SUBSTANCE NAME: CADMIUM OXIDE

EC NUMBER: 215-146-2

CAS NUMBER: 1306-19-0

MEMBER STATE COMMITTEE

SUPPORT DOCUMENT FOR IDENTIFICATION OF

CADMIUM OXIDE

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR[1] PROPERTIES AND BECAUSE OF ITS ADVERSE EFFECTS ON KIDNEY AND BONE TISSUES AFTER PROLONGED EXPOSURE, WHICH CAUSE PROBABLE SERIOUS EFFECTS TO HUMAN HEALTH WHICH GIVE RISE TO AN EQUIVALENT LEVEL OF CONCERN TO THOSE OF CMR AND PBT/vPvB[2] SUBSTANCES

Adopted on 12 June 2013

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

[2] PBT means persistent, bioaccumulative and toxic; vPvB means very persistent and very bioaccumulative

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TABLES

ABBREVIATIONS

CSA	Chemical Safety Assessment
CI	Confidence Interval
ICdA	Internal Cadmium Association
IOEL	Indicative Occupational Exposure Limit
NHANES	National Health and Nutrition Examination Survey
RAR	Risk Assessment Report
SCOEL	Scientific Expert Group on Occupational Exposure Limits
SMC	Swedish Mammography Cohort

Substance Name: Cadmium oxide

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- The substance is identified as a substance meeting the criteria of Article 57 (a) of Regulation (EC) 1907/2006 (REACH) owing to its classification as carcinogen category 1B[3], which corresponds to classification as carcinogen category 2[4].
- It is also identified as a substance of equivalent level of 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 Carcinogen 1B criteria and is considered to be a substance giving rise to an equivalent level of concern

Carcinogen 1B

Cadmium oxide is listed as Index number 048-002-00-0 in Regulation (EC) No 1272/2008[5] and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as carcinogen, Carc. 1B (H350: May cause cancer). The corresponding classification in 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) of Regulation (EC) No 1272/2008 is carcinogen, Carc. Cat. 2, R45 (May cause cancer).

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

Equivalent level of concern

The toxic effects of cadmium oxide are caused by cadmium ion and effects observed after exposure to other cadmium compounds are therefore relevant also for cadmium oxide. Human and environmental exposures to cadmium and its compounds are usually expressed as "cadmium", including all cadmium compounds.

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.

[3] 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

[4] 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.

[5] 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.

Cadmium oxide has the ability to cause a large number of toxic effects as is evident from the harmonised classification. It is thus clear that cadmium oxide 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.

A significant part of the European population is today exposed to levels of cadmium 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. The input of cadmium to soil is dominated by deposition from air, which therefore must be reduced, and 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;
- 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 impacts 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 (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 Cd exposure in the general population are reversible if exposure is substantially decreased. Severe tubular damage (urinary leakage of the proteins RBP or ß2M > 1,000-1,500 µg/g creatinine) is generally irreversible.

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

The biological half-life of cadmium in humans is extremely long (estimated to be 10-30 years) and the body burden of cadmium therefore increases, mainly via accumulation in the kidney, during the entire life span of an individual. 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 14 900 articles published during the last 10 years and 8700 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 report published by the Swedish Chemicals Agency, the annual societal costs in Sweden for cadmium in soil due to human activities is estimated to approximately 4.2 billion SEK (approx. 450 million Euros) (KemI 2012). 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 the shortening of life time and a decreased quality of life.

In conclusion

Cadmium oxide 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:	215-146-2
EC name:	cadmium oxide
CAS number (in the EC inventory):	1306-19-0
CAS number:	12139-21-8 (Monteponite (CdO))
CAS name:	cadmium oxide (CdO)
IUPAC name:	cadmium oxide
Index number in Annex VI of the CLP Regulation	048-002-00-0
Molecular formula:	CdO
Molecular weight range:	128.4104
Synonyms:	Cadmium(II)oxide Cadmium monoxide Monteponite Tienek kadmu
Structural formula:	

1.2 Composition of the substance

Name: cadmium oxide

Degree of purity: 80-100 % (w/w). The substance is a mono constituent substance.

The constituents and impurities as described by the "Cadmium Reach Consortium" (http://www.reach-cadmium.eu/) are shown in Table 2 and

Table 3.

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
Cadmium oxide EC no.: 215-146-2	> 99.45 % (w/w)	> 80.0 — < 100 % (w/w)	Total impurities measured are < 0.015 %, like Pb, Ni, Mn, Fe, Cu, Zn, Mg, Ca. They do not modify classification.

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
Cadmium carbonate	0.55 % (w/w)	> 0 - < 0.7 % (w/w)	
Water	≤ 0.1 % (w/w)	≥ 0 - < 0.2 % (w/w)	

1.3 Physico-chemical properties

Table 4: Overview of physico-chemical properties *(from dissemination database according to REACH, Article 119)*[6]

Property	Value	Remarks
Physical state at 20°C and 1013 hPa	Solid Form: powder Colour: red ochre Odour: odourless	From registration[6]
Melting/freezing point	The melting point of the substance was determined by thermo gravimetrical (TGA) measurements. There is no melting and no decomposition, sublimation starts in nitrogen at ca. 870°C and in air at ca. 950°C.	From registration[6]
Vapour pressure	The vapour pressure of cadmium oxide is considered negligible at 25°C.	From registration[6]
Water solubility	The experimentally determined average water solubility at 20 °C is 2.1 mg/L at pH 7.2-7.79. The calculated value for cadmium oxide is 6.1 mg/L.	From registration[6] **Value used for CSA:** 2.1 mg/L at 20 °C
Relative density	The density of the substance is 8.26 g/cm^3	From registration[6]
Oxidising properties	Cadmium oxide has no oxidizing properties.	From registration[6]
Granulometry	The D50 of the substance is 129 µm, the D80 is 215 µm.	From registration[6]

6 http://echa.europa.eu/information-on-chemicals

2 HARMONISED CLASSIFICATION AND LABELLING

Cadmium oxide (non-pyrophoric) is listed as Index number 048-002-00-0 in Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, as follows:

Table 5: Harmonised classification of cadmium oxide (non-pyrophoric) 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)
048-002-00-0	Cadmium oxide (non-pyrophoric)	215-146-2	1306-19-0	Carc. 1B	H350	GHS06	H350
				Muta. 2	H341	GHS08	H341
				Repr. 2	H361fd	GHS09	H361fd
				Acute Tox. 2	H330	Dgr	H330
				STOT RE 1	H372		H372
				Aquatic Acute 1	H400		H410
				Aquatic Chronic 1	H410		

H350: May cause cancer.
H341: May cause genetic defects.
H361fd: May damage fertility. May damage the unborn child.
H330: Fatal if inhaled.
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.

Table 6: Harmonised classification of cadmium oxide (non-pyrophoric) 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
048-002-00-0	Cadmium oxide (non-pyrophoric)	215-146-2	1306-19-0	Carc. Cat. 2; R45	R45	S45	T+
				Muta. Cat. 3; R68	R68	S53	N
				Repr. Cat. 3; R62	R62	S60	
				Repr. Cat. 3; R63	R63	S61	
				T+; R26	R26		
				T; R48/23/25	R48/23/25		
				N; R50/53	R50/53		

R45:	May cause cancer.
R68:	Possible risk of irreversible effects.
R62:	Possible risk of impaired fertility.
R63:	Possible risk of harm to the unborn child.
R26:	Very toxic by inhalation.
R48/23/25:	Toxic: 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

Anthropogenic and natural sources of cadmium exposure

Cadmium is a natural element, which is present in all environmental compartments (as Cd++). Cadmium emissions to the environment may therefore arise from both natural and anthropogenic or man-made sources. Estimates of the proportion of total cadmium emissions due to natural sources have ranged from 10% to 50%. Some of these natural emission sources include weathering and erosion of parent rocks, volcanic activity and forest fires (ICdA 2012). The overall cadmium anthropogenic exposure is then in the range of 50 to 90 %.

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 and influence the bioavailability. In **sediment**, cadmium binds to the sulphide fraction to form less soluble CdS. Due to the low solubility, 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. 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.

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).

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 reflects body burden, in the Swedish population. The results are summarized in the table below. For more information see section 9.5 in Part II of the Annex XV report.

Summary of the urinary concentrations observed in three Swedish population-based studies.

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

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

Women in the age group 50-69 years were also used to evaluate the proportion of women having urinary cadmium levels above the two predefined cutoffs 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.

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 1,363 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 oxide.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Lung retention may be up to 20 %, especially after short-term exposure (IARC 2012).

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.

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 are in the range of 7–16 years (IARC 2012). According to other references (KemI 2011) it is even longer (10-30 years).

Cadmium in urine is mainly influenced by the body burden of cadmium and is generally proportional to the concentration in the kidney. There is a close relationship between the cadmium concentrations in urine and kidneys; and urinary cadmium of 1.7 to 2.5 µg/g creatinine roughly corresponds to about 50 mg/kg in the renal cortex. Because the half-life of cadmium in the body is very long urinary cadmium is highly dependent on age (KemI 2011).

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. It is difficult to ascertain the exact lowest effect dose

for a clear adverse effect. However, also impaired glomerular filtration rate has been observed, the risk of which seems to start at 0.7 to 1.0 µg/g creatinine. 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. Thus, the observed associations, even those at very low exposure levels, may imply potentially adverse effects, which in combination with other stressors may affect the long-term health and function of the kidneys (KemI 2011).

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

It should 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 of proteins. There is however evidence of low-level cadmium exposure causing toxic bone effects, with decrease of bone mineral density, increase of osteoporosis and fractures (PHIME 2011).

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). Comprehensive data were available for all individuals undergoing renal replacement therapy (384 cases between 1978 and 1995, 250 men and 134 women) in a Swedish population living near a Cd battery production facility in the southeast of Sweden (Kalmar County). Based on the distance between the dwelling place, and to some extent environmental monitoring data, it was possible to identify groups with high (occupational), moderate (living within a 2 km radius of the point source), or low exposure (between 2 and 10 km) as well as a control group with no exposure (rest of the residents in the county). The incidence of renal replacement therapy (number of cases per million person-years between 20 and 79 years) was higher in the exposed groups than in the controls (201.4 versus 118.4 for genders cumulated, Mantel-Haenszel rate ratio, 1.8; 95% CI, 1.3-2.3). The age and sex adjusted rate ratio increased from 1.4 in the low exposure group to 2.3 in the high exposure group.

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

Swedish Mammography Cohort: For any first fracture (n=395) the odds ratio (OR) was 1.16 (95% CI, 0.89-1.50) comparing urinary Cd ≥0.5 µg/g creatinine with lower levels. Among never-smokers, the ORs (95% CIs) were 2.03 (1.33-3.09) for any first fracture, 2.06 (1.28-3.32) for first osteoporotic fracture, 2.18 (1.20-3.94) for first distal forearm fracture and 1.89 (1.25-2.85) for multiple incident fractures (Engström et al 2011).

Cohort of Swedish Men: In a population-based prospective cohort study, where individual cadmium intake was estimated using a food frequency questionnaire (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).

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for the SVHC identification of the substance in accordance with Articles 57 (a) and 57 (f).

6 CONCLUSIONS ON THE SVHC PROPERTIES

6.1 CMR assessment

Cadmium oxide is listed as Index number 048-002-00-0 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 carcinogen, Carc. 1B (H350: May cause cancer). The corresponding classification in 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) of Regulation (EC) No 1272/2008 is carcinogen, Carc. Cat. 2, R45 (May cause cancer).

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

6.2 Substances of equivalent level of concern assessment

The toxic effects of cadmium oxide are caused by cadmium ion and effects observed after exposure to other cadmium compounds are therefore relevant also for cadmium oxide. Human and environmental exposures to cadmium and its compounds are usually expressed as "cadmium", including all cadmium compounds.

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 oxide has the ability to cause a large number of toxic effects as is evident from the harmonised classification. It is thus clear that cadmium oxide 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.

A significant part of the European population is today exposed to levels of cadmium 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. The input of cadmium to soil is dominated by deposition from air, which therefore must be reduced, and 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;
- 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 impacts 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 (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 Cd exposure in the general population are reversible if exposure is substantially decreased. Severe tubular damage (urinary leakage of the proteins RBP or ß2M > 1,000-1,500 µg/g creatinine) is generally irreversible.

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

The biological half-life of cadmium in humans is extremely long (estimated to be 10-30 years) and the body burden of cadmium therefore increases, mainly via accumulation in the kidney, during the entire life span of an individual. 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 14 900 articles published during the last 10 years and 8700 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 assessments 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 report published by the Swedish Chemicals Agency, the annual societal costs in Sweden for cadmium in soil due to human activities is estimated to approximately 4.2 billion SEK (approx. 450 million Euros) (KemI 2012). 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 the shortening of life time and a decreased quality of life.

In conclusion

Cadmium oxide 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.

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