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 sulphate**
EC Number(s):	**233-331-6**
CAS Number(s):	**10124-36-4; 31119-53-6**
Submitted by:	**Sweden**
Date:	**2014-08-22**

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TABLES

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AGS	German Committee on Hazardous Substances
ß2M, B2M	ß(Beta)$_2$- Microglobulin
BMI	Body Mass Index
CI	Confidence Interval
C&L	Classification and Labelling
CMR	Carcinogenic, Mutagenic, toxic for Reproduction
CONTAM	The Scientific Panel on Contaminants in the Food Chain
EFSA	European Food Safety Authority
ERC	Environmental Release Category (use descriptor according to REACH)
Ery	Erythrocytes
ICdA	International Cadmium Association
IOEL	Indicative Occupational Exposure Limit
LOAEL	Lowest Observed Adverse Effect Level
ML	Maximum Level
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
PBT	Persistent and Bioaccumulative and Toxic
PC	Product Category (use descriptor according to REACH)
PROC	Process Category (use descriptor according to REACH)
PTWI	Provisional Tolerable Weekly Intake
RAR	Risk Assessment Report
RBP	Retinol Binding Protein
SCOEL	Scientific Expert Group on Occupational Exposure Limits
SEK	Swedish Crowns
SMC	Swedish Mammography Cohort
STOT RE	Specific Target Organ Toxicity - Repeated Exposure
SVHC	Substance of Very High Concern
SU	Sector of Use (use descriptor according to REACH)
TWA	(8-hour) Time-Weighted Average
TWI	Tolerable Weekly Intake
vPvB	Very Persistent and very Bioaccumulative

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 sulphate**

EC Number(s): **233-331-6**

CAS Number(s): **10124-36-4; 31119-53-6**

- 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].
- 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].
- The substance is proposed to be identified as a substance meeting the criteria of Article 57 (c) of Regulation (EC) No 1907/2006 (REACH) owing to its classification in the hazard class reproductive toxicity category 1B[3].
- 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 (c) 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 tissues after prolonged exposure (classification STOT RE 1)[4].

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

Carcinogen 1B – 57(a)

Cadmium sulphate is covered by index number 048-009-00-9 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 sulphate is covered by index number 048-009-00-9 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").

[1] Classification in accordance with section 3.6 of Annex I to Regulation (EC) No 1272/2008.
[2] Classification in accordance with section 3.5 of Annex I to Regulation (EC) No 1272/2008.
[3] Classification in accordance with section 3.7 of Annex I to Regulation (EC) No 1272/2008.
[4] Classification in accordance with section 3.9 of Annex I to Regulation (EC) No 1272/2008.

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.

Toxic for reproduction 1B – 57(c)

Cadmium sulphate is covered by index number 048-009-00-9 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 reproductive toxicity category 1B (hazard statement H360FD: May damage fertility; May damage the unborn child).

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

- Reproductive toxicity category 1B in accordance with Article 57(c) of REACH.

Equivalent level of concern – 57(f)

Cadmium sulphate is covered by index number 048-009-00-9 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 sulphate 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 (c) 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 sulphate.

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.

Already 25 years ago it was acknowledged within 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, stabilizers 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 7 on the US Agency for Toxic Substances & Disease Registry's priority list of hazardous substances (www.astdr.cadmiumc.gov), a prioritization 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 to be 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 minor tubular and glomerular dysfunction (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 life-time 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 17 000 articles published during the last 10 years and 9700 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 recent 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 recently 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-standardized 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 recent 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. 450 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 160 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 sulphate 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 (on-site/transported intermediate)

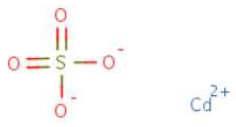
PART I

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:	233-331-6
EC name:	Cadmium sulphate
CAS number (in the EC inventory):	10124-36-4
CAS number: **Deleted CAS numbers:**	31119-53-6, "alternate registry number" (CAS 2014) 7790-84-3, Sulfuric acid, cadmium salt (1:1), hydrate (3:8) (CLP database). 15244-3-6, Sulphuric acid, cadmium salt (1:1), unspecified hydration rate 62642-07-3 (CAS 2014)
CAS name:	Sulfuric acid, cadmium salt (1:1)
IUPAC name:	Cadmium sulphate
Index number in Annex VI of the CLP Regulation	048-009-00-9
Molecular formula:	Cd.H2O4S
Molecular weight range:	208.472
Synonyms:	Cadmium sulfate hydrate Sulfuric acid, cadmium salt (1:1), hydrate (3:8) Cadmium(2+) sulfate hydrate cadmium(2+) trisulfate octahydrate
Structural formula:	

1.2. Composition of the substance

Name: Cadmium sulphate

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 sulphate.

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

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).

2. Harmonised classification and labelling

Cadmium sulphate is covered by Index number 048-009-00-9 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)		
048-009-00-9	Cadmium sulphate	233-331-6	10124-36-4	Carc. 1B Muta. 1B Repr. 1B Acute Tox. 2* Acute Tox. 3* STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H340 H360FD H330 H301 H372** H400 H410	GHS06 GHS08 GHS09 Dgr	H350 H340 H360FD H330 H301 H372** H410		Carc. 1B; H350: C ≥ 0,01% * oral STOT RE 1; H372: C ≥ 7% STOT RE 2; H373: 0,1% ≤ C < 7%	

*The classification as obtained from Annex VII shall then substitute the minimum classification indicated in this Annex if it differs from it.

**The classification under 67/548/EEC indicating the route of exposure has been translated into the corresponding class and category according to this Regulation, but with a general hazard statement not specifying the route of exposure as the necessary information is not available.

H350: May cause cancer
H340: May cause genetic defects
H360FD: May damage fertility. May damage the unborn child.
H330: Fatal if inhaled
H301: Toxic 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.

3. Environmental fate properties

3.1. Anthropogenic and natural sources of cadmium exposure

Cadmium is a natural element, which is present in all environmental compartments (as Cd^{2+}). 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 fertilizers 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 recent 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 can 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 intake, 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 summarized in the table below.

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

	Age	*Urinary cadmium µg/g creatinine*			
	(years)	*Median and (range)*		*% >0.5µg/g*	*%>1.0 µg/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 Helath in the Lund Area, SMC; The Swedish Mammography Cohort;

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.

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

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).

4. Human health hazard assessment

In 2011, the Swedish Chemicals Agency published a report (KemI 2011) containing a human health risk assessment of cadmium from a Swedish exposure perspective (Annex 3 in KemI 2011; Authors: A Åkesson & M Vahter, Karolinska Institutet, Sweden). The summaries on different toxicity endpoints given below are primarily from this report. Since the toxic effects of all cadmium compounds are caused by the cadmium ion, the conclusions for "cadmium" are relevant for cadmium sulphate.

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

According to (KemI 2011), a gastrointestinal absorption of cadmium ranging between 1 and 10 % seems most 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. New-borns and small children may have an even higher absorption, independent of iron status. Lung retention is higher; 25-50 % may be absorbed from fumes and 10-30 % from dust, depending on the particle size. Dermal uptake is considered to be low, likely significantly less than 1 %. Cadmium can cross the placenta but at a low rate (ECB 2007).
After absorption, cadmium is transported in the blood to the liver where cadmium induces 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, and the amounts excreted into urine and faeces are approximately equal. In humans, half-life estimates have been reported to be in the range of 7–16 years (IARC 2012). According to other references (KemI 2011) it is even longer (10-30 years) and in a recent study the biological half-time of Cd in the kidney was calculated to be between 18 and 44 years, depending on the model used (Åkerström et al. 2013a).
Cadmium in urine is mainly 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, and these recent data indicate that 25 mg/kg in the renal cortex roughly corresponds to a urinary cadmium concentration of 0.4 µg/g creatinine (Åkerström et al. 2013a). This indicates that the concentrations in urine correspond to considerably higher concentrations in the kidney cortex than previously observed at autopsy. Because the half-life of cadmium in the body is very long urinary cadmium is highly dependent on age in adults (KemI 2011). A large recent study from Belgium shows that 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 RAR of Cd and CdO (ECB 2007) it was concluded that there is ample and robust evidence of the nephrotoxic potential of cadmium. The main issue was therefore to define the dose-effect/response relationships for this endpoint as well as the health relevance of the endpoints used to establish these relationships. For workers occupationally exposed to cadmium (mainly by inhalation), a LOAEL of 5 µg Cd/g creatinine in urine was considered to constitute a reasonable estimate. The health significance of this threshold was justified by the frequent observation of irreversibility of tubular changes above this value and its association with further renal alteration. Further, it was considered plausible that the lower LOAEL (2 µg

Cd/g creatinine in urine) in the general population exposed by the oral route could be the 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 regarding the present hazard assessment.

According to a later risk assessment (KemI 2011), a number of studies, including the Swedish general population, 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. 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 recent study, using NHANES (National Health and Nutrition Examination Survey) data from 5426 subjects in the USA, 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, while only the concentration of cadmium in blood and not in urine was associated with increased risk of lowered glomerular filtration rates (Ferraro et al, 2010).

That these reported associations represent causal relationships is supported by the fact that associations were observed for several different biomarkers of kidney effects, in several different populations, and in both men and women. Also, the mechanistic studies support an effect at low exposure. 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 simply 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 also 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 (Åkesson et al. 2014).

Although there is strong evidence that elevated levels of several biomarkers of renal dysfunction and/or associations between cadmium burden and these biomarkers occur in populations environmentally exposed to cadmium, there is thus less agreement about the significance of these changes. In addition to the reversibility issue (see Section 6.2.2) there are data indicating an increased mortality risk in subjects having urinary ß2M levels only slightly above normal levels. 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 recent 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).

4.2.2. Bone toxicity

In the EU RAR of Cd and CdO (ECB 2007), it was concluded (based on previous extensive reviews) that it is evident that bone tissue constitutes a target organ for the general and occupational populations exposed to cadmium compounds. The hazard was considered relatively well identified both in experimental and epidemiological studies. The mechanism 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 intoxication is Itai-itai disease, which comprises severe signs of osteoporosis and osteomalacia associated with renal disease in aged women.

According to a more recent risk assessment (KemI 2011), the data supporting an adverse

effect of the present exposure to cadmium in Sweden on the risk of osteoporosis have increased substantially during the last few years. Only a couple of under-powered studies failed to show any association between cadmium and low bone mineral density. Moreover a few studies were considered inconclusive. 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 the new Swedish Mammography Cohort (SMC) (Engström et al. 2011; Engström et al. 2012) and the new American National Health and Nutrition Examination Survey (NHANES) (Gallagher et al. 2011 and Wu et al. 2010; In: KemI 2011) studies suggest that even a urinary concentration from around 0.5 µg/g creatinine is associated with increased risk of osteoporosis and fractures. There are increasing data suggesting that the effect of cadmium on bone is independent of kidney damage - and recent data support that these effects occur even before the kidney damage (Åkesson et al. 2014). Furthermore, the Swedish 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 (KemI 2011; Engström et al. 2012).

Osteoporosis and fractures (KemI 2011)
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 at the hip, spine and forearm. These fractures are a considerable public health problem causing a lot of 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 consumption of alcohol, inactivity, several medical disorders and certain drugs.
The prevalence of osteoporotic complications, fragility fractures, is particularly high in Sweden, as in Norway and Iceland. Statistically, every other women and one out of four men in Sweden will suffer from an osteoporotic fracture during their lifetime. The incidence of hip fractures is more than seven-fold higher in Northern Europe than in the rest of Europe. In fact, it is higher in men in Scandinavia than in women in Central Europe. The reasons for the large age-standardized geographical differences are still not known. It is, however, concluded that 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. Although several risk factors have been identified, they cannot fully explain the above mentioned differences, suggesting that several unknown risk factors or combinations of risk factors are involved.
How to study effects on bone in humans: 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 (assessed by x-ray in g/cm^2) gives an estimation of the status of the skeleton, but is not the only factor predicting the risk of fractures. The bone mineral density can be expressed as it is – a continuous variable – or by calculation of T-score or Z-score. These two scores are used to predict the risk of fractures clinically. 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.

Fractures
Whereas several epidemiological studies have observed an association between cadmium and bone mineral density (for a review see KemI 2011), only few published studies have so far considered fracture incidence – the most adverse endpoint with respect to effects on bone.

CadmiBel: In their prospective cohort, including 506 subjects, the 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 sampled in the relevant districts of residence were used as proxy f cadmium exposure instead of the urinary cadmium concentration (In: KemI 2011).

OSCAR: Fracture incidence was also assessed retrospectively in the Swedish OSCAR study. 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).

Swedish Mammography Cohort: For any first fracture (n=395) the odds ratio (OR) was 1.16 (95% CI, 0.89-1.50) comparing urinary Cd ≥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 from the Swedish Mammography Cohort. The individual dietary cadmium exposure was estimated using a food frequency questionnaire together with national data on cadmium in all foods. Comparing the women's dietary cadmium exposure above the median (13 µg Cd/day) to that below 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).

Cohort of Swedish Men: In a population-based prospective cohort study, where individual cadmium intake was estimated using a food frequency questionnaire in the same manner as in the Swedish Mammography Cohort (average intake 19 µg Cd/day), 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 recent study the association between hip fracture risk and cadmium in erythrocytes (Ery-Cd) was investigated (Sommar et al. 2014). 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 (never, former, or current), 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).

5. 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, 57(f) of REACH.

6. Conclusions on the SVHC Properties

6.1. CMR assessment

Carcinogen 1B – 57(a)

Cadmium sulphate is covered by index number 048-009-00-9 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 sulphate is covered by index number 048-009-00-9 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.

Toxic for reproduction 1B – 57(c)

Cadmium sulphate is covered by index number 048-009-00-9 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 reproductive toxicity category 1B (hazard statement H360FD: May damage fertility; May damage the unborn child).

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

- Reproductive toxicity category 1B in accordance with Article 57(c) of REACH.

6.2. Equivalent level of concern assessment

6.2.1. Summary of the data provided

Cadmium sulphate is classified as STOT RE[5] (hazard statement H372: Causes damage to organs through prolonged or repeated exposure). Cadmium sulphate is identified as a

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

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 (c) of Article 57 of REACH.

6.2.2. Equivalent level of concern assessment

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

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.

Already 25 years ago it was acknowledged within 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, stabilizers 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 7 on the US Agency for Toxic Substances & Disease Registry's priority list of hazardous substances (www.astdr.cadmiumc.gov), a prioritization 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 to be 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 minor tubular and glomerular dysfunction (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 life-time 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 17 000 articles published during the last 10 years and 9700 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 recent 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 recently 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-standardized 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 recent 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. 450 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 160 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.

6.2.3. Conclusion on whether the substance gives rise to an equivalent level of concern

Cadmium sulphate 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.

Part II

7. Manufacture, import and export

A search of the supply database "ChemicalBook" on the Internet June 2014 on CAS No 10124-36-4 revealed a relatively large number of suppliers worldwide. Compared to 2011, the number of suppliers appears to have slightly increased. For example, a search 2014 found a total of 38 suppliers in China (compared to 20 in 2011) and 39 suppliers (35 in 2011) in the rest of the world. Nine of them are in the EU (the same as in 2011).

Most of these suppliers appear to be supplying the substance only in small quantities (laboratory/research scale at quantities of 1 kg or less). However, there were at least two (one 2011) suppliers listed that are reported to be supplying bulk quantities (situated in China and Switzerland) and another supplier of 500 kg quantities (a company in the United States)(ChemExper 2014).

Cadmium sulphate is also marked with the CAS No. 7790-84-3 and 15244-35-6 (Chemical Books 2014). The CAS No 7790-84-3 gave almost the same number of suppliers (72) as CAS No. 10124-36-4. The number of suppliers for the CAS No 15244-35-6 was less (24). The suppliers for the three CAS numbers show different nationality distributions; CAS No. 7790-84-3 and 15244-35-6 were more commonly used by suppliers outside China (compared to the CAS No 10124-36-4). There were no suppliers found for the monohydrate form, CAS No. 13577-20-8.

7.1. Imports and exports of the substance into and from the EU

See the confidential "Annex III".

8. Information on uses of the substance

8.1. Overview of uses

In the registrations, the identified uses of cadmium sulphate are as an intermediate for industrial production of inorganic cadmium compounds, and as laboratory reagent (see Figure 1).

Other non-registered uses identified are as a raw material for metal surface coating and for restoring of lead acid batteries. Since there are numerous C&L notifications, and several different CAS No. appear to be in use, other minor uses may occur.

Further, PROC 21 (Low energy manipulation of substances bound in materials and/or articles) and PC 20 (Products such as pH-regulators, flocculants, precipitants, neutralisation agents), which are indicated in the industrial use "Use of cadmium sulphate as component for production of inorganic cadmium compounds" (ECHA 2014), raise also the question whether all uses of cadmium sulphate in the REACH registrations can be considered as intermediate use. The statement that cadmium sulphate is relevant for "Subsequent service life" also indicates an existing non-intermediate use.

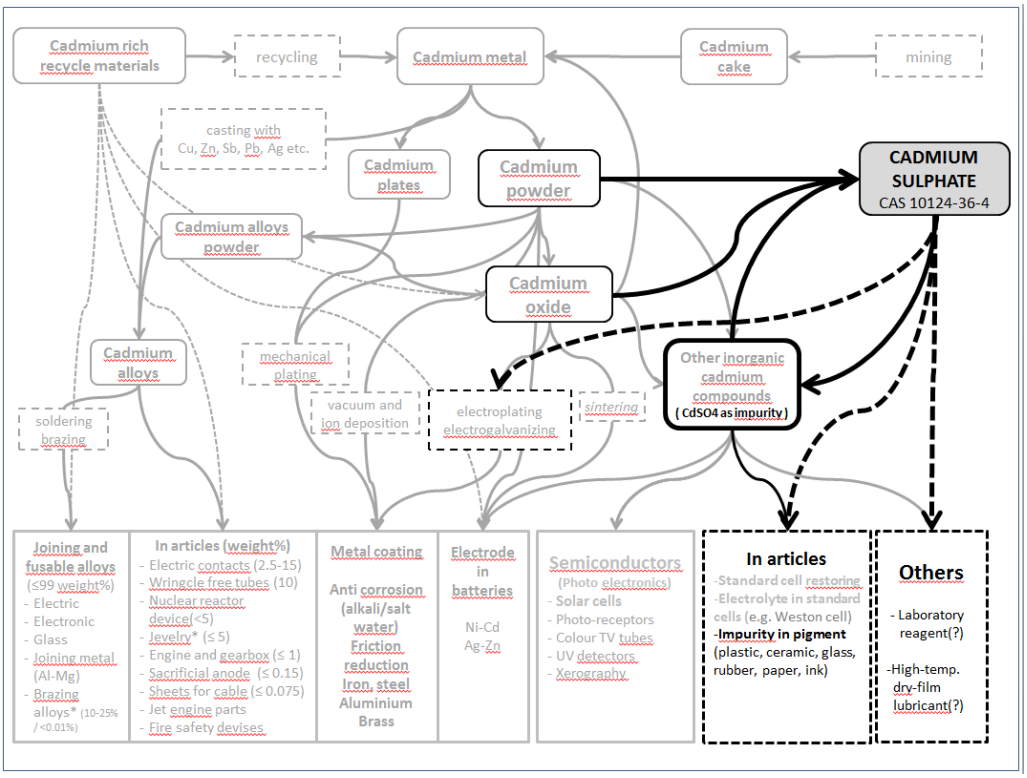


Figure 1: Overview of the cadmium downstream uses with focus on cadmium sulphate. Unregistered or unclear usages are marked with dotted bold lines.

8.2. Substance use for production of inorganic cadmium compounds

8.2.1. Description of industrial use (including use type)

The registrations of cadmium sulphate include the use as raw material for production of inorganic cadmium compounds.

The following **Process Categories** are covered:

- Use in closed process, no likelihood of exposure [PROC 1] and/or Use in closed, continuous process with occasional controlled exposure [PROC 2] and/or Use in closed batch process (synthesis or formulation)[PROC 3].
- Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities [PROC 8b] and/or Transfer of substance or preparation into small containers (dedicated filling line, including weighing) [PROC 9]
- Use as laboratory reagent [PROC 15]
- Low energy manipulation of substances bound in materials and/or articles [PROC 21] and/or potentially closed processing operations with minerals/metals at elevated temperature [PROC 22].

The following **Product Categories** are covered:

- Intermediates [PC 19]
- Products such as pH-regulators, flocculants, precipitants, neutralisation agents [PC 20]
- Laboratory chemicals [PC 22]

The following **Environmental release category** is covered:

- Industrial uses resulting in manufacture of another substance (use of intermediates) [ERC 6a].

The following **Sectors of use** are covered:

- Manufacture of bulk, large scale chemicals (including petroleum products) [SU 8]
- Manufacture of fine chemicals [SU 9]
- Formulation [mixing] of preparations and/or re-packaging (excluding alloys) [SU 10].

8.2.2. Locations and quantities used

See the confidential "Annex III".

8.2.3. Recent and future trends (KemI 2014)

The volumes of cadmium sulphate on the Swedish market as preparations (as such or in mixtures) during 1992 to 2012[6] have been low (≤ 0.04 tpa) and show a slowly decreasing trend. The number of products varies between one and five during the period. None of the uses in the Product register was covered by the uses registered in REACH.

8.3. Substance use as laboratory reagent

One registration of cadmium sulphate includes the use as laboratory reagent. The following **Use descriptors** define the registered use:

- Use as laboratory reagent [PROC 15]
- Laboratory chemicals [PC 21]
- Manufacture of bulk, large scale chemicals (including petroleum products) [SU 08] and/or Manufacture of fine chemicals [SU 09]
- Scientific research and development [SU 24]
- Industrial use resulting in manufacture of another substance (use of intermediates) [ERC6a].

The registration indicates that the substance is supplied for this use as such, and that there are no subsequent service life cycle stages.

[6] Available data years in the Swedish product register

8.4. Non-registered use - Use for battery restoring

Cadmium sulphate containing additives are marked within EU (Omega 2014) and on the Internet (Inox 2014). This use is not covered by the registration but may still occur, probably at low volumes.

The additive increases the performance of lead acid batteries. It can be used on both old and new batteries and also acts as a pacifier and an equalizer on the self-discharge impurities in the electrolyte solution and plates. A one-time treatment will remain active through the extended life of the battery, preventing the formation of excessive sulphation. It is stated that even badly sulphated and disused batteries respond positively. The cadmium sulphate concentration is 5-10% (according to the safety data sheet).

One product has been in use in Sweden since at least 1992 (Omega 2014). However, the Swedish importer has, since 2012, decided to stop the import.

8.5. Non-registered uses – Metal electroplating

Cadmium sulphate is a component in a mixture ("LDC 4803-Cadmium S") used within EU for brushplating or selective plating to put on metal on scratched, worn, corroded or in other ways damaged surfaces (e.g. aircraft components). It is a cold metal coating process. The concentration in the mixture is 10-20% (LDC 2014).

8.6. Other potential uses

Kirk-Othmer (1992) indicates that, at the time, solutions of cadmium sulphate were used in the standard Weston cell and as electrolytes in electroplating (as alternatives to cyanide baths). Other reported uses include phosphors and as a nematocide.

Cadmium sulphate (67%) and graphite has been shown to be an effective high-temperature (room temp.→1000°F) dry-film lubricant (Marshal et.al. 1956). It was considered for aeronautic applications. It is unclear if this potential use is relevant outside the aeronautic area.

8.7. Imports and exports of articles into and from the EU

Cadmium sulphate is not expected to be a component of new made articles.

9. Release and exposure from uses

9.1. Introduction

Since cadmium sulphate is only registered as an intermediate, emissions and exposures are expected to be low. However, since there are numerous C&L notifications (34 notifications for CAS number 10124-36-4 and 77 notifications for CAS number 7790-84-3), other minor uses where exposure may occur cannot be ruled out. Further, PROC 21 (Low energy manipulation of substances bound in materials and/or articles) and PC 20 (Products such as pH-regulators, flocculants, precipitants, neutralisation agents), which are indicated in the industrial use " Use of cadmium sulphate as component for production of inorganic cadmium compounds" (ECHA

2014) raise the question whether all uses of cadmium sulphate can be considered as intermediate use.

9.2. Industrial uses

The exposure of the environment and humans is expected to be low, from the identified industrial uses, mainly because of low releases from (semi)closed industrial systems.

9.3. Professional uses

There are no registered professional uses of cadmium sulphate. There are no data on exposure of the environment and humans from the two identified non-registered professional uses.

9.4. Consumer uses

There are no known consumer uses of cadmium sulphate. However, all cadmium compounds will contribute to the overall release of cadmium to the environment, which indirectly cause exposure of the general population via the environment.

9.5. Releases from use of articles (as impurities)

Cadmium sulphate may occur as an impurity in other cadmium compounds. The origin can be as a raw material and/or a transformation product formed during use. This has been shown for cadmium sulphide based pigments (Leone et.al. 2005). Occurrence of cadmium sulphate may be a source for slow and diffuse releases (e.g. leaching into water or migration into skin).

It is unclear whether use of cadmium sulphate in restoring of acid lead batteries contaminates the recycled lead originating from batteries.

9.6. Summary of releases

The releases of cadmium sulphate are expected to be low due to the (semi)closed industrial intermediate processes. Non-registered end uses may be a contributing source. Occurrence of cadmium sulphate as an impurity in other cadmium compounds may be a possible source for minor diffuse releases.

10. Current knowledge on alternatives

Other cadmium salts can be used as raw material for synthesis of cadmium compounds. There is no information available about alternatives for battery recovery and for electroplating of damaged metal.

11. Existing EU legislation (related to cadmium and its compounds, including cadmium sulphate)

11.1. REACH – Annex XVII

Cadmium sulphate is covered under entries 28-30 of Annex XVII of REACH, which relates to substances which appear in Part 3 of Annex VI of Regulation (EC) No 1272/2008 and are classified as carcinogen category 1A or 1B, mutagenic category 1A or 1B or toxic to

reproduction category 1A or 1B (Table 3.1). Cadmium sulphate shall thus not be used as a substance or in preparations placed on the market for sale to the general public in concentrations above those set as a classification limit (i.e. 0.01 % for cadmium sulphate). Suppliers shall ensure, before the placing on the market, that the packaging of such substances and mixtures is marked visibly, legibly and indelibly as follows: "Restricted to professional users". This restriction does not apply to medicinal or veterinary products, cosmetic products, certain motor fuels, certain mineral oil products, fuels sold in closed systems, and certain artists' paints.

Cadmium and its compounds are further listed in Annex XVII of REACH under entry number 23, which relates to specific uses of cadmium and its compounds that are restricted as cited below:

For the purpose of this entry, the codes and chapters indicated in square brackets are the codes and chapters of the tariff and statistical nomenclature of Common Customs Tariff as established by Council Regulation (EEC) No 2658/87 (OJ L 256, 7.9.1987, p. 42).

1. Shall not be used in mixtures and articles produced from the following synthetic organic polymers (hereafter referred to as plastic material):

   — polymers or copolymers of vinyl chloride (PVC) [3904 10] [3904 21]

   — polyurethane (PUR) [3909 50]

   — low-density polyethylene (LDPE), with the exception of low-density polyethylene used for the production of coloured master batch [3901 10]

   — cellulose acetate (CA) [3912 11]

   — cellulose acetate butyrate (CAB) [3912 11]

   — epoxy resins [3907 30]

   — melamine-formaldehyde (MF) resins [3909 20]

   — urea-formaldehyde (UF) resins [3909 10]

   — unsaturated polyesters (UP) [3907 91]

   — polyethylene terephthalate (PET) [3907 60]

   — polybutylene terephthalate (PBT)

   — transparent/general-purpose polystyrene [3903 11]

   — acrylonitrile methylmethacrylate (AMMA)

   — cross-linked polyethylene (VPE)

   — high-impact polystyrene — polypropylene (PP) [3902 10]

   Mixtures and articles produced from plastic material as listed above shall not be placed on the market if the concentration of cadmium (expressed as Cd metal) is equal to or greater than 0,01 % by weight of the plastic material.

   By way of derogation, the second subparagraph shall not apply to articles placed on the market before 10 December 2011.

   The first and second subparagraphs apply without prejudice to Council Directive 94/62/EC (**) and acts adopted on its basis.

   By 19 November 2012, in accordance with Article 69, the Commission shall ask the European Chemicals Agency to prepare a dossier conforming to the requirements of Annex XV in order to assess whether the use of cadmium and its compounds in plastic material, other than that listed in subparagraph 1, should be restricted.

2. Shall not be used in paints [3208] [3209].

   For paints with a zinc content exceeding 10 % by weight of the paint, the concentration of cadmium (expressed as Cd metal) shall not be equal to or greater than 0,1 % by weight.

   Painted articles shall not be placed on the market if the concentration of cadmium (expressed as Cd metal) is equal to or greater than 0,1 % by weight of the paint on the painted article.

3. By way of derogation, paragraphs 1 and 2 shall not apply to articles coloured with mixtures containing cadmium for safety reasons.

4. By way of derogation, paragraph 1, second subparagraph shall not apply to:

   — mixtures produced from PVC waste, hereinafter referred to as 'recovered PVC',

   — mixtures and articles containing recovered PVC if their concentration of cadmium (expressed as Cd metal) does not exceed 0,1 % by weight of the plastic material in the following rigid PVC applications:

   (a) profiles and rigid sheets for building applications;

   (b) doors, windows, shutters, walls, blinds, fences, and roof gutters;

   (c) decks and terraces;

   (d) cable ducts;

   (e) pipes for non-drinking water if the recovered PVC is used in the middle layer of a multilayer pipe and is entirely covered with a layer of newly produced PVC in compliance with paragraph 1 above.

   Suppliers shall ensure, before the placing on the market of mixtures and articles containing recovered PVC for the first time, that these are visibly, legibly and indelibly marked as follows: '*Contains recovered PVC*' or with the following pictogram:

   In accordance with Article 69 of this Regulation, the derogation granted in paragraph 4 will be reviewed, in particular with a view to reducing the limit value for cadmium and to reassess the derogation for the applications listed in points (a) to (e), by 31 December 2017.

5. For the purpose of this entry, 'cadmium plating' means any deposit or coating of metallic cadmium on a metallic surface.

   Shall not be used for cadmium plating metallic articles or components of the articles used in the following sectors/applications:

   (a) equipment and machinery for:

   — food production [8210] [8417 20] [8419 81] [8421 11] [8421 22] [8422] [8435] [8437] [8438] [8476 11]

   — agriculture [8419 31] [8424 81] [8432] [8433] [8434] [8436]

   — cooling and freezing [8418]

   — printing and book-binding [8440] [8442] [8443]

   (b) equipment and machinery for the production of:

— household goods [7321] [8421 12] [8450] [8509] [8516]

— furniture [8465] [8466] [9401] [9402] [9403] [9404]

— sanitary ware [7324]

— central heating and air conditioning plant [7322] [8403] [8404] [8415]

In any case, whatever their use or intended final purpose, the placing on the market of cadmium-plated articles or components of such articles used in the sectors/applications listed in points (a) and (b) above and of articles manufactured in the sectors listed in point (b) above is prohibited.

6. The provisions referred to in paragraph 5 shall also be applicable to cadmium-plated articles or components of such articles when used in the sectors/applications listed in points (a) and (b) below and to articles manufactured in the sectors listed in (b) below:

(a) equipment and machinery for the production of:

— paper and board [8419 32] [8439] [8441]

—textiles and clothing [8444] [8445] [8447] [8448] [8449] [8451] [8452]

(b) equipment and machinery for the production of:

— industrial handling equipment and machinery [8425] [8426] [8427] [8428] [8429] [8430] [8431]

— road and agricultural vehicles [chapter 87]

— rolling stock [chapter 86]

— vessels [chapter 89]

7. However, the restrictions in paragraphs 5 and 6 shall not apply to:

— articles and components of the articles used in the aeronautical, aerospace, mining, offshore and nuclear sectors whose applications require high safety standards and in safety devices in road and agricultural vehicles, rolling stock and vessels,

— electrical contacts in any sector of use, where that is necessary to ensure the reliability required of the apparatus on which they are installed.

8. Shall not be used in brazing fillers in concentration equal to or greater than 0.01 % by weight.

Brazing fillers shall not be placed on the market if the concentration of cadmium (expressed as Cd metal) is equal to or greater than 0.01 % by weight.

For the purpose of this paragraph brazing shall mean a joining technique using alloys and under- taken at temperatures above 450 °C.

9. By way of derogation, paragraph 8 shall not apply to brazing fillers used in defence and aerospace applications and to brazing fillers used for safety reasons.

10. Shall not be used or placed on the market if the concentration is equal to or greater than 0,01 % by weight of the metal in:

(i) metal beads and other metal components for jewellery making;

(ii) metal parts of jewellery and imitation jewellery articles and hair accessories, including:

— bracelets, necklaces and rings,

— piercing jewellery,

— wrist-watches and wrist-wear,

— brooches and cufflinks.

11. By way of derogation, paragraph 10 shall not apply to articles placed on the market before 10 December 2011 and jewellery more than 50 years old on 10 December 2011.

11.2. Workers legislations

Cadmium sulphate and other carcinogenic substances are regulated in Directive 2004/37/EC, which aims at the protection of workers from risks to their health and safety from exposure to carcinogens at work. Based on a determination and assessment of risks by the employer, the Directive provides a step-by-step approach for risk control, ranging from replacement of the substance to measures that limit the quantities of a carcinogen at the place of work and keeping as low as possible the number of workers exposed or likely to be exposed. Further requirements include the use of existing appropriate procedures for the measurement of carcinogens, the application of suitable working procedures and methods and the use of collective and/or, where exposures cannot be avoided by other means, individual protection measures. Provisions are made for employers to ensure that workers receive sufficient information and appropriate training as well as for Member States who shall establish arrangements for carrying out relevant health surveillance of workers.

Cadmium and compounds are listed in Annex II of the European Schedule of occupational diseases (C (2003) 3297). It is thus suspected of being a causal agent for professional diseases.

11.3. Selected EU regulations on use and emissions of cadmium

Regulation (EC) 1223/2009 on cosmetics

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

11.4. EU regulations on cadmium in food or materials in contact with food

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

11.5. Other related EU regulations

Regulation (EC) No 2003/2003 of the European parliament and of the 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

12. Previous assessments by other authorities

12.1. 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.

12.2. 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/m^3 (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).

12.3. Swedish risk assessment of cadmium (KemI 2011)

In a recent 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 localized 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.

12.4. Risk via food intake (EFSA 2009, 2012)

The European Food Safety Authority (EFSA) has recently 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 recognized 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.

13. Executive summary of information on manufacture, use, exposure and alternatives

13.1. Manufacture, imports and exports

Cadmium sulphate is manufactured and imported in EU for intermediate use only.

13.2. Uses

The main use of cadmium sulphate is as an intermediate for production of other inorganic cadmium substances. Another registered use is as laboratory reagent. Two non-registered probably low volume uses have been identified, in preparations for restoring acid lead battery and for restoring old cadmium coatings of metal components.

13.3. Releases from manufacture and use

Only minor volumes are expected to be released from manufacture and industrial and professional uses. Minor releases may occur from cadmium sulphate as impurity in other cadmium substances.

13.4. Current knowledge of alternatives

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

REFERENCES

References for Part I

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.

CAS (2014). Chemical Abstract Service via the STN Chemical Online database. Searched 27 June 2014. http://www.stn-international.de

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.

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. Part I – Environment. 3rd Priority List, Volume 72, EUR 22919 EN, European Chemicals Bureau. European Union Risk Assessment Report: Cadmium metal. Part II – human health. 3rd Priority List, Volume 74, EUR 22767 EN, European Chemicals Bureau.

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.

EFSA (2012) European Food Safety Authority. Cadmium dietary exposure in the European population. EFSA Journal **10(1)**, 2551. European Food Safety Authority; Cadmium dietary exposure in the European population. EFSA Journal, 2012;10(1):2551 [37 pp.] doi:10.2903/j.efsa.2012.2551. Available online: 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.

Gallagher CM, Kovach JS & Meliker JR. (2008) Urinary cadmium and osteoporosis in U. S. women ≥50 years of age: NHANES 1988-1994 and 1999-2004. Environmental Health Perspectives, **116(10)**, 1338-1343.

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

ICdA (2012). The release of cadmium to the environment due to corrosion from anthropogenic Sources, by Hugh Morrow, International Cadmium Association.
http://www.chem.unep.ch/pb_and_cd/SR/Files/Submission%20NGO/ICdA/Cadmium%20Corrosion%20Paper_and_presentation2003.pdf

KemI (2011) Kadmiumhalten måste minska–för folkhälsans skull. Rapport Nr 1/11. Bilaga 3. Health effects of cadmium in Sweden. Available at:
http://www.kemi.se/Documents/Publikationer/Trycksaker/Rapporter/KemI_Rapport_1_11.pdf

KemI (2013). Economic costs of fractures caused by dietary cadmium exposure. Swedish Chemicals Agency. Report No 4/13. Available at:
http://www.kemi.se/Documents/Publikationer/Trycksaker/Rapporter/Rapport-4-13-cadmium.pdf

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.

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

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/auvaportal/content/contentWindow?contentid=10008.544427&action=b&cacheability=PAGE

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, 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. Environmental Health, **12:9**. doi: 10.1186/1476-069X-12-9.

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.

Thomas LDK, Michaelsson K, Julin B, Wolk A, Åkesson A. (2011) Dietary cadmium exposure and fracture incidence among men: A population-based prospective cohort study. Journal of Bone and Mineral Research, **26(7)**, 1601-1608.

Wu Q, Magnus JH, Hentz JG. (2010) Urinary cadmium, osteopenia, and osteoporosis in the US population. Osteoporosis International, **21(8)**, 1449-1454.

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.

Åkesson A, Barregård L, Bergdahl IA, Nordberg GF, Nordberg M & Skerfving S. (2014) Non-renal effects and the risk assessment of environmental cadmium exposure. Environmental Health Perspectives, **122(5)**, 431-438.

References for Part II

Chemical Book (2014). Chemical supplier database. Accessed on 2 July 2014. http://www.chemicalbook.com/

ChemExper (2014). Chemical supplier database. Accessed on 2 July 2014. http://www.chemexper.com/

ECB (2007) European Union Risk Assessment Report: Cadmium oxide and cadmium metal. Part I – Environment. 3rd Priority List, Volume 72, EUR 22919 EN, European Chemicals Bureau. European Union Risk Assessment Report: Cadmium metal. Part II – human health. 3rd Priority List, Volume 74, EUR 22767 EN, European Chemicals Bureau.

ECHA (2014). Cadmium sulphate. Information on registered substances, published on ECHA's website http://apps.echa.europa.eu/registered/registered-sub.aspx#search (accessed on 8 July 2014).

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.

EFSA (2012) European Food Safety Authority. Cadmium dietary exposure in the European population. EFSA Journal **10(1)**, 2551. European Food Safety Authority; Cadmium dietary exposure in the European population. EFSA Journal, 2012;10(1):2551 [37 pp.] doi:10.2903/j.efsa.2012.2551. Available online: www.efsa.europa.eu/efsajournal.

Inox (2014). Material Safety Data Sheet. For Inox Lubricants mx2 Battery Conditioner, updated March 2010. http://www.inoxmx.com/wp-content/uploads/MX2-MSDS-INOX-mx2-Battery-Conditioner-AUSTRALIA.pdf. Accessed on 4 July 2014.

KemI (2011) Kadmiumhalten måste minska–för folkhälsans skull. Rapport Nr 1/11. Bilaga 3. Health effects of cadmium in Sweden. Available at: http://www.kemi.se/Documents/Publikationer/Trycksaker/Rapporter/KemI_Rapport_1_11.pdf

KemI (2014). Search in the Swedish Product register 8 July 2014. The Swedish Chemical Agency.

Kirk-Othmer (1992). Cadmium compounds. Kirk-Othmer Encyclopedia of Chemical Technology, Volume 4, Fourth Edition, p771.

LDC (2014). MSDS for the chemical product "LDC-4803 Camium S". LDC Sales & Consulting AB, Sweden http://www.ldc-brushplating.com/ . 8 July 2014.

Leone B., Burnstock A., Jones C., Hallebeek P., Keune K. & Boon J. (2005). The deterioration of cadmium sulphide yellow artists' pigments, **In:** 14th triennial meeting The Hague, 12-16 September 2005 : ICOM Committee for Conservation : preprints volume 2 / I. Verger London: James & James, 2005. - pp.803-813.

Omega (2014). Product datasheet for the chemical product OMEGA 908. http://www.sovereign-omega.co.uk/Datasheets/Omega908-1.pdf. Internet search 4 July 2014.

Marshall B., Peterson B. & Johnson L. (1956). National Advisory Committee for Aeronautics (NACA). Technical note 3657. Friction studies of graphite and mixture of graphite with several metallic oxides and salts at temperature to 1000°F. Washinton February 1956.

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

Annex I - Additional information on hazard and risk

In 2011, the Swedish Chemicals Agency published a report (KemI 2011) containing a human health risk assessment of cadmium from a Swedish exposure perspective (Annex 3 in KemI 2011; Authors: A Åkesson & M Vahter, Karolinska Institutet, Sweden). The summaries on different toxicity endpoints given below are primarily from this report.

Developmental toxicity

Neurotoxicity and child development

The risk assessments of Cd and CdO performed according to the Existing Substances legislation (ESR) concluded that "*information is needed to better document the possible neurotoxic effects of Cd suggested in experimental animals, especially on the developing brain. The collection of this additional information should, however, not delay the implementation of appropriate control measures needed to address the concerns expressed for several other health effects including repeated dose toxicity and carcinogenicity*" (ECB 2007). A few small cross-sectional epidemiological studies indicate an adverse effect of cadmium exposure on child development, supported by experimental studies showing cadmium-induced neurotoxicity. Although available data does not allow quantitative health risk assessment, these effects should be kept in mind (Swedish Chemicals Agency 2011).

A recent investigation in U.S. children, using NHANES data on approximately 2 200 individuals, suggests that low-level environmental cadmium exposure in children may be associated with adverse neurodevelopmental outcomes (Ciesielski et al. 2012). Median urinary cadmium (µg/L) ranged from 0.078 (age 6-7 yrs) to 0.146 (age 14-15 yrs). When comparing children in the highest quartile of urinary cadmium with those in the lowest quartile, adjusted odds ratios were 3.21 (95% CI: 1.43-7.17) for learning disabilities, 3.00 (95% CI: 1.12-8.01) for special education and 0.67 (95% CI: 0.28-1.61) for attention deficit hyperactivity disorder (ADHD). The urinary cadmium levels in U.S. children are probably similar to what can be expected within EU. For example, the median urinary level in young (age 20-29 yrs) non-smoking women in Sweden is approximately 0.1-0.2 µg/g creatinine, corresponding roughly to 0.1-0.2 µg/L. For urinary cadmium levels in Sweden, see the following link: http://www.imm.ki.se/Datavard/Tidsserier/Cadmium%20in%20urine.htm.
A study on early-life low-level cadmium exposure in rural Bangladesh also indicates effects on child development, showing lower child intelligence, particularly in girls (Kippler et al. 2012).

Endocrine effects *(primarily from KemI 2011 and references therein)*

The significance of the estrogen-mimicking effects such as the well-characterized estrogenic responses of the endometrial lining (hypertrophy and hyperplasia) observed in animals exposed to environmentally relevant doses of cadmium (Johnson et al 2003), was further explored in humans (Åkesson et al 2008). In a large population-based prospective cohort among Swedish postmenopausal women (n = 32 210) the association between dietary cadmium intake and endometrial cancer incidence, the cancer form most suited to explore potential estrogenic effects, was assessed. This is the first study exploring health effects in relation to dietary cadmium intake, which is in contrast to smaller studies where cadmium has been monitored in urine. Thus, based on the construction of a food-cadmium database in the cohort, a large study population was utilized and the incidence was assessed prospectively. This design reduces the selection bias that often occurs in case-control studies, but is on the other hand, dependent on the assumption that estimated dietary cadmium intake is a valid reflection of the internal dose. The average estimated cadmium intake was 15 µg/day (1.5 µg/kg bw per week). During 16 years of follow-up, 378 cases of endometroid adenocarcinoma were ascertained through computerized linkage to the Swedish Cancer Registry with virtually no loss to follow-up. The highest versus lowest tertile of cadmium intake was associated with

risk of endometrial cancer, RR 1.39 (95 % confidence interval, CI, 1.04-1.85; P for trend 0.02). To reduce the influence of endogenous estrogen exposure, analyses were stratified by body mass index and by use of postmenopausal hormone use. Analyses were also stratified by smoking status because an anti-estrogenic effect of cigarette smoking is shown on circulating estrogen concentrations due to increased metabolic clearance, a reduction in relative body weight, and an earlier age at menopause. Among never-smoking, non-overweight women the RR was 1.86 (95 % CI 1.13-3.08; P for trend 0.009). A 2.9-fold increased risk (95 % CI 1.05-7.79) was observed with long-term cadmium intake consistently above the median intake in both 1987 and in 1997 in never-smoking women with low available estrogen (non-overweight and non-users of postmenopausal hormones). Although the data support the hypothesis that cadmium may exert estrogenic effects and possibly increase the risk of hormone-related cancers this needs to be confirmed by other studies (KemI 2011).

In the same study population as for the study on endometrial cancer incidence (Swedish Mammography Cohort; a population-based prospective cohort), the association between dietary cadmium exposure and risk of overall and estrogen receptor defined (ER+ or ER-) post-menopausal breast cancer was assessed. In 55 987 postmenopausal women who completed a food frequency questionnaire at baseline in 1987 a total of 2112 incident cases of invasive breast cancer were ascertained (1626 ER+ and 290 ER-) during an average follow-up of 12.2 years. It was found that dietary cadmium was positively associated with overall breast cancer tumors. The risk ratio when comparing the highest tertile with the lowest was 1.21 (95% CI 1.07-1.36) (Julin et al 2012). These results are in line with the results of the endometrial cancer study (Åkesson el al 2008).

In a recent thesis from the Karolinska Institutet (Ali 2013) investigations on the estrogen-like effects of cadmium as well as possible involvement of classical/non-classical estrogen receptor signaling was studied in mice, and these mechanisms were further scrutinized in cell-based models. Furthermore, associations of biomarker of cadmium exposure with endogenous circulating sex hormones were evaluated in a population-based study of women. The data collectively suggests that cadmium-induced estrogen-like effects do not involve classical estrogen receptor signalling but rather appear to be mediated via membrane-associated signalling. The activation/ transactivation of GPR30/EGFR-Raf-MEK-ERK/MAPKs and Mdm2 represent a general mechanism by which cadmium may exert its effects. Since EGFR, ERK and Mdm2 are all known key players in cancer promotion, cadmium-induced activation of these and disturbance in the estradiol/testosterone balance in women may have implications for the promotion/development of hormone-related cancers.

A recent meta-analysis showed statistically significant positive associations between dietary cadmium intake and hormone-related cancers in humans. The relative risks, in the highest dietary group compared with the lowest dietary group, were RR= 1.15 (95% CI 1.04-1.28), RR= 1.40 (95% CI 1.06-1.84) and RR= 1.14 (95% CI 1.04-1.24) for breast cancer, endometrial cancer and prostate cancer, respectively (Cho et al 2013).

Overall mortality

Two recent studies from Belgium and USA (described in KemI 2011) indicate associations between cadmium and increased mortality which is alarming. Both studies are of high quality (prospective) and the Belgian study has even included repeated measurements of exposure. Still, it is difficult to judge whether the results could be due to confounding. For instance, low urinary creatinine excretion is associated with all-cause mortality and cardiovascular disease. Thus, adjusting a urine-based exposure marker by creatinine may result in falsely high associations between exposure and disease or mortality. Noteworthy, is that the Belgian study employed urinary cadmium per 24 hours and blood cadmium. Nevertheless, these data clearly add to the concern that cadmium might exert severe effects on human health (KemI 2011).

References (Annex I)

Ali I. (2013) Modulation of hormone signaling by cadmium: From molecular mechanisms to health implications. Academic thesis at Karolinska Institutet.

Cho YA, Kim J, Woo HD & Kang M. (2013) Dietary cadmium intake and the risk of cancer: A meta-analysis. PLoS One, **8(9)**, e75087.

Ciesielski T, Weuve J, Bellinger DC, Schwarz J, Lanphear B & Wright RO. (2012) Cadmium exposure and neurodevelopmental outcomes in U.S. children. Environmental Health Perspectives, **120**, 758-763.

ECB (2007). European Union Risk Assessment Report: Cadmium oxide and cadmium metal. Part I – Environment. 3rd Priority List, Volume 72, EUR 22919 EN, European Chemicals Bureau. European Union Risk Assessment Report: Cadmium metal. Part II – human health. 3rd Priority List, Volume 74, EUR 22767 EN, European Chemicals Bureau.

Johnson MD, Kenney N, Stoica A, et al. (2003) Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. Nature Medicine, **9(8)**, 1081-1084.

Julin B, Wolk A, Bergkvist L, Bottai M & Åkesson A. (2012). Dietary cadmium exposure and risk of postmenopausal breast cancer: A population-based prospective cohort study. (2012) Cancer Research, **72**, 1459-1466.

KemI (2011) Kadmiumhalten måste minska–för folkhälsans skull. Rapport Nr 1/11. Bilaga 3. Health effects of cadmium in Sweden.
http://www.kemi.se/Documents/Publikationer/Trycksaker/Rapporter/KemI_Rapport_1_11.pdf

Kippler M, Tofail F, Hamadani JD, Gardner RM, Grantham-McGregor SM, Bottai M & Vahter M. (2012). Early-life cadmium exposure and child development in 5-year-old girls and boys: A cohort study in rural Bangladesh. Environtal Health Perspectectives, **120(10)**, 1462-1468.

Official Statistics of Sweden:
http://www.imm.ki.se/Datavard/Tidsserier/Cadmium%20in%20urine.htm

Åkesson A, Julin B & Wolk A. (2008) Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: A population-based prospective cohort study. Cancer Research, **68(15)**, 6435-6441.