Substance Name: Cadmium sulphate

EC Number: 233-331-6

CAS Number: 10124-36-4; 31119-53-6

MEMBER STATE COMMITTEE

SUPPORT DOCUMENT FOR IDENTIFICATION OF

CADMIUM SULPHATE

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR[1] PROPERTIES AND BECAUSE OF ITS ADVERSE EFFECTS ON KIDNEY AND BONE TISSUES AFTER PROLONGED EXPOSURE, WHICH CAUSE PROBABLE SERIOUS EFFECTS TO HUMAN HEALTH WHICH GIVE RISE TO AN EQUIVALENT LEVEL OF CONCERN TO THOSE OF CMR PROPERTIES

Adopted on 27 November 2014

[1] CMR means carcinogenic, mutagenic or toxic for reproduction

CONTENTS

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

Substance name: Cadmium sulphate

EC Number(s): 233-331-6

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

- The substance is identified as a substance meeting the criteria of Article 57 (a) of Regulation (EC) No 1907/2006 (REACH) owing to its classification in the hazard class carcinogenicity category 1B[2].

- The substance is identified as a substance meeting the criteria of Article 57 (b) of Regulation (EC) No 1907/2006 (REACH) owing to its classification in the hazard class germ cell mutagenicity category 1B[2].

- The substance is 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[2].

- The substance is identified as a substance of equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of Regulation (EC) No 1907/2006 (REACH) according to Article 57(f) of REACH Regulation owing to the scientific evidence of probable serious effects to human health because of adverse effects on kidney and bone tissues after prolonged exposure (classification STOT RE 1)[2].

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

Carcinogen 1B – Article 57(a)

Cadmium sulphate is listed as 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 – Article 57(b)

Cadmium sulphate is listed as 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 – Article 57(c)

[2] Classification in accordance with section 3.6 of Annex I to Regulation (EC) No 1272/2008.

Cadmium sulphate is listed as 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 – Article 57(f)

Cadmium sulphate is listed as 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 (e) of Article 57 REACH.

Since the toxic effects of all cadmium compounds are caused by the cadmium ion, the conclusions for “cadmium” are relevant for cadmium 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 database 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 (2010), 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;

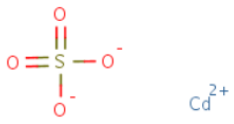
- the adverse effects on kidney and bones, effects that depending on dose may be serious and even contribute to premature death,
- the continuous accumulation of cadmium in the body, which leads to continuous internal exposure and in practice irreversible effects once adverse effect levels are reached,
- 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)

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). 15244-35-6, 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 listed as 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 (years)	*Urinary cadmium µg/g creatinine*			
		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). Likewise, data on young individuals from Germany do not suggest a decreasing trend (Becker et al. 2013).

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 – Article 57(a)

Cadmium sulphate is listed as 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 – Article 57(b)

Cadmium sulphate is listed as 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 – Article 57(c)

Cadmium sulphate is listed as 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[3] (hazard statement H372: Causes damage to organs through prolonged or repeated exposure). Cadmium sulphate is identified as a

[3] 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 (e) 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 (2010), 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.

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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).

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