats exposed to inorganic cadmium compounds of high, moderate and poor water solubility, RAC considers that repeated inhalation of cadmium hydroxide can reasonably be assumed to present such a carcinogenic hazard and that it should be classified in the same way as these other cadmium compounds.

The DS described a study which showed 87% solubility of cadmium carbonate (which has a low water solubility similar to that of cadmium hydroxide) in artificial gastric juice (pH 1.47) during a 2 hour incubation period at 37°C. This suggests that Cd^{2+} species can evolve in the highly acidic regions of the gastro-intestinal tract following oral exposure to cadmium compounds with low water solubilities, and be available for systemic absorption. Therefore, RAC is of the opinion that the data relating to the possible carcinogenicity of water soluble cadmium chloride following oral treatment of rats is also relevant for cadmium hydroxide.

During the public consultation, one MS queried whether a category 1A classification might be more appropriate for cadmium hydroxide, citing the recent review of IARC on cadmium and its compounds. . The DS did not provide an assessment of the relevant data and, had a category 1A classification have been proposed, it would have been inconsistent with the existing 1B classification for the other cadmium compounds. Taking this into consideration, RAC concluded that it would be inappropriate to initiate an independent review of its own on the human carcinogenicity of cadmium hydroxide in the absence of a proposal from the DS.

In conclusion, RAC agrees with the proposal of the DS to classify cadmium hydroxide as a **category 1B carcinogen** in line with the existing harmonised classification of other inorganic cadmium compounds. The carcinogenic findings in the lungs of rats especially are of relevance to humans.

RAC notes the response of the DS to the query from one MS about the setting of a specific concentration limit for this endpoint and agrees that it would be inappropriate to extrapolate estimates of potency from the very soluble cadmium compounds to the less soluble cadmium hydroxide, despite the inherent hazards being comparable.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and by RAC (excluding confidential information).