Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Cadmium nitrate

EC Number: 233-710-6
CAS Number: 10325-94-7

CLH-O-0000001412-86-79/F

Adopted

4 December 2015

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CLH-O-0000001412-86-79/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 nitrate**

EC Number: **233-710-6**

CAS Number: **10325-94-7**

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 nitrate	233-710-6	10325-94-7	Muta. 1B Carc. 1B STOT RE 1	H340 H350 H372 (kidney, bone)	GHS08	H340 H350 H372 (kidney, bone)		-	A1
RAC opinion	TBD	cadmium nitrate	233-710-6	10325-94-7	Muta. 1B Carc. 1B STOT RE 1	H340 H350 H372 (kidney, bone)	GHS08	H340 H350 H372 (kidney, bone		Carc. 1B; H350: C ⩾ 0,01 %	A1
Resulting Annex VI entry if agreed by COM	TBD	cadmium nitrate	233-710-6	10325-94-7	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		Carc. 1B; H350: C ⩾ 0,01 %	A1

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Background information in support of the proposal

Cadmium nitrate 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 nitrate 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).

Cadmium nitrate is highly soluble in water and in this respect it is similar to the chloride, sulphate and fluoride salts of cadmium, for which individual entries for harmonised classification already exist in Annex VI. The DS has described how the Cd^{2+} is readily bioavailable on exposure to these substances and that it is this species that is responsible for their systemic toxicity following oral and inhalational exposure. The chloride, sulphate and fluoride salts are classified differently to the salts covered by the general entry, with a more severe classification for acute inhalational toxicity (Acute Tox. 2*; H330), and additional classifications for repeated oral and inhalational toxicity (STOT RE 1; H372**), germ cell mutagenicity (Muta. 1B; H340), carcinogenicity (Carc. 1B; H350) and reproductive toxicity (Repr. 1B; H360FD).

The Table below summarises the water solubilities and relevant classifications of the cadmium sulphate, chloride, fluoride and nitrate (data received from the International Cadmium Association during the public consultation).

Ranking of solubility	**Cadmium compound**	**Water solubility (mg/L)**[2]	**Harmonized classification**[1]		
			Carcinogenicity	**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

[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).

RAC agrees with the DS that the systemic toxicity of these cadmium salts will be dependent on the bioavailability of the Cd^{2+} ion following exposure. This is in line with previous regulatory decisions made in the EU in relation to the classification of these substances. As they are all very water soluble, it is anticipated that they will all have comparable bioavailability and will possess similar systemic hazards.

The DS has provided an assessment only of repeated dose toxicity, mutagenicity and carcinogenicity in their CLH report. Although it could be argued that the remaining elements of the classification of the other highly soluble salts could also be applied to the nitrate, the DS chose instead only to retain the additional classification provided in the group entry 048-001-00-5. It

was assumed by the DS that by doing this they did not need to provide a toxicological assessment for the other endpoints.

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 nitrate 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 associated to 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 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 nitrate as STOT RE 1 (H372).

One of the two MS requested to set an SCL but the DS replied that it is impossible to assess the potency of cadmium nitrate 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 and females, 20-80 years old. Effect biomarker: β2M, RBP, NAG, amino acids, calcium.	Significant correlation between U-Cd and effect biomarkers. Dose-response relationship between U-Cd and prevalence of abnormal effect biomarker levels.	When 24-hour U-Cd levels were >3.05, 2.87, 2.74, 4.29, or 1.92 µg, the probability of displaying abnormal values of β2-M, RBP, amino acid, and calcium values would be higher than 10%, respectively.	Buchet *et al*. (1990).
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	Dose-response relationship between cadmium in rice	Cadmium levels in rice were considered	Nogawa *et al*. (1989).

area (Japan);878 males, 972 females, ⩾50 years old. Effect biomarker: β2M.	and effect biomarker.	to be representative of cadmium intake because over 70% of the total cadmium intake has been shown to come from rice.	
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 females, ≥50 years old. Effect biomarker: β2M, total protein, NAG.	Mean U-Cd level: 1.8 µg/g creatinine (M), 2.4 µg/g creatinine (F). Significant correlation between U-Cd and protein and β2M. Dose-response relationship between urinary cadmium and prevalence of abnormal effect biomarker levels.	Blood cadmium levels were significantly associated with urinary protein and NAG levels in males and urinary protein, β2M and NAG levels in females.	Suwazono *et al*. (2000).
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	Dose-response relationship between U-Cd and prevalence of abnormal effect biomarker levels.	-	Jin *et al*. (2004a).

females, moderate exposure group. Effect biomarker: β2M, NAG, NAG-B, RBP, albumin.			
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 levels.	Adverse effect level (U-Cd): 13.3 µg/g creatinine.	Shaikh *et al*. (1987).
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	Järup and Elinder (1994).

		creatinine for <60 years of age.	
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 creatinine levels.	Adverse effect level: cumulative exposure 300 mg/m^3.	Thun *et al*. (1989).
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/m^3/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 women, and postmenopausal women with blood cadmium levels of >20 µg/g creatinine.	Nordberg *et al*. (2002).
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	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.	Chen *et al*. (2009).

cadmium-non-polluted areas (China).	Significantly higher prevalence of osteoporosis in women from the polluted areas which increased with urinary cadmium levels.	
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 plate maker.	Osteomalacia observed.	Blainey *et al*. (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 concentrations > 4 µg/L; while the available information shows that associations with bone effects

occur in population strata with low 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 nitrate was specifically able to induce any of the previously reported effects in humans.

However, cadmium nitrate belongs to the group of cadmium salts with high solubility (540 g/L) in water. Thus, bioavailability is not expected to be a limiting factor and RAC considers that the exposure to cadmium nitrate entails the release of cadmium into the blood that can reach bones and kidney to induce the reported adverse effects.

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 (CLP Guidance; 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 as Category 1 on the basis of *"reliable and good quality evidence from human cases or epidemiological studies".*

Thus, taking in to consideration all the above stated information, RAC agrees with the DS that cadmium nitrate warrants classification for **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 nitrate and provided the following data and supporting statements.

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. Most studies on the induction of gene mutations in bacteria produced negative results, among the latter a study including cadmium nitrate.

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.

Following intraperitoneal and subcutaneous injection of cadmium chloride in mice, numerical and structural chromosome aberrations were induced in germ cells *in vivo*. One study on numerical chromosome aberrations in germ cells of mice exposed to cadmium chloride by subcutaneous injection was negative. In contrast, 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 considered that there was sufficient evidence to conclude 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, it is the view of the DS that the dominant lethal test is generally considered to be rather insensitive.

The DS described how the toxicity of cadmium salts results from the intrinsic properties of the Cd^{2+} ion. Since it is reasonable to assume that the Cd^{2+} ion is bioavailable after oral and inhalation exposure to cadmium nitrate, the mutagenic effects of other cadmium salts, such as cadmium chloride, are also relevant for cadmium nitrate. Accordingly, the DS concluded that cadmium nitrate 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 from studies with cadmium chloride showing that structural chromosome aberrations were induced by Cd^{2+} 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 concluded that there were sufficient grounds to conclude that cadmium nitrate meets the criteria for classification as a Category 1B mutagen i.e. that 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.

Comments received during public consultation

Two MS and the International Cadmium Association supported the classification of cadmium nitrate in Cat. 1B for germ cell mutagenicity.

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.

RAC agrees with the DS that cadmium nitrate, being highly water soluble, has an equivalent mutagenic hazard to cadmium chloride.;RAC's opinion is that based on the evidence, cadmium nitrate should also be classified in **Cat 1B for mutagenicity**.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

The DS proposed a Carc. 1B; H350 classification for cadmium nitrate based on the following evidence.

In rats, oral exposure to cadmium chloride induced proliferative lesions in the prostate, leukaemia and testicular tumours. Inhalation exposure to cadmium chloride aerosols induced primary lung carcinomas and adenomatous hyperplasia. In another study, cadmium chloride, cadmium sulphate, cadmium sulphide, cadmium oxide dust and cadmium oxide fume all induced primary lung tumours (mostly adenomas and adenocarcinomas but bronchioalveolar adenomas and squamous-cell carcinomas were also observed in a few rats) following inhalation exposure.

In mice, cadmium oxide dust and cadmium oxide fume, but not cadmium chloride, cadmium sulphate and cadmium sulphide, induced lung tumours 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 nitrate, 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 nitrate meets the criteria for a Category 1B carcinogen. There was no basis to specify any specific route of exposure for the classification.

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 (ICdA) agreed with the proposed Carc. 1B; H350 classification for cadmium nitrate. They noted that cadmium nitrate belonged to a group of highly water soluble substances that are already classified in this way and that animal carcinogenicity of cadmium nitrate could be assumed. The ICdA also commented that there was no available evidence from human epidemiological studies to justify a Carc. 1A classification.

One MS suggested that Carc. 1A may be a more appropriate classification because in 2012, IARC considered that sufficient evidence was available in humans to demonstrate the carcinogenicity of cadmium compounds. In response, the DS explained that IARC also considered that the assessment of human studies was constrained by various flaws or that results of different studies are inconsistent.

The same MS also asked why the DS had not proposed a specific concentration limit for the carcinogenicity classification of cadmium nitrate, 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. 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.

As cadmium nitrate is also highly water soluble, Cd^{2+} will also be readily bioavailable following oral and inhalational exposure to this substance. Although no carcinogenicity data are available specifically for cadmium nitrate, RAC is of the opinion that there is sufficient basis to classify its as a category1B carcinogen.

During the public consultation, one MS queried whether a category 1A classification might be more appropriate for cadmium nitrate, 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 of the other highly soluble 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 nitrate in the absence of a proposal from the DS.

In conclusion, RAC agrees with the proposal of the DS to classify cadmium nitrate in **category 1B for carcinogenicity**.

RAC notes the response of the DS to the query from one MS about the setting of a specific concentration limit for this endpoint. However, RAC considers that it would be appropriate to apply a limit of 0.01% to the classification of cadmium nitrate. Although there is no data on the carcinogenic potency of this substance specifically, the same limit is already in place for each of the other highly soluble salts, cadmium chloride, cadmium sulphate and cadmium fluoride. It is RAC's view that it is reasonable, given the bioavailability of the Cd^{2+} ion, to assume that all these highly water soluble cadmium compounds would have a comparable carcinogenic potency in animals.

Therefore, RAC concludes in contrast to the DS that a **specific concentration limit of 0.01%** could also be applied for this endpoint for cadmium nitrate.

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).