Annex XV report

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

**Substance Name: Cadmium carbonate**

**EC Number: 208-168-9**

**CAS Number: 513-78-0**

**Submitted by: Swedish Chemicals Agency**

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

**Substance Name:** Cadmium carbonate

**EC Number: 208-168-9**

**CAS number: 513-78-0**

* The substance is proposed to be 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[[1]](#footnote-1).
* The substance is proposed to be 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[[2]](#footnote-2).
* It is proposed to identify the substance 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)[[3]](#footnote-3).

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

***Carcinogen 1B – 57(a)***

Cadmium carbonate is covered by Index number 048-012-00-5 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 – 57(b)***

Cadmium carbonateis covered by Index number 048-012-00-5 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.

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

Cadmium carbonate is covered by Index number 048-012-00-5 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). Cadmium carbonate is proposed to be 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 REACH.

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

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 ß2M > 1,000-1,500 μg/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/m³ 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 conclusion***

Cadmium carbonate 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”, 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.

**Registration dossiers submitted for the substance? Yes**

PART I

Justification

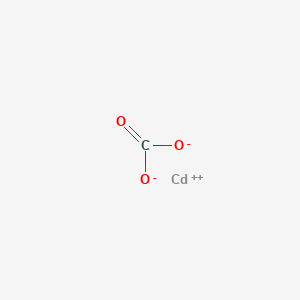
# Identity of the substance and physical and chemical properties

## Name and other identifiers of the substance

**Table 1: Substance identity**

|  |  |
| --- | --- |
| EC number: | 208-168-9 |
| EC name: | Cadmium carbonate |
| CAS number (in the EC inventory): | 513-78-0 |
| CAS number:  Deleted CAS numbers: |  |
| CAS name: | Cadmium carbonate |
| IUPAC name: | Cadmium carbonate |
| Index number in Annex VI of the CLP Regulation | 048-012-00-5 |
| Molecular formula: | CdCO3 |
| Molecular weight range: | 172.42 g/mol |
| Synonyms: |  |

**Structural formula:**

****

## 1.2 Composition of the substance

**Name: cadmium carbonate**

**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 carbonate.

**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 SVHC in accordance with Article 57 points (a) to (c) and, in this case, 57 (f).

# Harmonised classification and labelling

Cadmium carbonate is covered by Index number 048-012-00-5 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 state-ment code(s) | Pictogram, Signal Word Code(s) | Hazard state-ment code(s) | Suppl. Hazard state-ment code(s) |
| 048-012-00-5 | cadmium carbonate | 208-168-9 | 513-78-0 | 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 |  |  | 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.

# 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 Cd2+). 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 (KemI 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

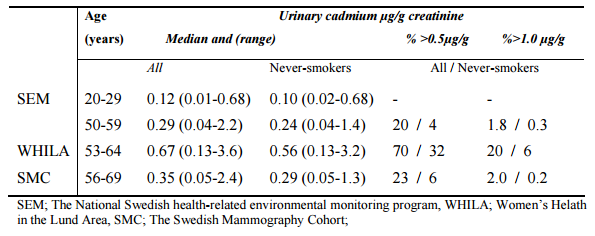
In a report from EFSA (2012) cadmium levels in food on the European market were reviewed and exposure estimated using detailed individual food consumption data. High levels of cadmium were found in algal formulations, cocoa-based products, crustaceans, edible offal, fungi, oilseeds, seaweeds and water 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 (KemI 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 μg/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 μg/g creatinine, respectively. The corresponding proportions for urinary cadmium concentrations above 1.0 μg/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**



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 µg/g crea; n=360) than non-smoking mothers (gm 0.18 µg/g crea; n=1272; p<0.0001), and children had lower UCd (gm 0.065 µg/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 μg/L for cadmium). The European differences were also small among 480 women (0.25-0.65 μg/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) μg/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).

# Human health hazard assessment

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

## 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).

## Repeated dose toxicity

## 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 ≥ 1 μg/g creatinine in urine or ≥ 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).

## 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 nonvertebral 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 nonvertebral 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.

### 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).

# **Environmental hazard assessment**

Not relevant for the identification of the substance as SVHC in accordance with Article 57 points (a) to (c) and, in this case, (f) of REACH.

# Conclusions on the SVHC Properties

## 6.1 CMR assessment

***Carcinogen 1B – 57(a)***

Cadmium carbonate is covered by Index number 048-012-00-5 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 – 57(b)***

Cadmium carbonate is covered by Index number 048-012-00-5 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 points (a) to (c) and, in this case, (f) of REACH.

## 6.3 Assessment under Article 57(f)

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

Cadmium carbonate has a harmonised classification as STOT RE 1 (hazard statement H372: Causes damage to organs through prolonged or repeated exposure). Cadmium carbonate is proposed to be 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 carbonate.

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 ß2M > 1,000-1,500 μg/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 (KemI 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/m³ 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 carbonate 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”, 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.

Part II

# Registration and C&L notification status

## Registration status

**Table 5: Registration status**

|  |  |
| --- | --- |
| **From the ECHA dissemination site[[4]](#footnote-4)** | |
| Registrations | ☒ Full registration(s)  (Art. 10)  ☐ Intermediate registration(s)  (Art. 17 and/or 18) |

Cadmium carbonate has 5 active registrations[[5]](#footnote-5).

## 7.2 CLP notification status

**Table 6: CLP notifications**

|  |  |
| --- | --- |
|  | **CLP Notifications[[6]](#footnote-6)** |
| Number of aggregated notifications | 5 |
| Total number of notifiers | 33 |

# Total tonnage of the substance

**Table 7: Tonnage status**

|  |  |
| --- | --- |
| Total tonnage band for the registered substance (excluding the volume registered under Art 17 or Art 18)[[7]](#footnote-7) | 10 - 100 t/pa |

# Information on uses of the substance

Uses of cadmium carbonate and other cadmium compounds has been summarised and visualised in figure 1 below, illustrating the complexity and interrelations of the uses of this group of compounds.



**Figure 1.** Overview of the cadmium downstream uses with focus on cadmium carbonate, summarised and visualised.

Table 8 below summarises the uses from the registration dossiers. A conclusion on whether the use is in the scope of Authorisation is not possible based on the general information available in the registration dossiers. Further information would be necessary to confirm whether the uses as reported by the registrants are intermediate uses.

**Table 8: Uses[[8]](#footnote-8)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Use(s)** | **Registered use**  *(If not, specify the source of the information)* | **Use in the scope of Authorisation** |
| **Uses as intermediate** | Component for production of Cadmium compounds and pigments | Yes | No |
| **Formulation or repacking** | Cadmium carbonate is used in the following products: pH regulators and water treatment products, laboratory chemicals and cosmetics and personal care products. Example of identified uses from ECHA dissemination site:  Laboratory reagent,  Component for production of Cadmium compounds and pigments,  Component for polymer-matrices, plastics and related preparations,  Additive for production of glass | Yes | Yes |
| **Uses at industrial sites** | Cadmium carbonate is used in the following products: pH regulators and water treatment products, polymers, laboratory chemicals, fillers, putties, plasters, modelling clay and cosmetics and personal care products. It is used in the following areas: formulation of mixtures and/or re-packaging and building & construction work. Example of identified uses from ECHA dissemination site:  Cadmium carbonate production – Wet,  Component for production of inorganic cadmium compounds,  Laboratory reagent,  Component for production of organic cadmium compounds,  Component for production of inorganic pigments,  Additive for production of glass,  Component for polymer-matrices, plastics and related preparations,  Use of CdCO3-containing polymers for cable protecting & isolating coatings,  Use of CdCO3-containing polymers for tube & sheet articles,  Use of CdCO3-containing polymers for moulded articles | Yes | Yes |
| **Uses by professional workers** | Cadmium carbonate is used in the following products: polymers, laboratory chemicals, perfumes and fragrances and cosmetics and personal care products. It is used in the following areas: formulation of mixtures and/or re-packaging, building & construction work, agriculture, forestry and fishing and scientific research and development. Examples of identified uses from ECHA dissemination site:  Laboratory reagent,  Use of CdCO3-containing polymers for cable protecting & isolating coatings,  Use of CdCO3-containing polymers for tube & sheet articles,  Use of CdCO3-containing polymers for moulded articles | Yes | Yes |
| **Consumer uses** | No consumer uses were registered for cadmium carbonate |  |  |
| **Article service life** | Cadmium carbonate can be found in complex articles, with no release intended: vehicles, electrical batteries and accumulators. It can be found in products with material based on: plastic (e.g. food packaging and storage, toys, mobile phones). Examples of identified uses from ECHA dissemination site:  Use of CdCO3-containing polymers for tube & sheet articles,  Use of CdCO3-containing polymers for cable protecting & isolating coatings,  Additive for production of glass,  Use of CdCO3-containing polymers for moulded articles  Component for polymer-matrices, plastics and related preparations | Yes | - |

Cadmium carbonate can be considered to have wide dispersive use because:

* + It has at least one reported use by professional workers.
  + It is registered for PROC 5 (mixing or blending in batch processes) and 6 (calendering operations) indicating a potential for exposure to humans[[9]](#footnote-9).

10. Information on structure of the supply chain

No information available.

# 11. Additional information

## 11.1 Substances with similar hazard and use profiles on the Candidate List

The following cadmium compounds are currently included on the Candidate List:

**Table 9 Cadmium compounds on the REACH candidate list**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Name** | **EC no.** | **CAS no.** | **Reason for inclusion** | **Date of inclusion** |
| Cadmium fluoride | 232-222-0 | 7790-79-6 | Carcinogenic (Article 57a) Mutagenic (Article 57b) Toxic for reproduction (Article 57c) Equivalent level of concern having probable serious effects to human health (Article 57 f) | 17/12/2014 |
| Cadmium sulphate | 233-331-6 | 10124-36-4, 31119-53-6 | Carcinogenic (Article 57a) Mutagenic (Article 57b) Toxic for reproduction (Article 57c) Equivalent level of concern having probable serious effects to human health (Article 57 f) | 17/12/2014 |
| Cadmium chloride | 233-296-7 | 10108-64-2 | Carcinogenic (Article 57a) Mutagenic (Article 57b) Toxic for reproduction (Article 57c) Equivalent level of concern having probable serious effects to human health (Article 57 f) | 16/06/2014 |
| Cadmium sulphide | 215-147-8 | 1306-23-6 | Carcinogenic (Article 57a) Equivalent level of concern having probable serious effects to human health (Article 57 f) | 16/12/2013 |
| Cadmium | 231-152-8 | 7440-43-9 | Carcinogenic (Article 57a) Equivalent level of concern having probable serious effects to human health (Article 57 f) | 20/06/2013 |
| |  | | --- | | Cadmium oxide | | 215-146-2 | 1306-19-0 | Carcinogenic (Article 57a) Equivalent level of concern having probable serious effects to human health (Article 57 f) | 20/06/2013 |

## 11.2 Alternatives

Other cadmium salts can be used as raw material for the synthesis of inorganic cadmium compounds.

## 11.3 Existing EU legislation

REACH Regulation, Entry 23 in Annex XVII includes restrictions of cadmium and its compounds, which will decrease the risk for consumers. However, given the wide range of potential uses of cadmium and its compounds, it cannot be completely ruled out that some consumer exposure from articles containing cadmium may still occur.

Selected EU regulations on use and emissions of cadmium include:

* [Regulation (EC) 1223/2009 on cosmetics](http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02009R1223-20140401&qid=1401104217811&from=SV)
* Directive 2009/48/EC about the safety of toys
* Directive 94/62/EC on packaging and packaging waste
* Directive 2006/66/EC on batteries and accumulators and waste batteries and accumulators
* Directive 2002/95/EC on the Restriction of the Use of certain Hazardous Substances in Electrical and Electronic Equipment (RoHS)
* Directive 2002/96/EC on Waste Electrical and Electronic Equipment (WEEE)
* Directive 2000/53/EC on end-of life vehicles
* Directive 2000/60/EC establishing a framework for the Community action in the field of water policy
* Directive 2006/11/EC on pollution caused by certain dangerous substances discharged into the aquatic environment of the Community
* Directive 86/278/EEC of 12 June 1986 on the protection of the environment, and in particular of the soil, when sewage sludge is used in agriculture
* Directive 2010/75/EU on industrial emissions (integrated pollution prevention and control).
* Directive 2008/1/EC concerning integrated pollution prevention and control
* Directive 2001/80/EC on the limitation of emissions of certain pollutants into the air from large combustion plants

Selected EU regulations on cadmium in food or materials in contact with food include:

* Regulation (EC) No 315/93 laying down Community procedures for contaminants in food
* Directive 96/77/EC laying down specific purity criteria on food additives other than colours and sweeteners
* Directive 98/83/EC on the quality of water intended for human consumption
* Directive 84/500/EC on the approximation of the laws of the Member States relating to ceramic articles intended to come into contact with foodstuffs

Other related EU regulations related to cadmium include:

* Regulation (EC) No 2003/2003 of the European parliament and of 13 October 2003 relating to fertilisers.
* Directive 86/278/EEC of 12 June 1986 on the protection of the environment, and in particular of the soil, when sewage sludge is used in agriculture
* Directive 1999/31/EC of 26 April 1999 on the landfill of waste

## 11.4 Previous assessments by other authorities

### 11.4.1 EU RAR

An EU risk assessment is available for cadmium and cadmium oxide (ECB 2007). It was concluded that there was a need for limiting the risks for workers and for humans exposed via the environment, whereas for consumers, no need for further risk reduction measures was identified.

### 11.4.2 Work environment – SCOEL assessment

SCOEL (Scientific Expert Group on Occupational Exposure Limits) has evaluated cadmium (and its inorganic compounds) and suggests an 8-hour time-weighted average (TWA) value of 4 µg/m3 (respirable fraction). Further, a biological limit value in urine is suggested: 2 µg/g creatinine. It may be noted that a lower value, 1 µg/g creatinine, was used by EFSA as a reference point for their risk evaluation of cadmium in food (EFSA 2009). The suggested values for the work environment have so far not been included in the list of indicative occupational exposure limit values (the most recent directive on indicative occupational exposure limit values, 2009/161/EU, was published 17 December 2009).

In the SCOEL document, the proposed limit values are based on effects on the kidney and, to some extent, bone tissue, representing the most sensitive targets of Cd toxicity after occupational exposure. The suggested IOEL (in air) is considered to be protective against long-term local effects (respiratory effects including lung cancer).

### 11.4.3 Swedish risk assessment of cadmium (KemI 2011)

In a report (KemI Rapport Nr 1/11) from the Swedish Chemicals Agency, health effects of cadmium in Sweden were evaluated. The summary is cited below.

***Summary***

*The main source of cadmium exposure is food, mainly food of plant origin, offal and seafood. The gastrointestinal absorption of cadmium is influenced by age, type of diet, and nutritional status, with iron status being particularly important.*

*Blood cadmium is localised mainly in the red blood cells and is a useful marker of ongoing exposure. Urinary cadmium is a useful biomarker of long-term exposure, as it reflects the concentration in the kidney, where cadmium is accumulating with very long half-life. It is the most frequently used biomarker of cadmium exposure. The measured concentrations need to be adjusted for variation in urine dilution, mainly by creatinine or specific gravity. In particular creatinine adjusted urinary cadmium will vary by age, body size, gender, and meat consumption. An alternative way of adjustment is by specific gravity. A critical review of the database on biomarkers of cadmium exposure provides no evidence for a decrease in cadmium exposure over time during the last 2-3 decades in Sweden.*

*Long-term cadmium exposure may cause various toxic effects. The kidney has generally been considered the critical target organ for cadmium toxicity. Circulating cadmium, after being filtered in the glomerular part of the kidney, is reabsorbed and retained in the proximal tubules causing high intracellular concentrations. A large number of studies, also in the Swedish general population, show significant association between cadmium in urine and/or blood and markers of impaired kidney function, mostly impaired tubular function. Critical review of recent studies, particularly those in Sweden, indicates that the risk of impaired function increases already below 1 μg/g creatinine in urine. In addition, cadmium exposure has been associated with impaired glomerular filtration rate, the risk of which seems to start at 0.7 to 1.0 μg/g creatinine.*

*There is a debate concerning the causality and the health significance of the associations between urine-based biomarkers of cadmium exposure and kidney effects (mainly tubular effects) that occur at very low cadmium concentrations. Thus, it is difficult to ascertain the exact lowest effect dose for a clear adverse effect. However, several recent mechanistic studies support effects at low exposure.*

*Because of the uncertainties of lowest effect dose for cadmium in the proximal tubules, the present risk assessment focuses on bone effects of cadmium. It is well established since long that excessive exposure to cadmium affects the metabolism of calcium, in severe cases leading to osteomalacia and osteoporosis, in addition to kidney damage (Itai-Itai disease). Data supporting adverse effects of much lower cadmium exposure on the risk of osteoporosis has increased substantially during the last few years. The effect of cadmium on bone seems to be independent of kidney damage, possibly the effects occur even before the kidney damage. Whereas several epidemiological studies have observed an association between cadmium and bone mineral density, only three published studies have so far considered fracture incidence – the most adverse endpoint with respect to effects on bone. Other studies have included markers of bone remodeling to increase the understanding of causal relationships and possible mechanisms involved. It appears that cadmium preferentially affects bone resorption.*

*Irrespective of whether the studies employed a decrease in the bone mineral density, increased risk of osteoporosis or increased risk of fractures, these changes seem to occur at very low urinary cadmium concentrations. Both a recent Swedish study (SMC) and an American study (NHANES) suggest that already a cadmium concentration in urine of around 0.5 μg/g creatinine is associated with increased risk of osteoporosis and fractures. Importantly, the Swedish studies showed increased risk of osteoporosis and fractures among those who never smoked, suggesting that dietary cadmium alone contribute to the risk. Statistically, every other women and one out of four men in Sweden will suffer from an osteoporotic fracture during their lifetime. Considering the high prevalence of osteoporotic fractures in Sweden, compared to central and southern Europe, it cannot be ruled out that the Swedish population might be more sensitive to cadmium exposure. It should be noted that even a small increase in the average exposure will result in a proportionally larger increase in the fraction of the population at risk of fractures.*

*Cadmium is classified as human carcinogen, mainly based on lung cancer among occupationally exposed people. Mechanistic studies support that cadmium is a carcinogen. The relationship between cadmium exposure and cancer risk has recently also been studied outside the occupational exposure and several studies show increased risks. Experimental studies also suggest that cadmium may have estrogen-like effects. Swedish epidemiological studies have been initiated and associations between estimated dietary exposure and increased risk of hormone-related cancer (endometrial cancer) have been shown. At present it is difficult to draw conclusions about the cancer risk linked to dietary exposure to cadmium, but the data are in support of the need for a precautionary approach. Knowledge on cadmium-related cardiovascular disease and diabetes do not provide sufficient information for risk assessment but also supports a precautionary approach. Two recent well performed prospective studies from Belgium and USA indicate associations between cadmium and increased mortality which is alarming. Still, it is difficult to judge whether the results could be affected by residual confounding. Nevertheless, these data clearly add to the concern that cadmium might exert severe effects on human health.*

*A number of fairly small cross-sectional studies indicate that cadmium exposure may have a negative effect of fetal growth and child development. Although available data does not allow quantitative health risk assessment, these effects should be born in mind.*

*In conclusion, a number of studies, several of which in Sweden, have shown associations between long-term low-level cadmium exposure and adverse health effects mainly in the form of kidney dysfunction, osteoporosis and fractures. Causal relationships are supported by mechanistic experimental studies. Although associations with all those effects are found at very low exposure levels, the main emphasis in this risk assessment has been put on recent data on bone effects of cadmium. Unlike the studies on subclinical kidney effects, the bone effects include several different endpoints, which are not based on urine-based biomarkers. Rather, they include clinical findings, the most severe of which are bone fractures. Thus, the data on bone effects are more suitable for evaluation of health risks at low exposure levels, i.e. levels observed in Sweden today.*

*Taken together, the recent comprehensive epidemiological studies strongly indicate that the effects of cadmium on bone among Swedish women starts somewhere between 0.5 and 1 μg/g creatinine in urine. A considerable part of the Swedish women have urinary cadmium concentrations in this range. Thus, it is clear that cadmium-related health effects occur at the present exposure levels in Sweden.*

*It should be noted that these risk levels (0.5-1 μg/g creatinine) are slightly lower than that (1 μg/g creatinine) reported in the recent EFSA risk assessment of cadmium, which was mainly based on dose-response relationship between urinary cadmium and markers of impaired renal tubular function obtained in a meta-analysis of selected, mainly Asian studies. Because of the associations with multiple health effects observed already at the present cadmium exposure in the general population, it is essential not to increase the exposure further. Compared to most other countries, the risk of fractures is very high in Sweden. In the light of this high prevalence of fractures, the population is likely to be extra sensitive to an exposure that further increases the risk. It should be noted that even a small increase in the average exposure will result in a proportionally large increase in the fraction of the population with increased risk of severe effects, such as fractures. Therefore, mitigation efforts are needed to decrease the exposure, the main part of which is through food.*

### 11.4.4 Risk via food intake (EFSA 2009, 2012)

The European Food Safety Authority (EFSA) has updated their exposure and risk evaluation of cadmium (EFSA 2009, 2012), see summary/abstract below.

***SUMMARY (EFSA 2009)***

*Cadmium (Cd) is a heavy metal found as an environmental contaminant, both through natural occurrence and from industrial and agricultural sources. Foodstuffs are the main source of cadmium exposure for the non-smoking general population. Cadmium absorption after dietary exposure in humans is relatively low (3–5 %) but cadmium is efficiently retained in the kidney and liver in the human body, with a very long biological half-life ranging from 10 to 30 years. Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells where it accumulates over time and may cause renal dysfunction. Cadmium can also cause bone demineralisation, either through direct bone damage or indirectly as a result of renal dysfunction. After prolonged and/or high exposure the tubular damage may progress to decreased glomerular filtration rate, and eventually to renal failure. The International Agency for Research on Cancer has classified cadmium as a human carcinogen (Group 1) on the basis of occupational studies. Newer data on human exposure to cadmium in the general population have been statistically associated with increased risk of cancer such as in the lung, endometrium, bladder, and breast. Cadmium bioavailability, retention and consequently toxicity are affected by several factors such as nutritional status (low body iron stores) and multiple pregnancies, preexisting health conditions or diseases.*

*A health based guidance value for cadmium of 7 μg/kg body weight (b.w.) per week (Provisional Tolerable Weekly Intake (PTWI)) was established previously by the Joint FAO/WHO Expert Committee on Food Additives and endorsed by the Scientific Committee for Food. Although available data indicated that most individuals had intake levels below this PTWI, several international bodies recognised that the margin between this PTWI and the actual weekly intake of cadmium by the general population was small and in some populations may be non-existent. The Scientific Panel on Contaminants in the Food Chain (CONTAM) was asked by the European Commission to assess the risks to human health related to the presence of cadmium in foodstuffs. To provide an updated assessment of exposure from foodstuffs, about 140,000 data covering the period from 2003 to 2007 on cadmium occurrence in various food commodities were received from 20 Member States and considered by the CONTAM Panel. The highest cadmium concentrations were detected in the following food commodities: seaweed, fish and seafood, chocolate, and foods for special dietary uses. For most foods only a small percentage of the analysed samples (<5 %) exceeded the maximum level (ML), where specified. Up to 20 % of the samples were above the MLs for celeriac, horse meat, fish, bivalve molluscs other than oysters and cephalopods. Highly contaminated areas may show higher cadmium concentrations in locally produced food and the use of cadmium-containing fertilisers in agriculture increases cadmium concentrations in the crops and derived products.*

*To assess cadmium dietary exposure, the occurrence data and the consumption data as reported in the EFSA’s Concise European Food Consumption Database were used. National food consumption dietary surveys were used to estimate the consumption pattern of specific sub-groups such as vegetarians and children. The food groups that contributed to the major part of the dietary cadmium exposure, primarily because of the high consumption, were cereals and cereal products, vegetables, nuts and pulses, starchy roots or potatoes, and meat and meat products. The mean dietary exposure across European countries was estimated to be 2.3 μg/kg b.w. per week (range from 1.9 to 3.0 μg/kg b.w. per week) and the high exposure was estimated to be 3.0 μg/kg b.w. per week (range from 2.5 to 3.9 μg/kg b.w. per week). Due to their high consumption of cereals, nuts, oilseeds and pulses, vegetarians have a higher dietary exposure of up to 5.4 μg/kg b.w. per week. Regular consumers of bivalve molluscs and wild mushrooms were also found to have higher dietary exposures of 4.6 and 4.3 μg/kg b.w. per week, respectively. Tobacco smoking can contribute to a similar internal exposure as that from the diet. House dust can be an important source of exposure for children.*

*Cadmium levels in urine are widely accepted as a measure of the body burden and the cumulative amount in the kidneys. The CONTAM Panel carried out a meta-analysis on a selected set of studies to evaluate the dose-response relationship between urinary cadmium and urinary beta-2-microglobulin (B2M). B2M, a low molecular weight protein, is recognised as the most useful biomarker in relation to tubular effects. A Hill model was fitted to the dose-response relationship between urinary cadmium and B2M for subjects over 50 years of age and for the whole population. From the model, a benchmark dose lower confidence limit for a 5 percent increase of the prevalence of elevated B2M (BMDL5) of 4 μg Cd/g creatinine was derived. A chemical-specific adjustment factor of 3.9, to account for inter-individual variation of urinary cadmium within the study populations, was applied, leading to a value of 1.0 μg Cd/g creatinine. Such a value was also supported by data from occupationally exposed workers and by the results of several individual studies using a variety of biomarkers.*

*A one-compartment model was fitted to a large data set based on non-smoking Swedish women (age range from 58 to 70 years), comprising both measurement of dietary cadmium exposure and urinary cadmium concentration to allow an estimation of the relationship between the two. The dietary cadmium exposure that corresponds to the critical urinary cadmium concentration of 1 μg/g creatinine after 50 years of exposure was then estimated using the model. In order to remain below 1 μg Cd/g creatinine in urine in 95 % of the population by age 50, the average daily dietary cadmium intake should not exceed 0.36 μg Cd/kg bw, corresponding to a weekly dietary intake of 2.52 μg Cd/kg b.w. The model calculation took into consideration the human variability in absorption rates (1–10 %) so that high absorption rates common in women of reproductive age groups due to high prevalence of low and empty iron stores as well as variations in half-life were included. Because the data used in the dose-response and kinetic modelling relate to an early biological response and a sensitive population, respectively, no adjustment or uncertainty factor was required for individual variability in susceptibility. Therefore, the CONTAM Panel established a tolerable weekly intake (TWI) for cadmium of 2.5 μg/kg b.w.*

*The mean exposure for adults across Europe is close to, or slightly exceeding, the TWI of 2.5 μg/kg b.w. Subgroups such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI by about 2-fold. Although the risk for adverse effects on kidney function at an individual level at dietary exposures across Europe is very low, the CONTAM Panel concluded that the current exposure to Cd at the population level should be reduced.*

***ABSTRACT (EFSA 2012)***

*Cadmium can cause kidney failure and has been statistically associated with an increased risk of cancer. Food is the dominating source of human exposure in the non-smoking population. The Joint FAO/WHO Expert Committee on Food Additives established a provisional tolerable monthly intake of 25 μg/kg body weight, whereas the EFSA Panel on Contaminants in the Food Chain nominated a tolerable weekly intake of 2.5 μg/kg body weight to ensure sufficient protection of all consumers. To better identify major dietary sources, 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 mollusks. 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 and grain products (26.9%), vegetables and vegetable products (16.0%) and starchy roots and tubers (13.2%). Looking at the food categories in more detail, potatoes (13.2%), bread and rolls (11.7%), fine bakery wares (5.1%), chocolate products (4.3%), leafy vegetables (3.9%) and water mollusks (3.2%) contributed the most to cadmium dietary exposure across age groups. The current review confirmed that children and adults at the 95th percentile exposure could exceed health-based guidance values.*

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# 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 (Ca2+)[[10]](#footnote-10). 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[[11]](#footnote-11).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cadmium compound** | **EC number** | **Structural**  **formula** | **CLP Harmonised classification** | | | |
| **Carc** | **Muta** | **Repro** | **STOT RE** |
| Cadmium carbonate | 208-168-9 | \\kemidom.se\root\Skrivbord\helena\Desktop\10122[1].png | 1B | 1B |  | 1 |
| Cadmium nitrate | 233-710-6 | \\kemidom.se\root\Skrivbord\helena\Desktop\23498[1].png | 1B | 1B |  | 1 |
| Cadmium chloride | 233-296-7 | \\kemidom.se\root\Skrivbord\helena\Desktop\23035[1].png | 1B | 1B | 1B | 1 |
| Cadmium fluoride | 232-222-0 | \\kemidom.se\root\Skrivbord\helena\Desktop\23036[1].png | 1B | 1B | 1B | 1 |
| Cadmium hydroxide | 244-168-5 | \\kemidom.se\root\Skrivbord\helena\Desktop\8488675[1].png | 1B | 1B |  | 1 |
| Cadmium sulphate | 233-331-6 | \\kemidom.se\root\Skrivbord\helena\Desktop\CdSO4.png | 1B | 1B | 1B | 1 |
| Cadmium metal | 231-152-8 | \\kemidom.se\root\Skrivbord\helena\Desktop\22410[1].png | 1B | 2 | 2 | 1 |
| Cadmium oxide | 215-146-2 | \\kemidom.se\root\Skrivbord\helena\Desktop\8373197[1].png | 1B | 2 | 2 | 1 |
| Cadmium sulphide | 215-147-8 | \\kemidom.se\root\Skrivbord\helena\Desktop\7969586[1].png | 1B | 2 | 2 | 1 |

# 

1. Classification in accordance with section 3.6 of Annex I to Regulation (EC) No 1272/2008. [↑](#footnote-ref-1)
2. Classification in accordance with section 3.5 of Annex I to Regulation (EC) No 1272/2008. [↑](#footnote-ref-2)
3. Classification in accordance with section 3.9 of Annex I to Regulation (EC) No 1272/2008. [↑](#footnote-ref-3)
4. <https://echa.europa.eu/registration-dossier/-/registered-dossier/14135> (accessed on 8 May 2017) [↑](#footnote-ref-4)
5. <https://echa.europa.eu/registration-dossier/-/registered-dossier/14135> (accessed on 26 June 2017) [↑](#footnote-ref-5)
6. C&L Inventory database, <http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database> (accessed on 8 May 2017) [↑](#footnote-ref-6)
7. <https://echa.europa.eu/registration-dossier/-/registered-dossier/14135> (accessed on 8 May 2017) [↑](#footnote-ref-7)
8. <https://echa.europa.eu/registration-dossier/-/registered-dossier/14135> (accessed on 26 June 2017) [↑](#footnote-ref-8)
9. ECHA guide to the manual screening of substances for CoRAP and for the SVHC Roadmap to 2020, page 15, 27 Jan 2017. [↑](#footnote-ref-9)
10. See dossiers for harmonised classification and labelling for the substances in the [C&L inventory](https://echa.europa.eu/information-on-chemicals/cl-inventory-database) [↑](#footnote-ref-10)
11. European Commission, 2007, European Union Risk Assessment Report (EU RAR) – Volume 74 cadmium metal, Part II Human Health [↑](#footnote-ref-11)