

Annex XV report

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR 1A OR 1B, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name(s): Cadmium chloride

EC Number(s): 233-296-7

CAS Number(s): 10108-64-2

Submitted by: Swedish Competent Authority (Swedish Chemicals Agency)

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ABBREVIATIONS

AC	Article Category (use descriptor according to REACH)
β2M	β ₂ - Microglobulin
CAREX	The CARcinogen EXposure database
CSA	Chemical Safety Assessment
CI	Confidence Interval
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)
ESR	Existing Substances Regulation
ICdA	International Cadmium Association
IOEL	Indicative Occupational Exposure Limit
NHANES	National Health and Nutrition Examination Survey
Ni-Cd	Nickel-Cadmium
PBT	Persistent and Bioaccumulative and Toxic
PC	Product Category (use descriptor according to REACH)
PROC	Process Category (use descriptor according to REACH)
PTVI	Provisional Tolerable Weekly Intake
PVC	Poly Vinyl Chloride
PVD	Physical Vapor Deposition
RAR	Risk Assessment Report
RBP	Retinol Binding Protein
SCOEL	Scientific Expert Group on Occupational Exposure Limits
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)
TWI	Tolerable Weekly Intake
vPvB	Very Persistent and very Bioaccumulative

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR 1A OR 1B, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name: Cadmium chloride

EC Number(s): 233-296-7

CAS Number(s): 10108-64-2

- The substance is proposed to be identified as substance meeting the criteria of Article 57 (a) of Regulation (EC) 1907/2006 (REACH) owing to its classification as carcinogen category 1B¹, which corresponds to classification as carcinogen category 2².
- The substance is proposed to be identified as substance meeting the criteria of Article 57 (b) of Regulation (EC) 1907/2006 (REACH) owing to its classification as mutagen category 1B¹, which corresponds to classification as mutagen category 2².
- The substance is proposed to be identified as substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction category 1B¹, which corresponds to classification as toxic for reproduction category 2².
- It is proposed to also identify the substance as substance of equivalent concern according to Article 57 (f), owing to the adverse effects on kidney and bone tissues after prolonged exposure (classification STOT RE1).

Summary of how the substance meets the criteria set out in Article 57(a), 57(b), 57(c) and 57(f) of REACH.

Carcinogen 1B

Cadmium chloride is listed as Index number 048-008-00-3 in Regulation (EC) No 1272/2008³ and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as carcinogenic, Carc. 1B (H350: May cause cancer). The corresponding classification in Annex VI, part 3, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I to Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is carcinogenic, Carc. Cat. 2, R45 (May cause cancer).

¹ Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances, OJ L 353, p.1, 31.12.2008

² Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC), OJ L 353, p.1, 31.12.2008.

³ Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

Therefore, this classification of cadmium chloride in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as carcinogenic in accordance with Article 57(a) of REACH.

Mutagen 1B

Cadmium chloride is listed as Index number 048-008-00-3 in Regulation (EC) No 1272/2008³ and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as mutagenic, Muta. 1B (H340: May cause genetic defects). The corresponding classification in Annex VI, part 3, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I to Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is mutagenic, Muta. Cat. 2, R46 (May cause heritable genetic damage).

Therefore, this classification of cadmium chloride in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as mutagenic in accordance with Article 57(b) of REACH.

Toxic for reproduction 1B

Cadmium chloride is listed as Index number 048-008-00-3 in Regulation (EC) No 1272/2008³ and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as toxic for reproduction, Repr. 1B (H360FD: May damage fertility; May damage the unborn child). The corresponding classification in Annex VI, part 3, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I to Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is toxic for reproduction, Repr. Cat. 2, R60-61 (May impair fertility. May cause harm to the unborn child.).

Therefore, this classification of cadmium chloride in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic for reproduction in accordance with Article 57(c) of REACH.

Equivalent level of concern

According to REACH Article 57(f), substances for which there is scientific evidence of probable serious effects to human health or the environment, which give rise to an equivalent level of concern to CMR or PBT/vPvB substances and which are identified on a case-by-case basis, may be included in Annex XIV in accordance with the procedure laid down in Article 58.

Cadmium chloride has the ability to cause a large number of toxic effects as is evident from the harmonised classification. It is thus clear that cadmium chloride may cause many different serious health effects in addition to the ability to cause cancer. Adverse effects on multiple organs after repeated exposure, in particular on *kidney* and *bone*, motivated the classification as STOT RE Category 1, and it is in particular effects on kidney and bone that justify the equivalent level of concern.

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

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 (see: The 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*)). 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 β 2M > 1,000-1,500 μ g/g creatinine) is generally irreversible.

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

The biological half-life of cadmium in humans is extremely long (estimated to be 10-30 years) and the body burden of cadmium therefore increases, mainly via accumulation in the kidney, during the entire life span of an individual (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 16 300 articles published during the last 10 years and 9300 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), 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 chloride is considered to fulfil the criteria according to Art. 57(f), i.e. there is scientific evidence of probable serious effects to human health which give rise to “equivalent level of concern”, due to;

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

Registration dossier(s) submitted for the substance? Yes

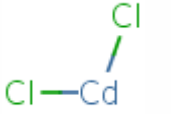
PART I

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:	233-296-7
EC name:	cadmium chloride
CAS number (in the EC inventory):	10108-64-2
CAS number:	7790-78-5 (cadmium chloride (CdCl ₂) hydrate (2:5)) Deleted: 34330-64; 143983-90-8
CAS name:	cadmium chloride (CdCl ₂)
IUPAC name:	cadmium dichloride
Index number in Annex VI of the CLP Regulation	048-008-00-3
Molecular formula:	CdCl ₂
Molecular weight:	183.317
Synonyms:	Cadmium dichloride Cadmium(II) chloride Dichlorocadmium
Structural formula:	$\text{Cd}^{2+} \quad \text{Cl}^- \quad \text{Cl}^-$ 

1.2 Composition of the substance**Name:** cadmium chloride**Degree of purity:** 80-100 % (w/w). The substance is a mono constituent substance.**1.3 Physico-chemical properties**Table 2: Overview of physicochemical properties (*data from dissemination database according to REACH, Article 119*)⁴

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	Solid Powder Colour: white Odour: odourless	From registration ⁴
Relative density	The density of the substance is 3.91 g/cm ³ at 22 °C.	From registration ⁴
Granulometry	The D50 of the powder is 123 µm, the D80 is 396 µm.	From registration ⁴
Water solubility	Experimental (at pH 3.8): 457 g Cd/L at 20 °C (very soluble)	From registration ⁴

⁴ <http://echa.europa.eu/information-on-chemicals>

2 HARMONISED CLASSIFICATION AND LABELLING

Cadmium chloride is listed as Index number 048-008-00-3 in Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, as follows:

Table 3: Harmonised classification of cadmium chloride according to 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		Labeling	
				Hazard Class and Category Code(s)	Hazard statement code(s)	Pictogram Signal Word Code(s)	Hazard Statement Code(s)
048-008-00-3	Cadmium chloride	233-296-7	10108-64-2	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
Specific Concentration Limits and M Factors							
Concentration				Classification			
C ≥ 0.01 % *oral				Carc. 1B; H350			
C ≥ 7 %				-			
0.1 % ≤ C < 7 %				STOT RE1; H372 STOT RE2; H373			

- 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.

ANNEX XV – IDENTIFICATION OF SVHC – CADMIUM CHLORIDE

Table 4: Harmonised classification of cadmium chloride according to part 3 of Annex VI, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification	Risk phrases	Safety phrases	Indication(s) of danger
048-008-00-3	Cadmium chloride	233-296-7	10108-64-2	Carc. Cat. 2; R45 Muta. Cat. 2; R46 Repr. Cat. 2; R60-61 T+; R26 T; R25-48/23/25 N; R50/53	45 46 60 61 25 26 48/23/25 50/53	53 45 60 61	T+ N
Concentration Limits							
Concentration				Classification			
$C \geq 0.01 \%$ $C \geq 10 \%$ $0.1 \% \leq C < 10 \%$ $C \geq 7 \%$ $0.1 \% \leq C < 7 \%$				Carc. Cat. 2; R45 T: R25 Xn; R22 T; R48/23/25 Xn; R48/20/22			

- R45: May cause cancer
R46: May cause heritable genetic damage
R60: May impair fertility
R61: May cause harm to the unborn child
R22: Harmful if swallowed
R25: Toxic if swallowed
R26: Very toxic by inhalation
R48/23/25: Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
R48/20/22: Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.
R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

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 Cd²⁺). Cadmium emissions to the environment may therefore arise from both natural and anthropogenic or man-made sources. Estimates of the proportion of total cadmium emissions due to natural sources have ranged from 10 % to 50 %. Some of these natural emission sources include weathering and erosion of parent rocks, volcanic activity and forest fires (ICdA 2012b). 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.

Some cadmium compounds have very low solubility and therefore release cadmium ions to a lower extent; this decreases their **bioavailability** potential. Distinction can therefore be made between cadmium compounds, as a function of their solubility. Cadmium chloride has very high water solubility. However, even cadmium forms with low solubility may be transformed into higher solubility forms due to chemical/physical transformation processes such as incineration or change of the redox potential.

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 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, 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. The results are summarized in the table below. For more information see section 9.6 in Part II of this report.

Table 5: 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 Health 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).

As part of 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 effect of all cadmium compounds are caused by the cadmium ion, the conclusions for “cadmium” are relevant for cadmium chloride.

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. Newborns 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 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 emphasized 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 PVD (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 the 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.

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 6.3) there are data indicating an increased mortality risk in subjects having urinary B2M 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. 2013a).

4.3 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) and the new American National Health and Nutrition Examination Survey (NHANES) 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. 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 characterized 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 reason(s) for the large age-standardized

geographical differences is still not known. It is 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 of 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; $\sim 1 \mu\text{g}/\text{g}$ 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 $\geq 0.5 \mu\text{g}/\text{g}$ 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. 2013b). 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 (\pm 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 SVHC identification of the substance in accordance with Articles 57(a), 57(b), 57(c) and 57(f).

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 CMR assessment

Cadmium chloride is listed as Index number 048-008-00-3 in Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as carcinogenic, Carc. 1B (H350: May cause cancer), mutagenic, Muta. 1B (H340: May cause genetic defects) and toxic for reproduction, Repr. 1B (H360FD: May damage fertility; May damage the unborn child). The corresponding classification in Annex VI, part 3, Table 3.2 (list of harmonized classification and labelling of hazardous substances from Annex I to Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is carcinogenic, Carc. Cat. 2, R45 (May cause cancer), mutagenic, Muta. Cat. 2, R46 (May cause heritable genetic damage) and toxic for reproduction, Repr. Cat. 2, R60-61 (May impair fertility; May cause harm to the unborn child).

Therefore, this classification of cadmium chloride in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as carcinogenic in accordance with Article 57(a), as

mutagenic in accordance with Article 57(b) and as toxic for reproduction in accordance with Article 57(c) of REACH.

6.2 Substances of equivalent level of concern assessment

According to REACH Article 57(f), substances for which there is scientific evidence of probable serious effects to human health or the environment, which give rise to an equivalent level of concern to CMR or PBT/vPvB substances and which are identified on a case-by-case basis, may be included in Annex XIV in accordance with the procedure laid down in Article 58.

Cadmium chloride has the ability to cause a large number of toxic effects as is evident from the harmonized classification. It is thus clear that cadmium may cause many different serious health effects in addition to the ability to cause cancer. Adverse effects on multiple organs after repeated exposure to cadmium, in particular on *kidney* and *bone*, motivated the classification as STOT RE Category 1, and it is in particular effects on kidney and bone that justify the equivalent level of concern.

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 (see: The 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*)). 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 substances, it should be acknowledged that also effects caused by these substances 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 β 2M > 1,000-1,500 μ g/g creatinine) is generally irreversible.

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

The biological half-life of cadmium in humans is extremely long (estimated to be 10-30 years) and the body burden of cadmium therefore increases, mainly via accumulation in the kidney, during the entire life span of an individual. 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 16 000 articles published during the last 10 years and 9200 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), 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 is considered to fulfil the criteria according to Art. 57(f), i.e. there is scientific evidence of probable serious effects to human health which give rise to “equivalent level of concern”, due to;

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

PART II

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

INFORMATION ON MANUFACTURE, IMPORT/EXPORT AND USES – CONCLUSIONS ON EXPOSURE

Conclusions:

Based on the reported information below, the following conclusions can be drawn:

- The dominating use of cadmium chloride is as raw material for production of other substances.
- The tonnages registered for different cadmium compounds show that the volume for cadmium chloride is comparatively low (10-1000 times lower). Official trade statistics on cadmium chloride is unclear mainly because it is aggregated with other cadmium compounds. There are thus no clear time trends available on the uses of cadmium chloride.
- The use of cadmium chloride as raw material for coating of metals is based on the corrosion inhibition function of cadmium metal, by sacrificial release. Metals coated with cadmium are used in articles, which are widely used in the society, and this use will therefore cause uncontrolled releases to surrounding environments. The application of cadmium on the surface of an article will also lead to particulate releases due to wear.
- Cadmium in cadmium chloride will in a life-cycle perspective mainly end up in different articles and contributes to the overall releases of cadmium ions from different articles.
- Occupational exposure to cadmium chloride occurs during several industrial and professional use scenarios, such as chemical synthesis, manufacturing of fabricated ferrous products and manufacturing of solar cells.
- Cadmium in cadmium chloride contributes to the overall exposure of the general population to cadmium via food and drinking water, smoking, ingestion of soil and dust, and inhalation of ambient air. The other cadmium sources are both natural and anthropogenic.

7 MANUFACTURE, IMPORT AND EXPORT

7.1 Manufacturing process

Cadmium chloride is produced by reaction of molten cadmium and chlorine gas at 600 °C or by dissolving the cadmium metal, the sulphide, carbonate, hydroxide or the oxide in hydrochloric acid, subsequently vaporizing the solution. Cadmium carbonate, sulphide, or hydroxide can thus be used as raw material (HSDB 2013, Kirk-Othmer 2004). Anhydrous material may be derived from several

alternative substances, including dicadmium chloride pentahydrate, cadmium nitrate, acetyl chloride, hydrogen chloride and/or cadmium metal (Kirk-Othmer 1978).

7.2 Quantities manufactured, import and export

Cadmium chloride is generally sold as the pentahydrate, technical grade (Kirk-Othmer 1978). In Chemical Books (Chemical Books 2013), cadmium chloride is marketed with three different CAS numbers. Even one of the deleted CAS numbers are thus still in use on the market (see Table 6).

Table 6: Number of suppliers per CAS number (Chemical Books 2013, 24 January 2014)

CAS No.	# Suppliers	Comments
10108-64-2	93	no crystal water
7790-78-5	63	with crystal water (pentahydrate)
34330-64-8	18	deleted CAS No.
143983-90-8	0	deleted CAS No.

China and US dominate (58-60 suppliers) followed by UK (20), Japan (9), Germany (7), India (5), Belgium (3), Canada (2), Switzerland (1), Italy (1), South Korea (1) and Mexico (1).

The total EU tonnage band imported and/or produced according to the REACH registration is 1 – 10 tonnes (22 November 2013). This is based on data from 4 registrants from Germany and Belgium.

Specific official statistics on cadmium chloride is lacking mainly because the trade statistics on cadmium do not always differentiate between cadmium metal and other forms of cadmium.

European countries⁵ contributed to 8.6 % of world production of cadmium in 2011 (Figure 1, Table 7). The Netherlands was the largest European producer accounting for 31 % of the EU production, followed by Poland (29 %), Bulgaria (24 %) and Norway (17 %). The European production level of cadmium shows an increase during 2007 to 2011 (BGS 2013).

The historical growth in production volumes during the years 1967 to 1982 was 0.6%, and increased between 1982 and 1995 to 0.8% (Kirk-Othmer 2004). The refined primary cadmium production has decreased in recent years as secondary recycled cadmium production has increased. Recycling of cadmium was estimated to 15-20% of the total production, of which >11% originate from Ni-Cd-batteries. This trend is expected to increase in the future (Kirk-Othmer 2004).

⁵ 35 European countries: 27 EU countries (1 Febr. 2008) + the EU associates Norway and Switzerland, and the EU candidates Croatia, Iceland, Macedonia, Montenegro, Serbia and Turkey.

Table 7: The European primary production of cadmium in tonnes 2006 to 2011 (EU35; BGS 2013)

Country	2006	2007	2008	2009	2010	2011
The Netherlands	524	495	530	490	560	560
Poland	373	421	603	534	451	526
Bulgaria	320	318	376	413	389	430
Norway	125	269	178	249	300	309
France	90	50	-	-	-	-
Total	1432	1553	1687	1686	1700	1825

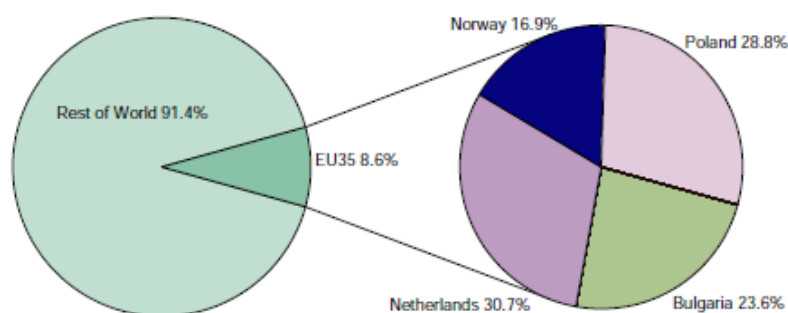


Figure 1: Production of total cadmium in Europe 2011 (BGS 2013)

The cadmium metal trade in EU 2011 was dominated by Belgium and Italy (high export) (see Table 8). Larger increases during 2007 to 2011 occur in the export from UK and the import from Sweden. Larger decreases during 2007 to 2011 occur in the export for Belgium and the import to France.

Table 8: European import and export of cadmium in tonnes (based on statistics from 2007 to 2011 (BGS 2013))

EU country	EXPORT					IMPORT				
	2007	2008	2009	2010	2011	2007	2008	2009	2010	2011
Italy	796	1633	2030	3104	1722	40	49	443	3	44
France	815	890	1022	763	549	1546	1620	985	228	106
Norway	544	816	305	606	617	0	0	0	0	0
Germany	...	287	276	523	348	492	497	468	583	468
Poland	368	558	590	484	579	0	0	0	0	0
Bulgaria	434	374	569	474	421	0	0	0	0	0
Belgium	5573	4536	3982	4059	3814	5040	5520	3464	6494	6027
Netherlands	544	816	305	606	617	437	186	50	102	1
Sweden	282	398	267	315	376	513	924	625	919	1278
United Kingdom	76	54	25	2545	1441	659	550	404	740	788
Czech Republic	0	0	0	0	0	296	405	323	406	426
Spain	0	0	0	0	0	0	21	118	153	38
Greece	0	0	0	0	0	1	18	39	1	0
Total	9432	10362	9371	13479	10484	9024	9790	6919	9629	9176

The total international cadmium **consumption** is dominated by the production of Ni-Cd batteries (USGS 2012). Other relevant uses are as pigments and anti-corrosion coatings of metals. The cadmium use is concentrated to industrialized countries with six countries accounting for 85 % of the world consumption. Japan is the leading consumer, followed by Belgium and the United States. In year 2000, an estimated 13 % of cadmium consumption in the United States came from recycled batteries and materials. However, cadmium usage in developed countries has declined in recent years owing to its toxicity (Klimasauskas 2005).

8 USES

8.1 General

Cadmium chloride is used as raw material for synthesis of other cadmium compounds, in electroplating and electrogalvanizing, for manufacturing of solar cells and as a laboratory reagent (Figure 2).

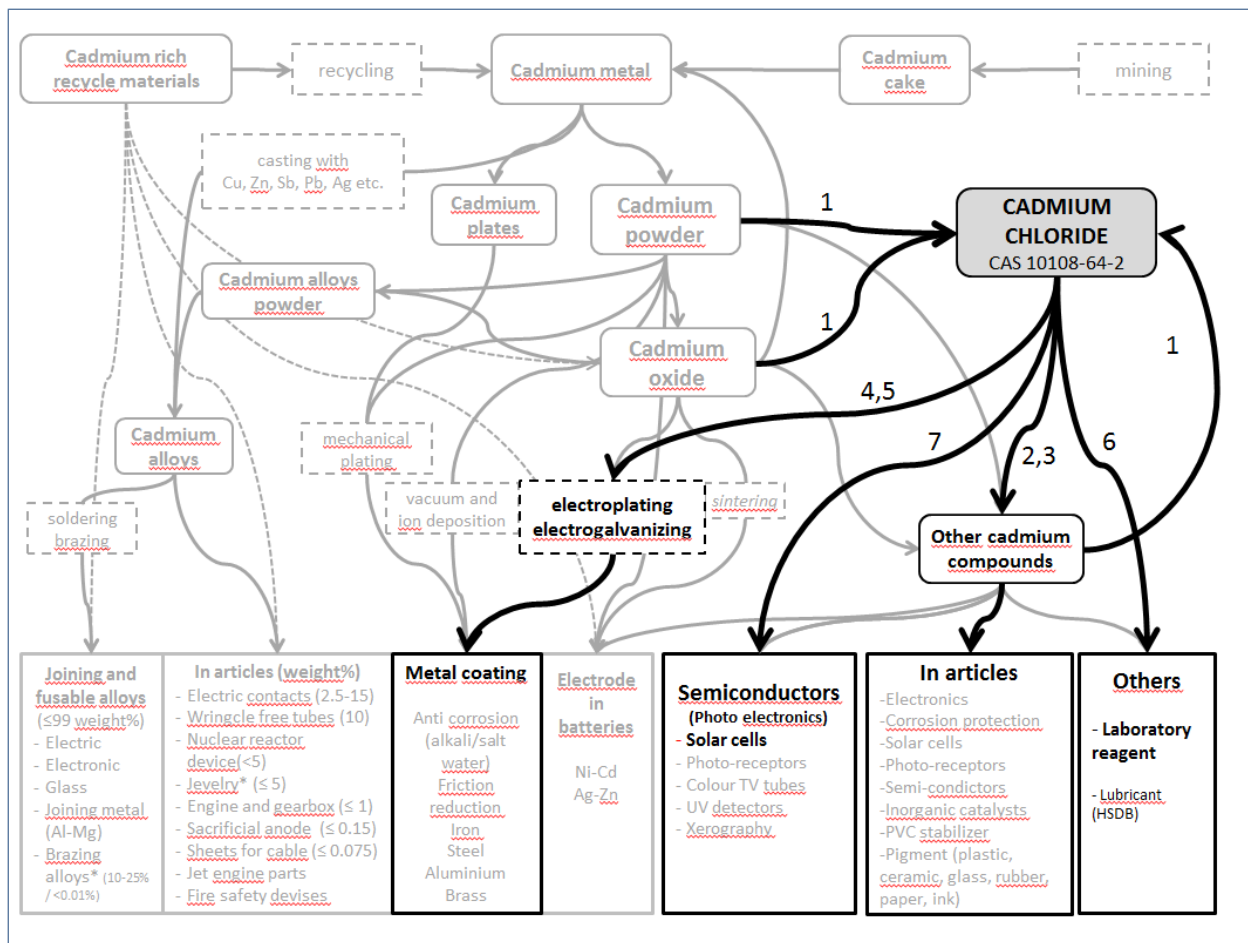


Figure 2: Overview of the use of cadmium chloride. The numbers refer to “identified uses” defined in section 9.1 (* is currently restricted under paragraph 8 of Entry 23 of Annex XVII of REACH).

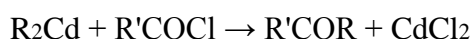
8.2 Industrial & professional uses of cadmium chloride

The industrial and professional uses of cadmium chloride can be divided into the following groups (ICdA 2013, ECHA 2013):

- For production of organic cadmium compounds
- For production of inorganic cadmium compounds
- Raw material for electrogalvanizing
- Raw material for electroplating
- Laboratory reagent (industrial & professional)
- Component for production of PV (photovoltaic) modules

8.2.1 Industrial use for production of organic cadmium compounds

In the laboratory, anhydrous CdCl_2 can be used for the preparation of organocadmium compounds of the type R_2Cd , where R is an aryl or a primary alkyl. These were once used in the synthesis of ketones from acyl chlorides (Wikipedia):



Cadmium chloride can be used as raw material for production of “cadmium soaps”, which are used as PVC stabilizers (based on saturated or unsaturated or branched, short-chain fatty acids). This use is decreasing because of the toxic properties (HSDB 2013).

8.2.2 Industrial use for production of inorganic cadmium compounds

Production of inorganic pigments and stabilizers

Cadmium chloride can be used as an intermediate in the production of cadmium-containing stabilizers and pigments, such as cadmium sulphide (e.g. Cadmium Yellow; Ullman Encyclopedia).

8.2.3 Use for cadmium coatings (ICdA 2012)

Cadmium chloride and cadmium oxide is used as an ingredient of electroplating and electrogalvanizing baths for metal coating (see Figure 2). There is no detailed information available describing if there are any differences between the oxide and the chloride for this purpose.

For the oxide the following information is available (source: the SVHC-dossier for CdO): Cadmium coatings are applied to iron, steel, brass and aluminium. During the process the cadmium oxide will be transformed to the metal form. The cadmium metal surface gives high resistance to corrosion under most conditions, especially in marine and alkaline environments, and reduces risks of operating mechanisms being jammed by corrosion debris for many components in a wide range of engineering applications throughout industry. Cadmium coatings are useful in the electrical, electronic, aerospace, mining, offshore, automotive and defence industries where they are applied to bolts and other fasteners, chassis, connectors and other components.

8.2.4 Component for production of PV (photovoltaic) modules (Singh 2008)

Cadmium chloride is used in the manufacturing of CdTe-based solar cells. CdTe-based solar cells is a photovoltaic module that uses CdTe thin films designed to absorb light and convert it to electricity. Cadmium telluride PV is the first and only thin film photovoltaic technology to surpass crystalline silicon PV in cheapness for a significant portion of the PV market. Cadmium chloride is well known to improve the efficiency in the building of the CdTe-film.

8.2.5 End uses of cadmium chloride (excluding the intermediate applications)

Laboratory reagent

As reagents in synthesis of organic substances

Among organic halides, cadmium chloride can be used in synthesis based on Grignard reaction (Kirk-Othmer 1978).

For analysis of lipids

Cadmium chloride can be used for purifying the lipid lecithine (phosphatidylcholine) in biochemical analysis of cells (Kirk-Othmer 1978).

8.2.6 Other uses

Cadmium can be used as a solid film lubricant with layer-lattice solids, in which the bounding between atoms in individual layers are by strong ionic forces and those between layers are relatively weak van der Waal's forces. Important properties are high melting point, high thermal stability in vacuum, low evaporation rate, good radiation resistance and effective friction-lowering ability (Kirk-Othmer 1978).

Cadmium chloride has been used as fungicide (HSDB 2013).

Cadmium chloride has been used in photography, photocopying, dyeing and calico printing (with thiosulphate), vacuum tube manufacture, cadmium pigment manufacture, galvanoplasty, ice-nucleation agents and in the manufacturing of special mirrors, in analysis of sulphides to absorb H₂S; in testing for pyridine bases (Kirk Othmer 2004; HSDB 2013).

8.3 Identified uses of cadmium chloride in the EU (ECHA 2013)

The registration of cadmium chloride includes the following use scenarios:

- Cadmium chloride production
- Component for production of inorganic cadmium compounds (formulation/production)
- Component for production of organic cadmium compounds (formulation/production)
- Electroplating (incl. formulation)
- Electroplating (incl. formulation)
- Laboratory reagent (incl. formulation)
- Component for production PV modules (semiconductors, formulation/production, solar panel manufacturing)

8.3.1 Uses advised against

According to the registration dossier for cadmium chloride, the “use of cadmium and cadmium compounds in brazing fillers > 0.01w/w % (with exceptions)” is advised against for all users (industrial, professional, consumer).

8.4 Volumes

There are no specific international trade statistics available for cadmium chloride. With a registered total annual tonnage band of 1-10 tonnes, cadmium chloride is one of the minor cadmium compounds (Figure 3).

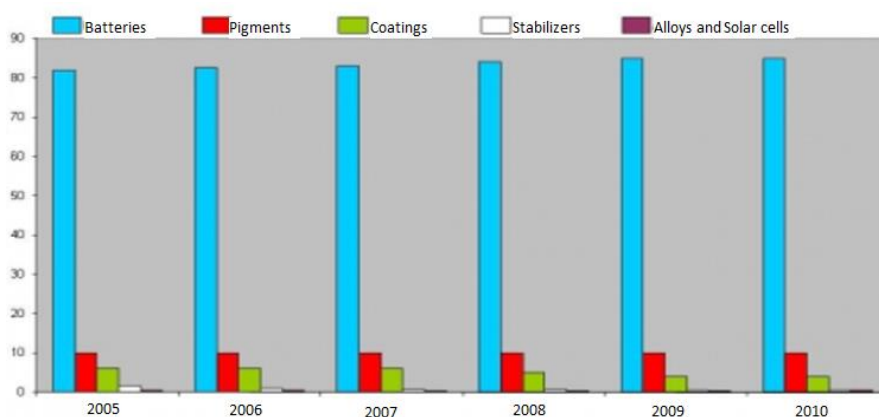


Figure 3: Trends in cadmium consumption patterns during 2005 to 2010, in per cent of the total consumption (ICdA 2013).

The final effect of REACH and others legislations on global cadmium consumption has yet to be seen. If recent legislation involving cadmium dramatically reduces long-term demand, a situation could arise, similar to what has recently been seen with mercury, where an accumulating oversupply of by-product will need to be permanently stockpiled (USGS 2012).

8.5 Recycling

There is no information available on recycling of cadmium chloride.

8.6 Functions of the substance according to its properties; mechanisms of action

8.6.1 Surface coating (ICdA 2012)

Cadmium, like zinc, also provides sacrificial protection to a substrate such as steel by being preferentially corroded when the coating is damaged and small areas of the substrate are exposed.

8.6.2 Lubricant

Cadmium chloride is among the solids which form strong layer-lattice with relatively weak van der Waal's forces between the layers. In combination with high melting point, high thermal stability in vacuum, low evaporation rates and good radiation resistance, cadmium chloride can be used as a friction-lowering agent (Kirk-Othmer 1978).

8.6.3 Component for production PV modules

Available information indicates that the mechanisms behind the function are not known fully understood (Singh 2008).

9 EXPOSURE

Human exposure to cadmium from cadmium chloride can potentially occur during the whole life-cycle of the substance. Industrial and professional workers will be exposed during several scenarios where cadmium chloride is produced, used, recycled and managed as waste.

Exposure of man via the environment occurs as a result of emissions from industrial and professional processes, and diffuse releases from private use of goods. Exposure from natural sources of cadmium needs also to be considered and show large variation due the local/regional ground conditions. The most important sources of cadmium exposure for the general population are: (i) food and drinking water contaminated from different diffuse releases; (ii) smoking; (iii) soil and dust ingestion, and inhalation of ambient air. Vegetarians, children, smokers and people living in highly contaminated areas are identified to have the highest potential exposure.

In nonsmokers, not occupationally exposed to cadmium, food is the primary exposure source. Cadmium in food mainly originates from uptake from the agricultural soil. The soil is mainly contaminated via the atmosphere from industrial releases and combustion of fossil fuel. Also end use of cadmium containing products, eg. mineral fertilizers, will contribute to the soil contamination.

From a regulatory point of view the origin of the different cadmium exposures can be divided into three categories:

1. Anthropogenic: **Deliberate use of cadmium** as such or in mixtures or articles, for example in NiCd batteries and as anticorrosion agent for metals. Exposure of workers and also the general population via the environment,
2. Anthropogenic: Exposure from **use of substances/mixtures/articles** containing cadmium as an **impurity**, such as phosphorous fertilizer, sewage sludge, residual in zinc and fossil fuel. Mainly exposure of the general population via the environment.
3. Natural: **Natural occurring cadmium** releases from minerals in soil/sediments. Exposure of the general population.

9.1 Releases and exposure during industrial and professional uses

The following identified use & exposure scenarios were considered relevant by ICdA (ICdA 2013). The scenario numbers below are also shown in the Figure 2 are use descriptors according to REACH 2010).

1. Cadmium chloride production: Cadmium or cadmium compounds are used in the manufacture of cadmium chloride. The production processes are closed and continuous or batchwise. It includes also transfer of substance between vessels/containers, and handling of solid substances at ambient temperature. [SU 8, 9], [PC 20], [PROC 2, 3, 8b, 9, 22, 26], [ERC 1].
2. Component for production of inorganic cadmium compounds: Industrial use of cadmium chloride or cadmium chloride-formulations in the manufacture of other inorganic cadmium-substances through different process routes, with potentially drying and packaging. [PC19, 20, 21],[PROC 2, 3, 8b, 9, 15, 21, 22],[SU 8, 9, 10],[ERC 1, 2, 6a].
3. Component for production of organic cadmium compounds: Industrial use of cadmium chloride formulations in the manufacture of organic preparations or organic cadmium-substances by mixing the starting materials in an organic-based matrix, with potentially filtering or casting. [PROC 1, 2, 3, 4, 8b, 9, 15], [PC 19, 20, 21, 24, 29, 39],[SU 8, 9, 10],[ERC 1, 2, 6a].
4. Electroplating: Cadmium is deposited from a cadmium-rich solution as a metallic coating for corrosion inhibition in electrolytic cells to galvanize effectively steel strips and other articles. [PROC 13, 21],[PC 7, 14],[SU 15, 17, 0 (Nace C25.6.1: treatment and coating of metals)] [AC 2, 7], [ERC 2, 5].
5. Electroplating: Cadmium is deposited from a cadmium-rich solution as a metallic coating for corrosion inhibition of the article, during a batch chemical or electrochemical process [PROC 3, 8b, 21],[PC 7, 14],[SU 15, 17, 0(Nace 25.6.1: treatment and coating of metals)],[AC 2, 7], [ERC 2, 5].
6. Laboratory reagent: Industrial and professional use of cadmium chloride as active laboratory reagent in aqueous or organic media, for analysis or synthesis. [SU 10, 16, 24],[PC 19, 21, 28, 39],[PROC 1, 2, 3, 4, 5, 8b, 9, 15], [ERC 1, 2, 4, 6a, 6b, 8a, 8d].
7. Component for production of photovoltaic modules (PV, solar cells): Industrial continuous or batch closed processing with no or controlled occupational exposure. Environmental exposure from industrial point sources during processing of semiconductors. Exposure may occur during subsequent service life of semiconductors such as solar cells (especially during the waste management). [SU 9, 16, 23, 24],[PROC 1, 2, 3],[PC 33][ERC 1, 2, 5][AC 3].

9.2 Release from use of professional use

Cadmium soaps can be used as stabilizers in PVC by catching chlorine atoms into cadmium chloride ((Kirk-Othmer 1978). The use of cadmium soaps is decreasing because of their toxic properties. Solid PVC stabilizers contain cadmium soaps of saturated fatty acids, whereas liquid stabilizers contain soaps of unsaturated or branched, short-chain fatty acids. The soaps act as heat and light stabilizers, and soaps of saturated fatty acids are used as lubricants in the processing of PVC. Unlike other metallic soaps used in the PVC sector, cadmium soaps do not affect transparency and are suitable for hard, transparent PVC products. However, for safety reason their

use is nowadays being replaced by mixtures of calcium-zinc stearate plus other stabilizers (HSDB 2013).

9.3 Releases during the service life

Release of cadmium during service life from anthropogenic sources includes products and materials to which cadmium chloride has deliberately been added to impart a specific chemical, mechanical or physical property and products or materials in which cadmium chloride is present as a residual or impurity element. In general, the cadmium content in products or materials in which cadmium is present as a deliberate additive is greater than the levels in the products or materials in which cadmium is present as a residual or unintentional impurity (ICdA 2012b).

Cadmium chloride will be formed as a transformation product in chlorine containing polymers (e.g. PVC) if the polymer contains cadmium based heat stabilizers (Kirk-Othmer 1978).

9.3.1 Release from use of coated articles

The emission rates from coatings during normal service life of 10-25 years are estimated to be 50% (Morrow 1996 in ICdA 2012b). 25% of coating is lost based on abrasive mechanisms (WS Atkins 1998 in ICdA 2012b). There are different cadmium coatings usages in different geographical areas (ICdA 2012b).

Cadmium can be released from automotive applications such as steering columns and disk brake parts due to abrasive conditions. Cadmium may also be used as protective coatings on fasteners. Some of the fastener applications would be subject to abrasion, but only on a limited basis. Fasteners might be torqued to a certain applied load level, but during their useful service life only disassembled and reassembled a few times. In the aircraft applications area, landing gear are frequently subjected to abrasion conditions and a heavy cadmium coating is utilized for this application to ensure that landing gear always may be safely raised and lowered during aircraft operation. Ammunition applications also result in abrasion and wear as well as railroad applications (ICdA 2012).

Corrosion of cadmium from unintentional impurities in metallic materials such as irons and steels and nonferrous metals is expected to be extremely low and not to contribute significantly to overall cadmium releases due to corrosion (ICdA 2012).

9.4 Releases during the waste life stage

There are no known end uses of cadmium chloride in articles.

9.5 Release from natural sources

Cadmium is a naturally occurring metallic element, one of the components of the earth's crust and present everywhere in our environment. 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 2012b).

Natural cadmium will also indirectly cause releases, via anthropogenic uses of a wide range of materials for industrial and consumer purposes. Cadmium is sometimes found in high concentrations in phosphate fertilizers (marine phosphates and phosphorites). It has also been reported at fairly low levels in iron and steel because all of the raw materials (iron ore, limestone, coke and scrap steel) utilized to make iron and steel usually contain residual amounts of cadmium. Virtually all fossil fuels contain various levels of cadmium depending on their specific type, and are a significant contributor to cadmium air pollution since they are all combusted when utilized. The raw materials employed to produce cement and concrete also contain residual amounts of cadmium and contribute to total cadmium environmental emissions. Cadmium is present as a residual element in zinc, lead and copper ores. However, cadmium is normally removed as a by-product during the smelting and refining processes for these metals and converted directly to cadmium metal for sale on the market. It is not generally left in zinc, lead or copper metals and alloys unless it is deliberately done to achieve an improvement in some mechanical, chemical or physical property. The tendency in recent years has been to produce these nonferrous metals, their alloys and their compounds with increasingly lower residual cadmium levels. Furthermore, deliberate cadmium additions to zinc, lead or copper alloys are generally quite low (<1%), and even in these cases they are almost never utilized for atmospheric exposure applications. Oxidation of cadmium from unintentional impurities in metallic materials such as irons and steels and nonferrous metals is expected to be extremely low and not to contribute significantly to overall cadmium releases. The presence of cadmium in and its emission into the environment from fossil fuels, cement manufacture or wear, and fertilizers do not arise from corrosion processes but represents chemical dissolution or wear/erosion processes rather than electrochemical corrosion processes. Residual or unintentional cadmium levels in various products or materials are summarized in Table 9 (ICdA 2012b).

Table 9: Concentration of cadmium as impurities in different types of products/materials (ICdA 2012b)

Product	% Cd
Phosphate fertilizers	3 – 90 ppm
Fossil fuels	0.1 – 1.5 ppm
Cement	2.0 – 2.5 ppm
Iron and steel	0.1 – 5.5 ppm
Nonferrous metals	1 – 50 ppm

9.6 General population - current exposure

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 were used to display the “current” urinary cadmium concentrations in the Swedish population (KemI 2011), for a summary see Table 10 below.

- The National Swedish health-related environmental monitoring program (SEM), financed by the Swedish Environment Protection Agency, coordinates longitudinal monitoring of cadmium concentrations in urine ($\mu\text{g/g}$ creatinine), representing long-term exposure, for younger (20-29 years of age) and middle aged (50-59 years) women in four geographical regions in Sweden. The urine sampling circulates by geographical area every second year.

Results are available for the period of 2002-2009 with 2 time points for most areas (<http://www.imm.ki.se/Datavard/Tidsserier/Cadmium%20in%20urine.htm>). In total, 1458 women (n=669 women 20-29 years, n=759 women 50-59 years of age) were sampled.

- The Women's Health in the Lund Area Study (WHILA) included women, aged 54 to 63 years, living in a rural area in Southern Sweden (with no known industrial cadmium emission). During 1999, 820 women were recruited (71% participation rate). Cadmium was assessed in both blood (median, 0.38 µg/L) and urine (median 0.52 µg/L; density adjusted = 0.67 µg/g creatinine).
- Data from the Swedish Mammography Cohort (SMC). During 2003 to 2009, 2831 women in the town of Uppsala, 56-69 years of age had urines samples determined for cadmium.

Table 10: Summary of the 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 Health in the Lund Area, SMC; The Swedish Mammography Cohort;

Proportion of the population with urinary cadmium above 0.5 and 1.0 µg/g creatinine

Women in the age group 50-69 years were also used to evaluate the proportion of women having urinary cadmium levels above the two predefined cut offs of 0.5 and 1.0 µg Cd/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 observed differences.

Cadmium exposure over time

Based on a Swedish study on *kidney biopsies* (from 2010) assessing cadmium content in the kidneys of 109 living donors (aged 24–70 years; median 51 years), the kidney cadmium concentrations were compared to results from published studies starting in the 1970s. Two earlier Swedish studies assessed kidney-cadmium in diseased people at autopsy. When comparing kidney cadmium concentrations in never-smokers in this recent study the levels were similar to or only marginally lower than those from the 1970s (KemI 2011 and references therein).

The reported concentrations in the National Swedish health-related environmental monitoring program for 2002-2009 may indicate a slight decrease in *urinary cadmium* with time in south-western and northern Sweden (see Figure 4). However, there has been a change in analytical instrumentation and the comparability is still under investigation. In the northern area, blood cadmium concentrations 1990-1999 showed no changes over time. In Stockholm, where the samples have been analyzed with the same method and instrumentation, there is no apparent decrease over time. If anything, there may be a slight increase in the younger age group. This longitudinal series of monitoring data also seems to indicate that there is a geographical variation in urinary cadmium concentrations with lower values in northern Sweden and higher in the south. This will be further evaluated in the future.

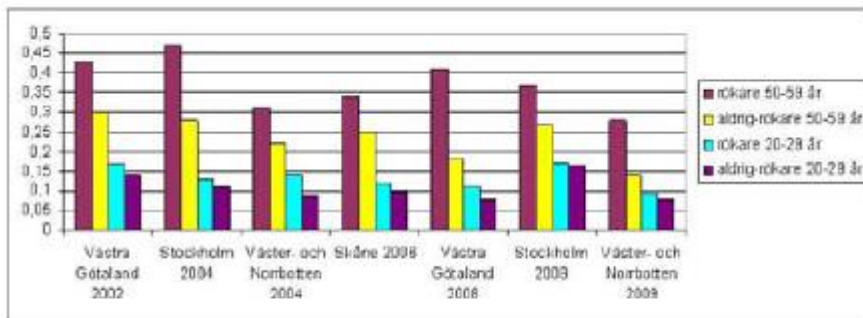


Figure 4: Urinary cadmium ($\mu\text{g/g}$ creatinine) among Swedish woman, 20-29 years and 50-59 years of age, presented as the median.

In summary, the comprehensive data base on cadmium exposure, based on biomarkers of exposure and measured dietary intake in Sweden, shows no decrease in cadmium exposure over time during the last 2-3 decades in Sweden.

9.7 Worker exposure to cadmium (see also the *CONFIDENTIAL ANNEX*)

The main route of cadmium exposure in the occupational setting is via the respiratory tract, although there may be incidental ingestion of dust from contaminated hands, and food. Occupations in which the highest potential exposures occur include cadmium production and refining, Ni–Cd battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, brazing with a silver–cadmium–silver alloy solder, and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased since the 1970s (IARC 2012).

Estimates of the number of workers potentially exposed to cadmium and cadmium compounds have been developed by CAREX in Europe. Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimates that 207 350 workers were exposed to cadmium and cadmium compounds in the European Union, with over 50 % of workers employed in the construction ($n = 32\,113$), manufacture of fabricated metal products ($n = 23\,541$), non-ferrous base metal industries ($n = 22\,290$), manufacture of plastic products not elsewhere classified ($n = 16\,493$), personal and household services ($n = 15\,004$), and manufacture of machinery except electrical ($n = 13\,266$) (IARC 2012).

CAREX Canada estimates that 35 000 Canadians (80% males) are exposed to cadmium in their workplaces. The largest exposed group are workers in polyvinyl chloride plastic product manufacturing ($n = 12\ 000$), who are exposed to cadmium bearing stabilizers. Other industries in which exposure occurs include: foundries, commercial and industrial machinery manufacturing, motor vehicle parts manufacture, architectural and structural metal manufacturing, non-ferrous metal (except aluminum) production and processing, metalworking machinery manufacturing, iron and steel mills and ferro-alloy manufacturing, alumina and aluminum production and processing, and other electrical equipment and component manufacture (IARC 2012).

9.8 Consumer exposure

According to the EU RAR, the consumer uses of cadmium metal fall into five categories corresponding to at least 5 scenarios of exposure: Active electrode material in Ni-Cd batteries; Pigments used mainly in plastics, glasses and ceramics, enamels and artists' paints; Use of cadmium as stabilizers for plastics or polymers; Metal plating (steel and some non-ferrous metals); Component of alloy.

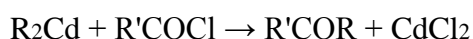
In the registration for cadmium chloride, no consumer use is given and therefore also no exposure assessments. The use of photovoltaic solar cells, a potential new use, is not expected to result in direct consumer exposure, since cadmium is enclosed in the product.

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

10 ALTERNATIVES

10.1 Synthesis of ketones from cadmium chloride

In the laboratory, anhydrous CdCl_2 can be used for the preparation of organocadmium compounds of the type R_2Cd , where R is an aryl or a primary alkyl group. These were once used in the synthesis of ketones from acyl chlorides:



Such reagents have largely been supplanted by organo-copper compounds, which are much less toxic (Wikipedia).

10.2 Other uses of cadmium chloride

Information of possible alternatives to the other registered uses of cadmium chloride is not available.

11 RISK-RELATED INFORMATION

An EU risk assessment is available for cadmium (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.

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

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

11.1 Risk estimation in the registration

Risk for workers (see also the *CONFIDENTIAL ANNEX*)

In the CSA, the suggested IOEL of 4 µg/m³ (respirable fraction) has been used as a DNEL. Although the exposure assessments from the EU RAR (on Cd and CdO) in many cases are higher than this value it is claimed that the more recent measured data show that exposures, at least in most cases, are below the IOEL. In this comparison measured inhalable concentrations have been divided with a factor of 2, or sometimes 2.5, to compensate for presumed higher values in the inhalable fraction compared to the respirable fraction. Comparisons with the proposed biological limit value are also made in the CSA, showing that most, but not all, tested workers have urinary cadmium concentrations below 2 µg/g creatinine.

According to the registration dossier, technical measures are taken to comply with the EU proposed indicative OEL of 4 µg respirable Cd/m³. If compliance with the IOEL cannot be ensured in a consistent way, protection of the worker is ensured by complementary risk reduction measures and compliance with biological indicator limit values at the individual level.

11.2 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 given 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 woman and one out of four men in Sweden will suffer from an osteoporotic fracture during their lifetime. Considering the high prevalence of osteoporotic fractures in Sweden, compared to central and southern Europe, it cannot be ruled out that the Swedish population might be more sensitive to cadmium exposure. It should be noted that even a small increase in the average exposure will result in a proportionally larger increase in the fraction of the population at risk of fractures.

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

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

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

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

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

11.3 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.

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13 ANNEX 1. 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.

13.1 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 ($\mu\text{g/L}$) 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 $\mu\text{g/g}$ creatinine, corresponding roughly to 0.1-0.2 $\mu\text{g/L}$. 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).

13.2 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 the 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 et 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).

13.3 Overall mortality

Two recent studies from Belgium and USA 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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