

Substance Name: Cadmium nitrate

EC Number: 233-710-6

CAS Number: 10325-94-7

MEMBER STATE COMMITTEE

SUPPORT DOCUMENT

FOR IDENTIFICATION OF

CADMIUM NITRATE

AS A SUBSTANCE OF VERY HIGH CONCERN  
BECAUSE OF ITS CARCINOGENIC (ARTICLE 57A),  
MUTAGENIC (ARTICLE 57B), SPECIFIC TARGET  
ORGAN TOXICITY AFTER REPEATED EXPOSURE  
PROPERTIES CAUSING PROBABLE SERIOUS  
EFFECTS TO HUMAN HEALTH WHICH GIVE RISE  
TO AN EQUIVALENT LEVEL OF CONCERN TO  
THOSE OF CMR<sup>1</sup> AND PBT/vPvB<sup>2</sup> PROPERTIES  
(ARTICLE 57(F))

Adopted on 30 November 2017

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<sup>1</sup> CMR means carcinogenic, mutagenic or toxic for reproduction

<sup>2</sup> PBT means persistent, bioaccumulative and toxic; vPvB means very persistent and very bioaccumulative

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## IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance Name: Cadmium nitrate

EC Number: 233-710-6

CAS number: 10325-94-7

- The substance is identified as a substance meeting the criteria of Article 57 (a) of Regulation (EC) No 1907/2006 (REACH) owing to its classification in the hazard class carcinogenicity category 1B<sup>3</sup>.
- The substance is identified as a substance meeting the criteria of Article 57 (b) of Regulation (EC) No 1907/2006 (REACH) owing to its classification in the hazard class germ cell mutagenicity category 1B<sup>4</sup>.
- The substance is identified as a substance of equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of Regulation (EC) No 1907/2006 (REACH) according to Article 57(f) of REACH Regulation owing to the scientific evidence of probable serious effects to human health because of adverse effects on kidney and bone after prolonged exposure (classification STOT RE 1)<sup>5</sup>.

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

### *Carcinogen 1B – Article 57(a)*

Cadmium nitrate is listed by Index number 048-014-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified in the hazard class carcinogenicity category 1B (hazard statement H350: "May cause cancer").

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that it meets the criteria for classification in the hazard class:

- Carcinogenicity category 1B in accordance with Article 57(a) of REACH.

### *Mutagen 1B – Article 57(b)*

Cadmium nitrate is listed by Index number 048-014-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified in the hazard class germ cell mutagenicity category 1B (hazard statement H340: "May cause genetic defects").

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that it meets the criteria for classification in the hazard class:

- Germ cell mutagenicity category 1B in accordance with Article 57 (b) of REACH.

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<sup>3</sup> Classification in accordance with section 3.6 of Annex I to Regulation (EC) No 1272/2008.

<sup>4</sup> Classification in accordance with section 3.5 of Annex I to Regulation (EC) No 1272/2008.

<sup>5</sup> Classification in accordance with section 3.9 of Annex I to Regulation (EC) No 1272/2008.

*Equivalent level of concern – Article 57(f)*

Cadmium nitrate is listed by Index number 048-014-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified as STOT RE1 (hazard statement H372: Causes damage to organs through prolonged or repeated exposure).

Since the toxic effects of all cadmium compounds are caused by the cadmium ion, the conclusions for “cadmium” are relevant for cadmium nitrate.

Based on the above, evidence that the substance is of an equivalent level of concern include:

A significant part of the European population is today exposed to levels of cadmium (originating from cadmium metal and cadmium compounds) that may cause effects on kidney and bone. Data indicate that over time, there seems to be only slight or no decrease of cadmium levels in humans. In non-smokers, food is the main intake source and it is therefore important to reduce all input of cadmium to foodstuff. Deposition from air is an important source to the input of cadmium to soil and must therefore be reduced. In order to achieve this all uses of cadmium and cadmium compounds should, wherever possible, be substituted.

Almost 30 years ago, it was acknowledged within the EU that cadmium exposure constitutes a problem for human health and the environment, and new action should be taken at Community level to control and reduce cadmium pollution (Council Resolution 1988). Major elements of the strategy for cadmium control in the interests of the protection of human health and the environment included for example:

- limitation of the uses of cadmium to cases where suitable alternatives do not exist;
- stimulation of research and development: - of substitutes and technological derivatives, in particular, encouragement to the development of further alternatives to the use of cadmium in pigments, stabilisers and plating;
- collection and recycling of products containing cadmium, for example batteries;
- development of a strategy designed to reduce cadmium input in soil;
- combatting significant sources of airborne and water pollution.

Cadmium is a toxic metal that ranks as no. 7 on the US Agency for Toxic Substances & Disease Registry's priority list of hazardous substances (<https://www.atsdr.cdc.gov/spl/index.html>), a prioritisation of substances based on a combination of their frequency, toxicity, and potential for human exposure. As a pollutant of worldwide concern, cadmium has been reviewed by the United Nations Environment Program, and included on the list of chemical substances considered potentially dangerous at the global level.

To assess whether a substance can be identified as SVHC based on REACH Article 57(f), the hazardous properties of the substance, the potential impact on health and the potential impact on society as a whole have to be compared to those effects elicited by CMR (or PBT/vPvB) substances. The following factors that are characteristic for most CMRs have been taken into account:

- Severity of health effects
- Irreversibility of health effects
- Delay of health effects
- Uncertainties on safe exposure
- Societal concern and impairment of quality of life

*Severity of health effect:* The severity of health effects due to exposure to cadmium is dependent on the concentration attained in body tissues and organs. Kidney effects range

from indications of impaired tubular and glomerular function (measured by the presence of proteins in the urine) to an increased risk of end stage renal disease, which necessitates dialysis treatment for survival. The effects on bone range from disturbances on bone tissue homeostasis to actual bone fractures, which especially for older people are considered quite serious and can contribute to a premature death. In a population-based study in patients aged 65 or older the risk of mortality in hip fracture patients was 3-fold higher than in the general population and included every major cause of death. The quality of life for affected individuals is clearly impaired (for example after a hip fracture), but may also have consequences for society as a whole if many individuals are affected. When comparing with CMR effects, it should be acknowledged that also these effects vary in severity.

*Irreversibility of health effects:* According to the EU RAR on Cd and CdO, some controversy exists as to the reversibility of renal effects of cadmium both in the general population and in workers. The (ir)reversibility of tubular proteinuria after reduction or cessation of exposure depends on the intensity of exposure and/or the severity of the tubular damage. It was concluded that, as for inhalation exposure, incipient tubular effects associated with low cadmium exposure in the general population are reversible if exposure is substantially decreased. Severe tubular damage (urinary leakage of the proteins RBP or  $\beta$ 2M > 1,000-1,500  $\mu$ g/g creatinine) is generally irreversible.

A longitudinal study on 74 inhabitants from a cadmium-polluted area in Japan showed irreversible and even progression of renal dysfunction 5 years after cessation of cadmium exposure. Likewise, a study from China indicates that the negative effects on bone still remains 10 years after the population abandoned ingestion of cadmium-polluted rice.

The biological half-life of cadmium in humans is extremely long (estimated to be 10-30 years) and the body burden of cadmium therefore increases, mainly via accumulation in the kidney, during the entire life span of an individual. All uses of cadmium and its compounds, including when present as a contaminant, contribute to this bioaccumulation in humans, which starts already in early life.

Unless exposure is substantially decreased kidney and bone effects therefore tend to be irreversible due to the continued internal exposure from stored cadmium. In that respect cadmium behaves in a way that resembles substances that are persistent and bioaccumulating in the environment.

*Delay of health effects:* The bioaccumulation over the lifetime of an individual also affects when effects appear; in most instances, the delay between first exposure and appearance of effects is very long, i.e. decades.

*Uncertainties on safe exposure:* There is uncertainty about identifying safe exposure levels for cadmium. Biomedical research on cadmium is intense. A search of the literature database PubMed revealed 19 000 articles published during the last 10 years and more than 10 000 articles during the last 5 years. Consequently, new findings on hazards and risks connected with cadmium and its compounds continuously appear. As an example, effects on bone tissue have recently been shown at exposure levels previously considered without effects. Since what can be considered as a "safe exposure level" is steadily decreasing, precautionary community wide actions are warranted.

Further, it is not clear whether an effect on bone/kidney or carcinogenesis is the critical end-point from a risk assessment point of view, although most risk assessments concerning cadmium exposure of the general population (for example the assessment from EFSA (2009, 2012)) are based on kidney effects. In the risk assessment for workers by SCOEL (2009), the proposed limit values are also based on effects on the kidney and, to some extent, bone tissue, representing the most sensitive targets of cadmium toxicity after occupational exposure. The suggested IOEL (in air) is considered to be protective

against long-term local effects (respiratory effects including lung cancer). Whether this value is also protective against cancer in other tissues was not assessed. According to a paper from the Austrian Workers' Compensation Board, the German Committee on Hazardous Substances (AGS) has endorsed a limit value of 16 ng Cd/m<sup>3</sup> based on the acceptable cancer risk of 1 : 25,000, i.e. a value 250-fold lower than the IOEL suggested by SCOEL.

*Societal concern and impairment of quality of life:* In particular the effects on bone tissue, with increased risk for bone fractures, are a considerable public health problem causing a lot of suffering and a burden to society in terms of cost, morbidity and mortality. Osteoporotic complications are particularly prevalent in northern Europe and, statistically, every second woman in Sweden will suffer from an osteoporotic fracture during her lifetime. The incidence of hip fractures is more than seven-fold higher in Northern Europe than in the rest of Europe. The reason(s) for the large age-standardised geographical differences is still not known, but the differences cannot be explained by differences in risk of slipping, low calcium intake, vitamin D deficiency or by inactivity. The fracture incidence has increased substantially since the 1950s. As the number of old and very old people in the population increases, a further increase in the prevalence of fractures is to be expected.

According to a report published by the Swedish Chemicals Agency, the Swedish annual societal economic cost of fractures caused by cadmium in food amounts to approximately 4.2 billion SEK (approx. 420 million Euros). This figure is based on the estimation that 7 and 13 %, in males and females respectively, of all fractures in Sweden are caused by cadmium exposure, mainly via food, and include direct treatment and care costs for bone fractures (approx. 1.5 billion SEK or 150 million Euros), as well as a valuation of a lower quality of life and shortened life expectancy for those who suffer fractures, mostly the elderly.

*In summary:*

Cadmium nitrate is considered to fulfil the criteria according to Art. 57(f), i.e. there is scientific evidence of probable serious effects to human health that give rise to "equivalent level of concern" to those of other substances listed in paragraphs (a) to (e) of Article 57 of REACH Regulation, due to:

- the adverse effects on kidney and bones, effects that depending on dose may be serious and even contribute to premature death,
- the continuous accumulation of cadmium in the body, which leads to continuous internal exposure and in practice irreversible effects once adverse effect levels are reached
- the occurrence of adverse effects in a significant part of the general population at present exposure levels, which are primarily of anthropogenic origin,
- uncertainties in deriving a safe exposure level, and
- high societal costs in terms of health care and shortening of life time and a decreased quality of life.

Conclusion: Cadmium nitrate is identified as a substance of very high concern in accordance with Article 57(a), (b) and (f) of Regulation (EC) 1907/2006 (REACH) because it is a carcinogenic and mutagenic substance which also causes adverse effects on multiple organs after prolonged exposure, in particular *kidney* and *bone*, for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of REACH Regulation.

Registration dossiers submitted for the substance: Yes

## Justification

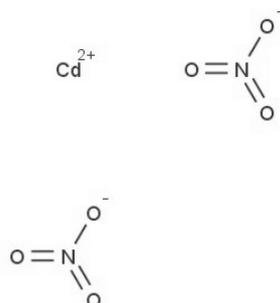
### 1. Identity of the substance and physical and chemical properties

#### 1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	233-710-6
EC name:	Cadmium nitrate
CAS number (in the EC inventory):	10325-94-7
CAS number: Deleted CAS numbers:	
CAS name:	Cadmium nitrate
IUPAC name:	Cadmium dinitrate Cadmium nitrate Cadmium(2+) ion dinitrate
Index number in Annex VI of the CLP Regulation	048-014-00-6
Molecular formula:	$\text{Cd}(\text{NO}_3)_2$
Molecular weight range:	236.421 g/mol
Synonyms:	

Structural formula:



#### 1.2 Composition of the substance

Name: cadmium nitrate

Description: 80-100 % (w/w)

Substance type: mono-constituent

### 1.3 Identity and composition of structurally related substances (used in a grouping or read-across approach)

Since the toxic effects of all cadmium compounds are caused by the cadmium ion, data on other cadmium compounds and conclusions for “cadmium” are relevant for cadmium nitrate.

Table 2: Structurally related substance(s) identity

EC number:	231-152-8
EC name:	Cadmium
SMILES:	
CAS number (in the EC inventory):	7440-43-9
CAS number:	
CAS name:	Cadmium
IUPAC name:	Cadmium
Index number in Annex VI of the CLP Regulation	048-002-00-0 048-011-00-X
Molecular formula:	Cd
Molecular weight range:	112.4099
Synonyms:	Cd rod Cd stangen kadmium stangen

Substance type: mono-constituent

Structurally related substance(s) formula:

### 1.4 Physicochemical properties

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (a), (b) and (f).

## 2. Harmonised classification and labelling

Cadmium nitrate is listed by Index number 048-014-00-6 in part 3 of Annex VI to the CLP Regulation as follows:

Table 3: Classification according to Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram, Signal Word Code(s)	Hazard statement code(s)	Suppl. Hazard statement code(s)		
048-014-00-6	cadmium nitrate; cadmium dinitrate	233-710-6	10325-94-7	Carc. 1B Muta. 1B Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H332 H312 H302 H372 (kidney, bone) H400 H410	GHS08 GHS07 GHS09 Dgr	H350 H340 H332 H312 H302 H372 (kidney, bone) H410		Carc. 1B; H350: C ≥ 0.01%	A1

- H350: May cause cancer  
H340: May cause genetic defects  
H332: Harmful if inhaled  
H312: Harmful in contact with skin  
H302: Harmful if swallowed  
H372: Causes damage to organs through prolonged or repeated exposure.  
H400: Very toxic to aquatic life.  
H410: Very toxic to aquatic life with long lasting effects.

Note A1: Without prejudice to Article 17(2), the name of the substance must appear on the label in the form of one of the designations given in Part 3.

## 3. Environmental fate properties

### 3.1 Anthropogenic and natural sources of cadmium exposure

Although environmental fate properties are usually relevant for identifying concerns in the environment, indirect exposure of humans via the environment (e.g. dietary exposure) can be affected by the environmental fate properties of cadmium. Hence, parts of this section are relevant for the identification of the substance as SVHC in accordance with Article 57 (f) REACH, i.e. for which there is scientific evidence of probable serious effects to human health and the assessment of equivalent level of concern (section 6.3.2.1).

Cadmium is a natural element, which is present in all environmental compartments (as Cd<sup>2+</sup>). Cadmium emissions to the environment may therefore arise from both natural and anthropogenic or man-made sources. Estimates of the proportion of total cadmium emissions due to natural sources have ranged from 10 % to 50 %. Some of these natural emission sources include weathering and erosion of parent rocks, volcanic activity and forest fires (ICdA 2012). The overall cadmium anthropogenic exposure is thus in the range

of 50 % to 90 %. In the environment, cadmium is mainly associated with zinc but also with lead and copper. Anthropogenic sources include by-products of metallurgy of these elements. The release of cadmium into the human environment occurs via emission from mining activities and metal industries (the smelting of other metals), the combustion of fossil fuels, the incineration of waste materials or inappropriate waste disposal, leaching from landfill sites and the use of cadmium-rich phosphate fertilisers and sewage sludge. These anthropogenic activities have contributed to the contamination by cadmium of the food chain. However, there are also areas with naturally elevated cadmium concentrations in soil. Because cadmium is easily taken up by many plants, plant-based food, in particular wheat, rice and potatoes, is a major source of exposure to cadmium. Another source of exposure is tobacco smoking, mainly because the absorption in the lungs is higher than in the gastrointestinal tract (Keml 2011).

When cadmium ions are present in the environment, they will interact with the environmental matrix and biota. The fate will depend on processes like dissolution, absorption, precipitation, complexation, inclusion into (soil) matrix, etc. In freshwater or seawater cadmium may occur in both suspended and dissolved forms and is partitioned over a number of chemical species. In the water, cadmium interacts with components of the water, which influences the bioavailability. In sediment, cadmium binds to the sulphide fraction to form less soluble CdS. Due to the low solubility of CdS, cadmium will be largely bound in the sediments as long as the sediment is kept under anaerobic condition. However, if the condition turns more aerobic, due to e.g. drainage or dredging, cadmium ions may be re-mobilised into the water. In soils, cadmium interacts with various reactive soil surfaces (mainly adsorption). The soil pH is an important parameter that affects the speciation and the distribution of the cadmium species over the soil and the solution. Cadmium tends to be more sorbed and complexed at higher pH (pH > 7) than at lower pH. The solubility of cadmium in soil decreases with increasing pH. Cadmium is an element and is therefore persistent in the environment. Cadmium is not biomagnifying in the aquatic food chain. However, the bioconcentration/bioaccumulation factors strongly increase when exposure concentrations decrease. This observation clearly shows some level of physiological regulation of uptake.

### 3.2 Food

In a report from EFSA (2012) cadmium levels in food on the European market were reviewed and exposure estimated using detailed individual food consumption data. High levels of cadmium were found in algal formulations, cocoa-based products, crustaceans, edible offal, fungi, oilseeds, seaweeds and water molluscs. In an attempt to calculate lifetime cadmium dietary exposure, a middle bound overall weekly average was estimated at 2.04 µg/kg body weight and a potential 95th percentile at 3.66 µg/kg body weight. Individual dietary survey results varied between a weekly minimum lower bound average of 1.15 to a maximum upper bound average of 7.84 µg/kg bodyweight and a minimum lower bound 95th percentile of 2.01 and a maximum upper bound 95th percentile of 12.1 µg/kg body weight, reflecting different dietary habits and survey methodologies. Food consumed in larger quantities had the greatest impact on dietary exposure to cadmium. This was true for the broad food categories of grains, vegetables, and starchy roots and tubers. The review confirmed that children and adults at the 95th percentile exposure could exceed health-based guidance values. The current TWI is 2.5 µg/kg bw (EFSA 2009, 2012).

### 3.3 Human exposure and body burden

The general population is exposed to cadmium primarily via food, but also via smoking, soil and dust ingestion, inhalation of ambient air and drinking water. Three large and fairly recent studies may be used to display the “current” urinary cadmium concentrations, which reflect body burden, in the Swedish population (Keml 2011). The results are summarised in Table 4 below.

Women in the age group 50-69 years were also used to evaluate the proportion of women having urinary cadmium levels above two predefined cut offs of 0.5 and 1.0  $\mu\text{g/g}$  creatinine. In these studies, 20%, 70% and 23% of all the women (4%, 32% and 6% in never-smokers) had urinary cadmium concentrations above 0.5  $\mu\text{g/g}$  creatinine, respectively. The corresponding proportions for urinary cadmium concentrations above 1.0  $\mu\text{g/g}$  creatinine were 1.8%, 20% and 2%, respectively (0.3%, 6% and 0.2% in never-smokers). Differences between studies may indicate higher exposure in Southern Sweden, but comparability of measurements may contribute to the differences observed.

Table 4: Summary of urinary concentrations observed in three Swedish population-based studies

	Age (years)	Urinary cadmium $\mu\text{g/g}$ creatinine			
		Median and (range)		% >0.5 $\mu\text{g/g}$	% >1.0 $\mu\text{g/g}$
		All	Never-smokers	All / Never-smokers	
SEM	20-29	0.12 (0.01-0.68)	0.10 (0.02-0.68)	-	-
	50-59	0.29 (0.04-2.2)	0.24 (0.04-1.4)	20 / 4	1.8 / 0.3
WHILA	53-64	0.67 (0.13-3.6)	0.56 (0.13-3.2)	70 / 32	20 / 6
SMC	56-69	0.35 (0.05-2.4)	0.29 (0.05-1.3)	23 / 6	2.0 / 0.2

SEM; The National Swedish health-related environmental monitoring program, WHILA; Women's Health in the Lund Area, SMC; The Swedish Mammography Cohort;

Biomonitoring data indicate that the exposure to cadmium has not changed during the last 2-3 decades in Sweden (KemI 2011).

Within a European human biomonitoring project (DEMOCOPHES - DEMONstration of a study to COordinate and Perform Human biomonitoring on a European Scale), exposure to e.g. cadmium was studied in 16 European countries (Belgium, Cyprus, Czech Republic, Denmark, Hungary, Ireland, Luxembourg, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom). The results showed that smoking mothers had higher geometric mean (gm) urinary cadmium (UCd; 0.24  $\mu\text{g/g}$  crea; n=360) than non-smoking mothers (gm 0.18  $\mu\text{g/g}$  crea; n=1272; p<0.0001), and children had lower UCd (gm 0.065  $\mu\text{g/g}$  crea; n=1689) than their mothers at the country level. Poland had the highest UCd in comparison between the 16 countries, while Denmark had the lowest. Whether the differences between countries are related to differences in the degree of environmental cadmium contamination or to differences in lifestyle, socioeconomic status or dietary patterns is not clear (Berglund et al. 2015).

In an EU research program (PHIME - Public health impact of long-term, low-level mixed element exposure in susceptible population strata), blood from 1363 children from six European (Croatia, Czech Republic, Poland, Slovakia, Slovenia, and Sweden), and three non-European countries (China, Ecuador, and Morocco), showed remarkably small differences between the European cities (the geometric means ranged 0.11-0.17  $\mu\text{g/L}$  for cadmium). The European differences were also small among 480 women (0.25-0.65  $\mu\text{g/L}$ ). As regards industrially polluted areas, the results clearly showed that children living in certain such areas in Europe may have cadmium and lead levels in blood that are about double those in less polluted regions (PHIME 2011).

Cadmium concentrations in blood was measured in Swedish children during 1986-2013. The median blood cadmium concentration (b-Cd) was 0.10 (geometric mean 0.10; range 0.01-0.61)  $\mu\text{g/L}$ . Over the studied time, b-Cd slightly decreased (0.7% per year, p<0.001), but the authors conclude that increase of cadmium and the risk of disease might

occur later in life. In addition, the decrease is dependent on the single observation from 1986 (Lundh et al. 2016).

## 4. Human health hazard assessment

Cadmium nitrate has harmonised classification as carcinogenic 1B, mutagenic 1B and STOT RE 1 (see section 2).

### 4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

A gastrointestinal absorption of cadmium ranging between 1 and 10 % is likely, with men and individuals with adequate iron status in the lower range and those with low iron stores and iron deficiency (mainly women) in the higher range (Swedish Chemicals Agency 2011). Newborns and small children may have an even higher absorption, independent of iron status.

Absorption via inhalation is higher; 25-50 % may be absorbed in the lungs from fumes and 10-30 % from dust, depending on the particle size. Dermal uptake is considered low, likely significantly less than 1 %. Cadmium can also cross the placenta, but at a low rate (ECB 2007).

Following absorption, cadmium is transported in the blood to the liver where cadmium induces production of metallothionein and forms a complex with this protein. The cadmium–metallothionein complex is released from the liver and transported in the blood to the kidneys. Metallothionein is inducible in different tissues (e.g. liver, kidney, intestine, and lung) by exposure to various agents, including cadmium. In the kidneys, cadmium–metallothionein is readily filtered at the glomerulus, and may be efficiently reabsorbed from the filtrate in the proximal tubules. In the tubules, the protein portion is rapidly degraded to release cadmium. Cadmium accumulates in kidney tubules and causes damage to tubular cells, especially in the proximal tubules. Absorbed cadmium is excreted very slowly, with the amounts excreted into urine and faeces being approximately equal. In humans, half-life estimates have been reported to be in the range of 7–16 years (IARC 2012) to 10-30 years (Swedish Chemicals Agency 2011) or 18 - 44 years (Åkerström et al. 2013a).

The concentration of cadmium in urine is primarily influenced by the body burden of cadmium and is generally proportional to the concentration in the kidney. In adults, there is a close relationship between the cadmium concentrations in urine and kidneys (correlation coefficient 0.70) based on living kidney donors (Åkerström et al. 2013a). Because the half-life of cadmium in the body is very long, urinary cadmium is highly dependent on age in adults (Swedish Chemicals Agency 2011). Urinary cadmium is high during childhood followed by a decrease during adolescence and a progressive rise until the age of 60 years, where urinary Cd concentrations level off (Chaumont et al. 2013).

### 4.2 Repeated dose toxicity

#### 4.2.1 Kidney toxicity

In the EU Risk Assessment Report (RAR) of Cd and CdO (ECB 2007) it was concluded that there is ample and robust evidence of the nephrotoxic properties of cadmium. The main issue was to define the dose-effect/response relationships as well as the relevance to human health of the endpoints used. For workers occupationally exposed to cadmium (mainly by inhalation), a LOAEL of 5 µg Cd/g creatinine in urine was derived. The health significance of this threshold was justified by frequent observations of irreversible tubular changes above this level and its association with additional renal effects. For the general

population exposed to cadmium primarily by the oral route a LOAEL of 2 µg Cd/g creatinine in urine was derived. However, this could be a consequence of an interaction of Cd exposure with pre-existing or concurrent renal disease. It was emphasised that the interpretation of the LOAELs and the margin of safety should take into account the long half-life of cadmium and the uncertainties in the present hazard assessment.

A number of studies show significant associations between cadmium in urine and/or blood and markers of impaired kidney function, mostly impaired tubular function, where the risk starts to increase already below 1 µg/g creatinine (Swedish Chemicals Agency 2011). Also impaired glomerular filtration rate has been observed, the risk of which seems to start at 0.7 to 1.0 µg/g creatinine.

A study using data from 5426 subjects in the USA (National Health and Nutrition Examination Survey) revealed that a cadmium concentration  $\geq 1$  µg/g creatinine in urine or  $\geq 1$  µg/L in blood was associated with statistically significant increased risk of albuminuria. The concentration of cadmium in blood, not in urine, was associated with increased risk of lowered glomerular filtration rates (Ferraro et al, 2010).

The reported associations between increased cadmium levels in blood and urine and nephrotoxicity represent causal relationships. This is supported by the fact that associations have been observed for several different biomarkers of kidney toxicity in several different populations, in both men and women. In addition, mechanistic studies support effects at low exposure levels. It should, however, be noted that associations between low-molecular-weight proteins and cadmium in urine at very low environmental exposure levels should be interpreted with caution, given the unspecific nature of the tubular reabsorption of proteins. The close relationships between low-molecular-weight proteins and cadmium in urine might reflect the inter-individual variations in the tubular reabsorption capacity (Chaumont et al, 2012; Åkerström et al, 2013b). Moreover, the clinical significance of slight proteinuria may be limited. Thus, doubts have recently been raised regarding the justification of basing the risk assessment on this relationship at very low cadmium exposure. There is however evidence of low-level cadmium exposure causing toxic bone effects, with decrease of bone mineral density, increase of osteoporosis and fractures (see section 3).

Although there is strong evidence of elevated levels of several biomarkers of renal dysfunction in populations environmentally exposed to cadmium and/or associations between cadmium burden and these biomarkers, there is less agreement about the significance for human health of these changes.

Cadmium may also potentiate diabetes-induced effects on the kidney (EFSA 2009). There are also indications that environmental and occupational exposures to cadmium affect the development of end-stage renal disease, measured as need for renal replacement therapy (Hellström et al. 2001). In a population based prospective case-referent study in Sweden, erythrocyte-Cd tended to be related to an increased risk of end-stage renal disease, but confounding by lead and mercury could partly explain this finding (Sommar et al. 2013). A recent systematic review of epidemiological studies including associations between cadmium exposure and chronic kidney disease (CKD) on in total 34 exposed groups with more than 3000 participants concluded that there was no convincing evidence supporting a risk of progression to CKD in populations exposed to Cd (Byber et al. 2016).

#### 4.2.2 Bone toxicity

In the EU RAR of Cd and CdO (ECB 2007) it was concluded that it is evident that bone tissue is a target organ for general and occupational populations exposed to cadmium. The hazard was considered relatively well identified both in experimental and epidemiological studies. The mechanisms of bone toxicity is however not fully understood, and the types of bone lesions associated with cadmium exposure are not clearly identified.

The most severe form of cadmium toxicity is Itai-itai disease, which comprises severe signs of osteoporosis and osteomalacia associated with renal disease in aged women. Osteoporosis is characterised by low bone mass and microarchitectural deterioration of the skeleton, leading to fragility and increased risk of fractures. The disease is silent until the first fracture occurs. Common osteoporotic fractures are those of the hip, spine and forearm. These fractures are a considerable public health problem, causing suffering and a burden to society in terms of cost, morbidity and mortality. Established or suggested risk factors for osteoporosis and fractures are female sex, old age, low body weight, early menopause, family history of osteoporosis, deficiency of vitamin D and calcium, smoking, excessive alcohol consumption, inactivity and certain medical disorders and drugs (Genant et al. 1999, NIH 2001).

A risk assessment of cadmium showed a substantially increasing amount of data supporting an association between present cadmium exposure levels in Sweden and increased risk of osteoporosis (Swedish Chemicals Agency 2011). Only a couple of under-powered studies failed to show any association between cadmium and low bone-mineral density, and a few studies were inconclusive. Irrespective of whether the studies employed a decrease in bone mineral density, increased risk of osteoporosis or increased risk of fractures, these changes seem to occur at very low urinary cadmium concentrations. Studies on the Swedish Mammography Cohort (SMC) and the American National Health and Nutrition Examination Survey (NHANES) suggest that a urinary concentration of around 0.5 µg/g creatinine is associated with increased risk of osteoporosis and fractures (Swedish Chemicals Agency 2011). There are an increasing amount of data suggesting that the effect of cadmium on bone is independent of kidney damage, and that these effects occur even before kidney damage (Swedish Chemicals Agency 2011). Furthermore, the Swedish Mammography Cohort studies showed very clear increased risk of osteoporosis and fractures even among those who never smoked. This finding suggests that dietary cadmium alone contribute to the risk (Swedish Chemicals Agency 2011; Engström et al. 2012).

The most adverse endpoint with respect to effects on bone is a fracture. A study investigating the risk of fractures in relation to biomarkers of cadmium exposure requires a large sample size in order to be adequately powered. In these studies the risk is calculated based on comparison of exposure in those who developed a fracture and those who did not. Bone mineral density gives an estimation of the status of the skeleton, but is not the only factor predicting the risk of fractures. Biochemical markers of bone remodelling are measured in serum or urine and give an indication of the activity of the continuously ongoing formation and degradation of bone tissue. Although these markers may increase our understanding of possible mechanisms involved and may also support inference with respect to causality, they cannot independently be used as markers of an adverse effect.

Whereas several epidemiological studies have observed an association between cadmium and bone mineral density (Swedish Chemicals Agency 2011), only few published studies have so far considered fracture incidence.

In the prospective cohort CadmiBel (Cadmium in Belgium), including 506 subjects, observed risk ratios associated with doubled urinary cadmium concentrations were 1.73 (95% CI 1.16–2.57; P = 0.007) for fractures in women and 1.60 (95% CI 0.94–2.72, P = 0.08) for height loss in men. Similar risk estimates were observed if cadmium concentrations in soil, leek and celery from the relevant districts of residence were used as proxy of cadmium exposure (Swedish Chemicals Agency 2011).

In the Swedish OSCAR (Osteoporosis Cadmium as a Risk factor) study, fracture incidence was assessed retrospectively. For fractures occurring after the age of 50 years (n = 558, 32 forearm fractures), the fracture hazard ratio, adjusted for sex and other relevant covariates, increased by 18% (95% CI 1.0–38%) per unit urinary cadmium (1 nmol/mmol

creatinine; ~ 1 µg/g creatinine). When subjects were grouped in exposure categories, the hazard ratio reached 3.5 (90% CI 1.1–11) in the group of subjects with urinary cadmium concentrations between 2 and 4 nmol/mmol creatinine and 8.8 (90% CI 2.6–30) in the group of subjects with urinary cadmium concentrations greater than or equal to 4 nmol/mmol creatinine (mainly men). The relatively high cadmium exposure in this study could be attributed to the inclusion of workers occupationally exposed to cadmium. Associations between cadmium and fracture risk were absent before the age of 50 (Alfvén et al. 2004).

In the Swedish Mammography Cohort it was shown that for any first fracture (n=395) the odds ratio (OR) was 1.16 (95% CI, 0.89-1.50) when comparing urinary Cd levels of ≥0.5 µg/g creatinine with lower levels. Among never-smokers, the ORs (95% CIs) were 2.03 (1.33-3.09) for any first fracture, 2.06 (1.28-3.32) for first osteoporotic fracture, 2.18 (1.20-3.94) for first distal forearm fracture and 1.89 (1.25-2.85) for multiple incident fractures (Engström et al. 2011). Similar risks were observed when dietary cadmium was used instead of urinary cadmium in the same women. Comparing the women's dietary cadmium exposure above the median (13 µg Cd/day) to that below the median was associated with OR 1.31 (1.02-1.69) for fractures in all women and OR 1.54 (1.06-2.24) in never smokers. In an analysis where women with both high dietary and high urinary cadmium were contrasted against the women with low exposure, the association with fractures was more pronounced OR 1.46 (1.00-2.15) in all women and 3.05 (1.66-5.59) in never-smokers (Engström et al. 2012).

In a study on 936 men from the Swedish cohort of the Osteoporotic Fractures (MrOS), associations between low-level cadmium exposure, from diet and smoking, and bone mineral density (BMD) and incident fractures in elderly men were examined (Wallin et al. 2015). The result showed significant associations between increasing urinary cadmium (U-Cd) levels and decreasing BMD. In addition, associations were found between increasing U-Cd and incident fractures, especially non-vertebral osteoporosis fractures in the fourth quartile of U-Cd, with hazard ratios of 1.8 to 3.3 in the different models used. U-Cd as a continuous variable was significantly associated with non-vertebral osteoporosis fractures (adjusted hazard ratio 1.3 to 1.4 per mg Cd/g creatinine), also in never-smokers, but not with the other fracture groups (all fractures, hip fractures, vertebral fractures, and other fractures).

In a population-based prospective cohort study on 22 000 Swedish men, dietary cadmium was associated with a statistically significant 19 % higher rate of any fracture comparing the highest Cd intake tertile with the lowest tertile (Thomas et al. 2011).

In a study by Sommar et al. (2013) the association between hip fracture risk and cadmium in erythrocytes (Ery-Cd) was investigated. Prospective samples from a Swedish biobank were used for 109 individuals who later in life had sustained a low-trauma hip fracture, matched with two controls of the same age and gender. The mean concentration of Ery-Cd (±SD) in case samples was 1.3 ± 1.4 versus 0.9 ± 1.0 µg/L in controls. The odds ratio (OR) was 1.63 (95 % confidence interval (CI) 1.10-2.42) for suffering a hip fracture for each microgram per liter increase in Ery-Cd. However, when taking smoking into consideration, neither Ery-Cd nor smoking showed a statistically significant increase in fracture risk. Using multiple conditional logistic regression with BMI, height, and smoking, the estimated OR for a 1-µg/L increase in Ery-Cd was 1.52 (95 % CI 0.77-2.97). Subgroup analysis showed an increased fracture risk among women (OR = 1.94, 95 % CI 1.18-3.20, for a 1 µg/L increase), which also remained in the multiple analysis (OR = 3.33, 95 % CI 1.29-8.56).

A recent meta-analysis to evaluate the relationship between cadmium exposure and risk of any fracture were performed by Cheng et al. (2016). In total 8 studies from 1999 – 2014 were included. The result showed that the pooled relative risk of any fracture for the highest versus lowest category of cadmium concentration was 1.30 (95% confidence

interval¼ 1.13–1.49). In subgroup analyses, the significant association remained consistent when stratified by study type, geographical region, method of cadmium exposure assessment, and gender.

#### 4.2.3 Summary of other effects

Cadmium carbonate have the potential to cause many serious health effects in addition to its ability to cause mutagenicity and cancer. Adverse effects on multiple organs after repeated exposure to cadmium, in particular on *kidney* and *bone* as described above, has motivated the classification of cadmium as STOT RE Category 1. It is in particular these effects on kidney and bone that justify cadmium to be regarded as a substance of equivalent level of concern (article 57f).

## 5. Environmental hazard assessment

Not relevant for the identification of the substance as an SVHC in accordance with Article 57 (a), (b) and (f) of REACH Regulation.

## 6. Conclusions on the SVHC Properties

### 6.1 CMR assessment

#### *Carcinogen 1B – Article 57(a)*

Cadmium nitrate is listed by Index number 048-014-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified in the hazard class carcinogenicity category 1B (hazard statement H350: “May cause cancer”).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that it meets the criteria for classification in the hazard class:

- Carcinogenicity category 1B in accordance with Article 57(a) of REACH.

#### *Mutagen 1B – Article 57(b)*

Cadmium nitrate is listed by Index number 048-014-00-6 of Regulation (EC) No 1272/2008 in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) and it is classified in the hazard class germ cell mutagenicity category 1B (hazard statement H340: “May cause genetic defects”).

Therefore, this classification of the substance in Regulation (EC) No 1272/2008 shows that it meets the criteria for classification in the hazard class:

- Germ cell mutagenicity category 1B in accordance with Article 57(b) of REACH.

### 6.2 PBT and vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (a), (b) and (f) of REACH Regulation.

## 6.3 Assessment under Article 57(f)

### 6.3.1 Summary of the data on the hazardous properties

Cadmium nitrate has a harmonised classification as STOT RE 1 (hazard statement H372: Causes damage to organs through prolonged or repeated exposure). Cadmium nitrate is identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with adverse effects on multiple organs after prolonged exposure, in particular *kidney* and *bone*, for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of REACH.

### 6.3.2 Equivalent level of concern assessment

#### 6.3.2.1 Human health

Where the equivalent level of concern relates to a human health effect, the key information in the report should be summarised taking into account, where relevant, the following (non-exhaustive) list of discussion points:

- Health effects:
  - Type and potential severity of possible health effects
  - Irreversibility of health effects
  - Delay of health effects
- Other factors:
  - Quality of life affected
  - Societal concern
  - Is derivation of a 'safe concentration' possible?

Since the toxic effects of all cadmium compounds are caused by the cadmium ion, the conclusions for "cadmium" are relevant for cadmium nitrate.

A significant part of the European population is today exposed to levels of cadmium (originating from cadmium metal and cadmium compounds) that may cause effects on kidney and bone. In non-smokers, food is the main intake route and it is therefore important to reduce all input of cadmium to foodstuff. Deposition from air is an important source to the input of cadmium to soil and must therefore be reduced. In order to achieve this all uses of cadmium and cadmium compounds should, wherever possible, be substituted.

Almost 30 years ago it was acknowledged within the EU that cadmium exposure constitutes a problem for human health and the environment and new action should be taken at Community level to control and reduce cadmium pollution (Council Resolution 1988). Major elements of the strategy for cadmium control in the interests of the protection of human health and the environment included for example:

- limitation of the uses of cadmium to cases where suitable alternatives do not exist;
- stimulation of research and development: - of substitutes and technological derivatives, in particular, encouragement to the development of further alternatives to the use of cadmium in pigments, stabilisers and plating;
- collection and recycling of products containing cadmium, for example batteries;
- development of a strategy designed to reduce cadmium input in soil;
- combatting significant sources of airborne and water pollution.

Cadmium is a toxic metal that ranks as no. 7 on the US Agency for Toxic Substances & Disease Registry's priority list of hazardous substances (<https://www.atsdr.cdc.gov/spl/index.html>), a prioritisation of substances based on a

combination of their frequency, toxicity, and potential for human exposure. As a pollutant of worldwide concern, cadmium has been reviewed by the United Nations Environment Program, and included on the list of chemical substances considered potentially dangerous at the global level.

To assess whether a substance can be identified as SVHC based on REACH Article 57(f) the hazardous properties of the substance, the potential impact on health and the potential impact on society as a whole have to be compared to those effects elicited by CMR (or PBT/vPvB) substances. The following factors that are characteristic for most of the CMRs have been taken into account:

- Severity of health effects
- Irreversibility of health effects
- Delay of health effects
- Uncertainties on safe exposure
- Societal concern and impairment of quality of life

*Severity of health effect:* The severity of health effects due to exposure to cadmium is dependent on the concentration attained in body tissues and organs. Kidney effects range from indications of impaired tubular and glomerular function (measured by the presence of proteins in the urine) to an increased risk of end stage renal disease, which necessitates dialysis treatment for survival. The effects on bone range from disturbances on bone tissue homeostasis to actual bone fractures, which especially for older people are considered quite serious and can contribute to a premature death. In a population-based study in patients aged 65 or older the risk of mortality in hip fracture patients was 3-fold higher than in the general population and included every major cause of death (Panula et al. 2011). The quality of life for affected individuals is clearly impaired (for example after a hip fracture), but may also have consequences for society as a whole if many individuals are affected. When comparing with CMR effects, it should be acknowledged that also these effects vary in severity.

*Irreversibility of health effects:* According to the EU RAR on Cd and CdO (ECB 2007) some controversy exists as to the reversibility of renal effects of cadmium both in the general population and in workers. The (ir)reversibility of tubular proteinuria after reduction or cessation of exposure depends on the intensity of exposure and/or the severity of the tubular damage. It was concluded that, as for inhalation exposure, incipient tubular effects associated with low cadmium exposure in the general population are reversible if exposure is substantially decreased. Severe tubular damage (urinary leakage of the proteins RBP or  $\beta$ 2M > 1,000-1,500  $\mu$ g/g creatinine) is generally irreversible.

A longitudinal study on 74 inhabitants from a cadmium-polluted area in Japan (Kido et al. 1988) showed irreversible and even progression of renal dysfunction 5 years after cessation of cadmium exposure. Likewise, a study from China indicates that the negative effects on bone still remains 10 years after the population abandoned ingestion of cadmium-polluted rice (Chen et al. 2009).

The biological half-life of cadmium in humans is extremely long (estimated to be 10-30 years) and the body burden of cadmium therefore increases, mainly via accumulation in the kidney, during the entire life span of an individual (Keml 2011). All uses of cadmium and its compounds, including when present as a contaminant, contribute to this bioaccumulation in humans, which starts already in early life. Unless exposure is substantially decreased kidney and bone effects therefore tend to be irreversible due to the continued internal exposure from stored cadmium. In that respect cadmium behaves in a way that resembles substances that are persistent and bioaccumulating in the environment.

*Delay of health effects:* The bioaccumulation over the lifetime of an individual also

affects when effects appear; in most instances, the delay between first exposure and appearance of effects is very long, i.e. decades.

*Uncertainties on safe exposure:* There is uncertainty about identifying safe exposure levels for cadmium. Biomedical research on cadmium is intense. A search of the literature data base PubMed revealed 19 000 articles published during the last 10 years and more than 10 000 articles during the last 5 years. Consequently, new findings on hazards and risks connected with cadmium and its compounds continuously appear. As an example, effects on bone tissue have been shown at exposure levels previously considered without effects. Since what can be considered as a “safe exposure level” is steadily decreasing, precautionary community wide actions are warranted.

Further, it is not clear whether an effect on bone/kidney or carcinogenesis is the critical end-point from a risk assessment point of view, although most risk assessments concerning cadmium exposure of the general population (for example the assessment from EFSA (2009, 2012)) are based on kidney effects. In the risk assessment for workers by SCOEL (2009), the proposed limit values are also based on effects on the kidney and, to some extent, bone tissue, representing the most sensitive targets of cadmium toxicity after occupational exposure. The suggested IOEL (in air) is considered to be protective against long-term local effects (respiratory effects including lung cancer). Whether this value is also protective against cancer in other tissues was not assessed. According to a paper from the Austrian Workers’ Compensation Board (Püringer 2011), the German Committee on Hazardous Substances (AGS) has endorsed a limit value of 16 ng Cd/m<sup>3</sup> based on the acceptable cancer risk of 1 : 25,000, i.e. a value 250-fold lower than the IOEL suggested by SCOEL.

*Societal concern and impairment of quality of life:* In particular, the effects on bone tissue, with increased risk for bone fractures, are a considerable public health problem causing a lot of suffering and a burden to society in terms of cost, morbidity and mortality. Osteoporotic complications are particularly prevalent in northern Europe and, statistically, every second woman in Sweden will suffer from an osteoporotic fracture during her lifetime. The incidence of hip fractures is more than seven-fold higher in Northern Europe than in the rest of Europe. The reason(s) for the large age-standardised geographical differences is still not known, but the differences cannot be explained by differences in risk of slipping, low calcium intake, vitamin D deficiency or by inactivity. The fracture incidence has increased substantially since the 1950ies. As the number of old and very old people in the population increases, a further increase in the prevalence of fractures is to be expected.

According to a report published by the Swedish Chemicals Agency, the Swedish annual societal economic cost of fractures caused by cadmium in food amounts to approximately 4.2 billion SEK (approx. 420 million Euros) (KemI 2013). This figure is based on the estimation that 7 and 13 %, in males and females respectively, of all fractures in Sweden are caused by cadmium exposure, mainly via food, and include direct treatment and care costs for bone fractures (approx. 1.5 billion SEK or 150 million Euros), as well as a valuation of a lower quality of life and shortened life expectancy for those who suffer fractures, mostly the elderly.

### 6.3.3 Conclusion on the hazard properties and equivalent level of concern assessment

Cadmium nitrate is considered to fulfil the criteria according to Art. 57(f), i.e. there is scientific evidence of probable serious effects to human health which give rise to “equivalent level of concern” to those of other substances listed in paragraphs (a) to (e) of Article 57 of REACH Regulation, due to:

- the adverse effects on kidney and bones, effects that depending on dose may be

- serious and even contribute to premature death,
- the continuous accumulation of cadmium in the body, which leads to continuous internal exposure and in practice irreversible effects once adverse effect levels are reached,
- the occurrence of adverse effects in a significant part of the general population at present exposure levels, which are primarily of anthropogenic origin,
- uncertainties in deriving a safe exposure level, and
- high societal costs in terms of health care and shortening of life time and a decreased quality of life.

Conclusion: Cadmium nitrate is identified as a substance of very high concern in accordance with Article 57(a), (b) and (f) of Regulation (EC) 1907/2006 (REACH) because it is a carcinogenic and mutagenic substance which also causes adverse effects on multiple organs after prolonged exposure, in particular *kidney* and *bone*, for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of REACH Regulation.

## REFERENCES

- Åkerström M, Barregård L, Lundh T, Sällsten G. (2013a) The relationship between cadmium in kidney and cadmium in urine and blood in an environmentally exposed population. *Toxicology and Applied Pharmacology*, 268, 286-293.
- Åkerström M, Sällsten G, Lundh T, Barregård L. (2013b) Associations between urinary excretion of cadmium and proteins in a nonsmoking population: Renal toxicity or normal physiology? *Environmental Health Perspectives*, 121(2), 187-191.
- Alfvén T, Elinder CG, Hellström L, Lagarde F & Järup L. (2004) Cadmium exposure and distal forearm fractures. *Journal of Bone and Mineral Research*, 19(6), 900-905.
- Berglund M, Larsson K, Grandér M, Casteleyn L, Kolossa-Gehring M, Schwedler G, et al. (2015). Exposure determinants of cadmium in European mothers and their children. *Environ. Res.* 2015 Aug; 141:69-76.
- Byber K, Lison D, Verougstraete V, Dressel H, Hotz P (2016). Cadmium or cadmium compounds and chronic kidney disease in workers and the general population: a systematic review. *Crit Rev Toxicol.* 46:191-240.
- Chaumont A, Nickmilder M, Dumont X, Lundh T & Skerfving S. (2012) Associations between proteins and heavy metals in urine at low environmental exposures: Evidence of reverse causality. *Toxicology Letters*, 210, 345-352.
- Chaumont A, Voisin C, Deumer G, Haufroid V, Annesi-Maesano I, Roels H, Thijs L, Staessen J & Bernard A. (2013) Associations of urinary cadmium with age and urinary proteins: Further evidence of physiological variations unrelated to metal accumulation and toxicity. *Environmental Health Perspectives*, 121(9), 1047-1053.
- Chen X, Zhu G, Jin T, Åkesson A, Bergdahl IA, Lei L, Weng S & Liang Y. (2009). Changes in bone mineral density 10 years after marked reduction of cadmium exposure in a Chinese population. *Environmental Research*, 109, 874-879.
- Cheng X, Niu Y, Ding Q, Yin X, Huang G, Peng J, Song J (2016). Cadmium Exposure and Risk of Any Fracture: A PRISMA-Compliant Systematic Review and Meta-Analysis. *Medicine (Baltimore)*. 95(10):e2932.
- Council Resolution (1988) Council Resolution of 25 January 1988 on a Community action programme to combat environmental pollution by cadmium. *Official Journal C 030*, 04/02/1988 P. 0001 – 0001
- ECB (2007). European Union Risk Assessment Report, Cadmium oxide and cadmium metal, Volume 72, European Commission, Joint Research Centre, Institute of Health and Consumer Protection (IHCP), Toxicology and Chemical Substances (TCS), EU 22919 EN. Editors: S.J. Munn, K. Aschberger, O. Cosgrove, W. de Coen, S. Pakalin, A. Paya-Perez, B. Schwarz-Schulz, S. Vegro. Luxembourg: Office for Official Publications of the European Communities.
- EFSA (2009) European Food Safety Authority. Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from the European Commission on cadmium in food. *The EFSA Journal*, 980, 1-139. Available at: [http://www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/980.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/980.pdf) (accessed on 21 June 2017)
- EFSA (2012) European Food Safety Authority. Cadmium dietary exposure in the European population. *EFSA Journal*, 2012; 10(1):2551 [37 pp.]. Available online: [www.efsa.europa.eu/efsajournal](http://www.efsa.europa.eu/efsajournal)
- Engström A, Michaëlsson K, Suwazono Y, Wolk A, Vahter M & Åkesson A. (2011) Long-term cadmium exposure and the association with bone mineral density and fractures in a

population-based study among women. *Journal of Bone and Mineral Research*, 26(3), 486-495.

Engström A, Michaëlsson K, Vahter M, Julin B, Wolk A & Åkesson A. (2012) Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women. *Bone*, 50(6):1372-8.

Ferraro PM, Costanzi S, Naticchia A, Sturniolo A & Gambaro G. (2010). Low level exposure to cadmium increases the risk of chronic kidney disease: analysis of the NHANES 1999-2006. *BMC Public Health*, 10: 304.

Genant HK, Cooper C, Poor G, et al. (1999). Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. *Osteoporos Int*. 10: 259-264.

Hellström L, Elinder CG, Dahlberg B, Lundberg M, Järup L, Persson B & Axelson O. (2001) Cadmium exposure and end-stage renal disease. *American Journal of Kidney Disease*, 38(5), 1001-1008.

IARC (2012) Cadmium and cadmium compounds. In *Monographs, Vol 100C, A review of Human carcinogens*, pp. 121-145.

<http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-8.pdf> (accessed on 21 June 2017)

ICdA. Cadmium emissions. Available at:

<http://www.cadmium.org/environment/cadmium-emissions> (accessed on 21 June 2017).

Kemi (2011) Kadmiumhalten måste minska–för folkhälsans skull. Rapport Nr 1/11. Bilaga 3: Health effects of cadmium in Sweden. Available at:

<https://www.kemi.se/global/rapporter/2011/rapport-1-11.pdf> (accessed on 21 June 2017).

Kemi (2013). Economic costs of fractures caused by dietary cadmium exposure. Swedish Chemicals Agency. Report No 4/13. Available at:

<https://www.kemi.se/global/rapporter/2013/rapport-4-13-cadmium.pdf> (accessed on 21 June 2017).

Kido T, Honda R, Tsuritani I, Yamaya H, Ishizaki M, Yamada Y & Nogawa K. (1988) Progress of renal dysfunction in inhabitants environmentally exposed to cadmium. *Archives of Environmental Health* 43(3), 213-217.

Lundh T, Axmon A, Skerfving S, Broberg K (2016). Cadmium and mercury exposure over time in children in southern Sweden (1986 – 2013). Report to the Swedish Environmental Protection Agency, August, 2016. Available at: <http://www.diva-portal.org/smash/get/diva2:967690/FULLTEXT01.pdf> (accessed on 21 June 2017).

NIH, Consensus Development Panel Osteoporosis prevention, diagnosis, and therapy. *JAMA*. Feb 14 2001;285(6): 785-795.

Panula J, Pihlajamäki H, Mattila VM, Jaatinen P, Vahlberg T, Aarnio P & Kivilä S-L. (2011) Mortality and cause of death in hip fracture patients aged 65 or older – a population-based study. *BMC Musculoskeletal Disorders* 12: 105.

PHIME (2011) Public health impact of long-term, low-level mixed element exposure in susceptible population strata Project no. FOOD-CT-2006-016253. Final report, August 2011. Available at:

[http://www.med.lu.se/labmedlund/amm/forskning/haelsorisker\\_av\\_metaller/phime](http://www.med.lu.se/labmedlund/amm/forskning/haelsorisker_av_metaller/phime) (accessed on 21 June 2017).

Püringer J. (2011) Derived Minimal Effect Levels (DMELs): Shortcomings one year after the REACH registration deadline. *Slightly revised translation of the original paper* »Püringer J., "Derived Minimal Effect Levels" (DMEL): Defizite ein Jahr nach der REACH-Registrierungspflicht, *Gefahrstoffe – Reinhaltung der Luft* 71 (Nov./Dec. 2011), 471–479«. Available

at: <http://www.auva.at/portal27/portal/auvaporportal/content/contentWindow?contentid=10008.544427&action=b&cacheability=PAGE> (accessed on 21 June 2017)

SCOEL/SUM/136, February 2009, For public consultation. Recommendation from the Scientific Expert group on Occupational Exposure Limits for Cd and its organic compounds.

Sommar JN, Pettersson-Kymmer U, Lundh T, Svensson O, Hallmans G, Bergdahl IA. (2014) Hip fracture risk and cadmium in erythrocytes: A nested case-control study with prospectively collected samples. *Calcified Tissue International*, 94(2), 183-190.

Sommar JN, Svensson MK, Björ BM, Elmståhl SI, Hallmans G, Lundh T, Schön SM, Skerfving S, Bergdahl IA (2013). End-stage renal disease and low level exposure to lead, cadmium and mercury; a population-based, prospective nested case-referent study in Sweden. *Environ Health*. 12:9.

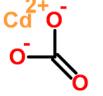
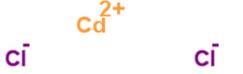
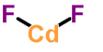
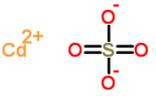
Swedish Chemicals Agency (2011). Kadmiumhalten måste minska–för folkhälsans skull. Report 1/11. Appendix 3. Health effects of cadmium in Sweden. <http://www.kemi.se/global/rapporter/2011/rapport-1-11.pdf>

Thomas LD, Michaëlsson K, Julin B, Wolk A, Åkesson A (2011). Dietary cadmium exposure and fracture incidence among men: a population-based prospective cohort study. *J Bone Miner Res*. 26: 1601-8.

Wallin M, Barregard L, Sallsten G, Lundh T, Karlsson MK, Lorentzon M, Ohlsson C, Mellstrom D (2016). Low-Level Cadmium Exposure Is Associated With Decreased Bone Mineral Density and Increased Risk of Incident Fractures in Elderly Men: The MrOS Sweden Study. *J Bone Miner Res*, 31: 732–741.

## Annex I - Additional information on read across approach

All inorganic cadmium salts listed in the table below are considered as carcinogenic and toxic to bone and kidney due to the inherent properties of the cadmium ion ( $\text{Cd}^{2+}$ )<sup>6</sup>. Hence, from a toxicological point of view they can be considered as a group based on the presence of the cadmium ion. It is generally considered that the systemic toxicity of all inorganic cadmium salts is attributed to the cadmium ion<sup>7</sup>.

Cadmium compound	EC number	Structural formula	CLP Harmonised classification			
			Carc	Muta	Repro	STOT RE
Cadmium carbonate	208-168-9		1B	1B		1
Cadmium nitrate	233-710-6		1B	1B		1
Cadmium chloride	233-296-7		1B	1B	1B	1
Cadmium fluoride	232-222-0		1B	1B	1B	1
Cadmium hydroxide	244-168-5		1B	1B		1
Cadmium sulphate	233-331-6		1B	1B	1B	1
Cadmium metal	231-152-8		1B	2	2	1
Cadmium oxide	215-146-2		1B	2	2	1
Cadmium sulphide	215-147-8		1B	2	2	1

<sup>6</sup> See dossiers for harmonised classification and labelling for the substances in the [C&L inventory](#)

<sup>7</sup> European Commission, 2007, European Union Risk Assessment Report (EU RAR) – Volume 74 cadmium metal, Part II Human Health