

Annex XV dossier

**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 oxide

EC Number(s): 215-146-2

CAS Number(s): 1306-19-0

Submitted by: Swedish Competent Authority (Swedish Chemicals Agency)

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ABBREVIATIONS

AC	Article Category (use descriptor according to REACH)
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
CSA	Chemical Safety Assessment
CEC	Cation Exchange Capacity
CI	Confidence Interval
DU	Downstream User
EB	Electron Beam
EBPVD	Electron Beam Physical Vapor Deposition
ERC	Environmental Release Category (use descriptor according to REACH)
ESR	Existing Substances Regulation
ICdA	Internal Cadmium Association
IOEL	Indicative Occupational Exposure Limit
NHANES	National Health and Nutrition Examination Survey
Ni-Cd	Nickel-Cadmium
PC	Product Category (use descriptor according to REACH)
PROC	Process Category (use descriptor according to REACH)
PVD	Physical Vapor Deposition
RAR	Risk Assessment Report
RLE	Production method for cadmium (roasting leaching electrolysis)
SCOEL	Scientific Expert Group on Occupational Exposure Limits
SMC	Swedish Mammography Cohort
SU	Sector of Use (use descriptor according to REACH)

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 oxide

EC Number(s): 215-146-2

CAS number(s): 1306-19-0

- 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 1B.
- 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 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 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 harmonized 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).

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.

Cadmium oxide has the ability to cause a large number of toxic effects as is evident from the harmonized 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 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 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 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 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 report from EFSA (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 physicochemical properties (from dissemination database according to REACH, Article 119)¹

Property	Value	Remarks
Physical state at 20°C and 1013 hPa	Solid Form: powder Colour: red ochre Odour: odourless	From registration ¹
Melting/freezing point	The melting point of the substance was determined by thermo gravimetric (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 ¹
Vapour pressure	The vapour pressure of cadmium oxide is considered negligible at 25°C.	From registration ¹
Water solubility	The average water solubility at 20 °C is 2.1 mg/L at pH 7.2-7.79. The calculated value for cadmium oxide is 5.4 mg/L.	From registration ¹ 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 ¹
Oxidising properties	Cadmium oxide has no oxidizing properties.	From registration ¹
Granulometry	The D50 of the substance is 129 µm, the D80 is 215 µm.	From registration ¹

¹ <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 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 Muta. 2 Repr. 2 Acute Tox. 2 STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H350 H341 H361fd H330 H372 H400 H410	GHS06 GHS08 GHS09 Dgr	H350 H341 H361fd H330 H372 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 harmonized 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 Muta. Cat. 3; R68 Repr. Cat. 3; R62 Repr. Cat. 3; R63 T+; R26 T; R48/23/25 N; R50/53	R45 R68 R62 R63 R26 R48/23/25 R50/53	S45 S53 S60 S61	T+ N

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 2012b). The overall cadmium anthropogenic exposure is then 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 the 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 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 (current TWI is 2.5 µg/kg bw).

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 this report.

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;

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.

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.

Once absorbed, cadmium will bind to metallothionein, forming a cadmium–metallothionein complex that is transferred (via blood) primarily to the liver and the kidney. Metallothionein is inducible in different tissues (e.g. liver, kidney, intestine, and lung) by exposure to various agents including cadmium. When transported to the kidney, 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).

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/cm²) 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; $\sim 1 \mu\text{g/g}$ 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 the 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 $\geq 0.5 \mu\text{g/g}$ 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 $19 \mu\text{g Cd/day}$), 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 this dossier.

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 harmonized 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 harmonized 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 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 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 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 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 report from EFSA (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.

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:

- Official trade statistics on cadmium oxide are unclear mainly because it is aggregated with other cadmium compounds. There are thus no clear time trends on the use pattern of cadmium oxide. The dominating use of cadmium oxide is as a raw material for batteries.
- The use of cadmium oxide 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 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.
- Recycling of cadmium products is expected to increase. The recycling can, however, not fully exclude releases of cadmium to the environment during the service life and waste life cycle stages.
- Occupational exposure occurs during several industrial and professional use scenarios, such as base metal productions, manufacturing of fabricated ferrous and non-ferrous products (incl. batteries) and manufacturing of plastic products.
- The general population is exposed to cadmium via food and drinking water, smoking, ingestion of soil and dust, and inhalation of ambient air. The sources for the contaminations are both natural and anthropogenic.

7 MANUFACTURE, IMPORT AND EXPORT

7.1 Manufacturing process (ICdA 2012)

Two production methods are described, the “Indirect” method and the “Wet” method:

- Cadmium oxide production – Indirect: Primary or secondary cadmium is used in the manufacture of cadmium oxide by a pyro-metallurgical process (including vaporization, oxidization) and packaging.

- Cadmium oxide production – Wet: A Cadmium containing solution is used in the manufacture of cadmium oxide by a wet process (including purification, precipitation and calcination) and packaging.

7.2 Quantities manufactured, import and export

The total tonnage band according to the REACH registration is 1 000 – 10 000 tonnes (17 February 2013). This is based on data from 7 registrants Czech Republic, Belgium, Germany, Poland, Sweden, France and Italy.

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

The annual world production of cadmium during 1990 to 1999 was 18 000 to 21 000 tonnes (Kirk-Othmer 2004). Most of the world’s primary cadmium metal was produced in Asia and the Pacific - specifically China, Japan, and the Republic of Korea, followed by North America, Central Europe and Eurasia, and Western Europe. Secondary cadmium production takes place mainly at Ni-Cd battery recycling facilities (USGS 2012).

The European countries² contributed to 9.3 % of world production in 2010 (Figure 1, Table 7). The Netherland was the largest EU producer accounting for 28 per cent of the EU production, followed by Poland (22 %), Bulgaria (21 %), Germany (14 %) and Norway (14 %). The production level was stable around 2000 tonnes per annum during 2006 to 2010. This production level is within the “total tonnage band” registered to ECHA (see above).

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 shown decreases 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% origin are from Ni-Cd-batteries. This trend is expected to increase in the future (Kirk-Othmer 2004).

Table 7: Primary production of total cadmium in Europe 2006 to 2010 (BGS 2012)

Country	Unit	2006	2007	2008	2009	2010
The Netherlands	tonnes	524	495	530	490	580
Poland	tonnes	373	421	603	534	451
Bulgaria	tonnes	320	318	376	413	440
Germany	tonnes	490	475	420	250	300
Norway	tonnes	125	269	178	249	300
France	tonnes	90	50	-	-	-
Total	tonnes	1900	2000	2100	1900	2100

² 34 European countries: 27 EU countries (1 Febr. 2008) + Norway, Switzerland, Croatia, Island, Macedonia, Montenegro, Turkey.

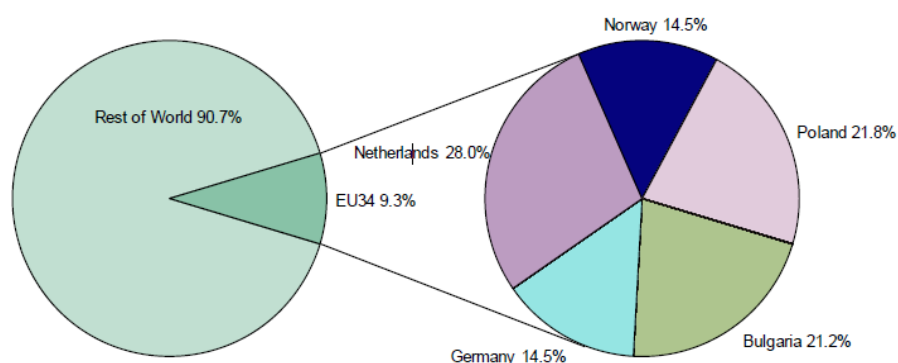


Figure 1: Production of total cadmium in Europe 2010 (BGS 2012)

The cadmium oxide trade in EU 2010 is dominated by Belgium (high export) and Germany and Czech (high import, Table 8).

Table 8: European import and export of cadmium oxide 2006 to 2010 (BGS 2012)

Country	Unit	2006	2007	2008	2009	2010
Export						
Belgium	tonnes	5283	6160	4677	4033	4413
Sweden	tonnes	...	322	448	305	360
Total	tonnes	>5283	6482	5125	4338	4773
Import						
Germany	tonnes	337	423	507	522	625
Czech Republic	tonnes	285	338	463	396	464
Sweden	tonnes	102	25	83	42	107
France	tonnes	593	885	1114	605	18
Total	tonnes	1317	1671	2167	1565	1214

Cadmium use in batteries accounted for the majority of the global consumption. The volumes for Ni-Cd batteries on the EU market reached a stable level in the late 1990's of around 13 500 tonnes/year for consumer/sealed portable nickel-cadmium batteries and 3 500 to 4 000 tonnes/year for the industrial nickel-cadmium battery market. Between 1996 and 1999 the portable Ni-Cd battery market in the EU was around 13 000 -14 000 tonnes. In the EU RAR the maximum future volume for portable batteries were assumed to be 13 500 tonnes, and 3 600 tonnes for industrial batteries (ECB 2007). The volumes for industrial Ni-Cd batteries may increase in the future due to new market opportunities³ (USGS 2012).

8 USES

8.1 General

Once cadmium metal is produced, it may be converted to an intermediate product in one country, incorporated into different semi-products/articles in another country, and finally produced and sold in an end-product/article in a third country. It is therefore, difficult to establish a geographic consumption pattern.

The sources for cadmium oxide are both mining and recycled materials. Cadmium oxide is used as raw material for electrodes, metal coating⁴, metal cadmium, alloy production and to give other materials special characteristics (Figure 3). The oxide is also a raw material for producing other cadmium compounds, e.g. pigments and catalysts. The electrodes are used in batteries and are produced by sintering technique. The oxide is also used to increase the heat resistance of polymers. Other uses of the oxide are in ceramic glaze, catalysts, photo-electronics and as a veterinary biocide (GlobalSpec 2012).

In Europe is Belgium a large cadmium consumer for production of cadmium oxide for export to battery producers over the world. Japan is the largest producer of raw material for Ni-Cd-batteries in the world (Kirl-Othmer 2004).

Nickel cadmium (Ni-Cd) batteries are the dominating end products in the world consumption of cadmium (Figure 2), followed by minor uses for pigments, metal coatings, stabilizers, alloys and solar cells.

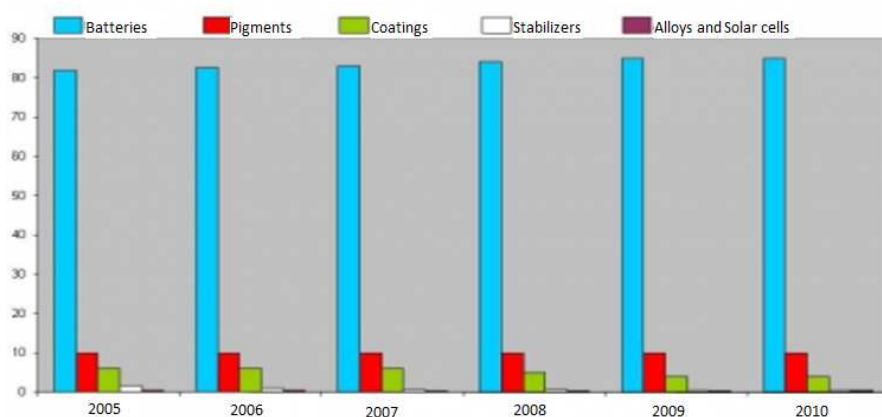


Figure 2: Trends in cadmium consumption patterns during 2005 to 2010, in per cent of the total consumption (ICdA 2013).

⁴ The vacuum ion deposition process for coating of iron, steel, aluminium and brass is not based on cadmium oxide.

ANNEX XV – IDENTIFICATION OF SVHC – CADMIUM OXIDE

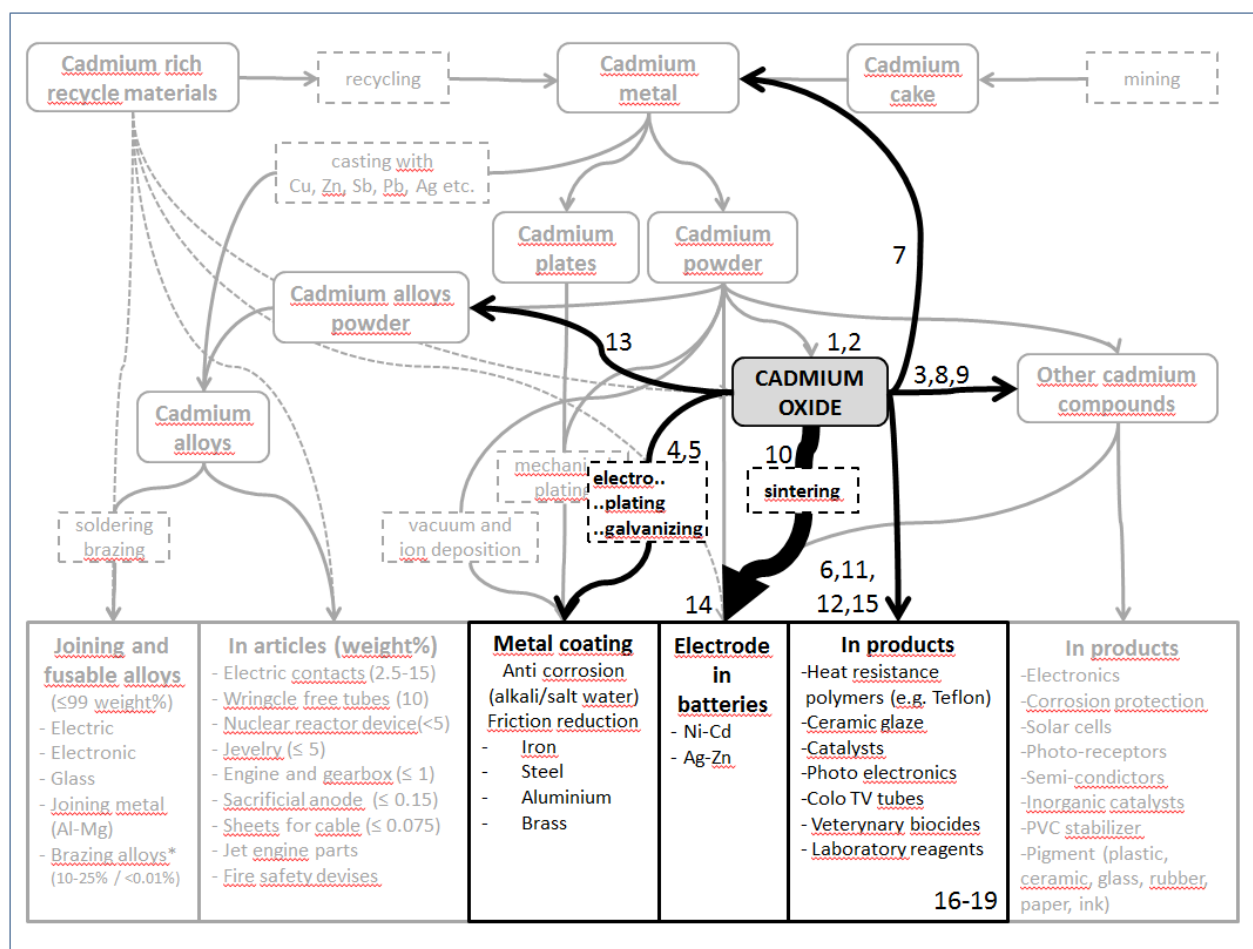


Figure 3: Overview of the use of cadmium oxide. The numbers refer to “identified uses” defined in section 0. (* is currently restricted under paragraph 8 of Entry 23 of Annex XVII of REACH).

The highest concentrations of cadmium are used in Ni-Cd batteries and in some alloys, with up to 25% (Table 9). Cadmium may occur as impurity in fertilizer, fossil fuel, cement and in different metals. The concentrations as impurities are normally in the range of 0.1 to 90 ppm (as cadmium). For many literature data on impurities is it unclear if it is in the form of metal. Even the metal form contains traces of cadmium oxide because of the oxidation of the surface, exposed to the atmosphere. The concentrations of cadmium oxide in coatings are less than 0.2%.

Table 9: Concentration of different intentional cadmium uses (US 2003, ICdA 2012b).

Product	% Cd	Comment
Ni-Cd batteries	7-25%	Cd, CdO, Cd(OH) ₂
Cd pigments	~1%	Cd(Zn)S(Se)
Cd coatings	~0.2%	Cd, CdO, Cd-Ti, Cd-Sn
Cd stabilizers	~1%	Cd-laurate, Cd-stearate
Cd alloys <i>et.al.</i>	1-25%	Cu-Cd, Ag-CdO

8.2 End uses of cadmium oxide (excluding the intermediate applications)

8.2.1 Use in Nickel-Cadmium batteries (ICdA 2012)

Cadmium oxide is used as a raw material for producing electrodes in Ni-Cd batteries (the negative electrode).

A number of types of Ni-Cd cell constructions are possible. These variations in cell construction lie mostly in the nature of the electrode support utilised. For the positive electrode, three principal types are recognized - pocket plates, sintered plates and fiber plates. Negative electrode designs make use of an even broader range of materials including pocket plates, sintered nickel powder, fiber, foam and plastic bonded supports. It is the physical stability of the active material (cadmium hydroxide) in the negative electrode that permits such a wide variety of support materials.

Nickel-cadmium batteries are characterized by their resistance to electrical abuse, high cycle lives, reliability and versatility and have found a wide range of applications. The several types of cell constructions are manufactured in a wide range of size, capacity and shape and the choice of a particular battery will depend upon the application and its current load requirements. There are principally two applications types, industrial and portable batteries.

- **Industrial Ni-Cd batteries:** Nickel-cadmium batteries for industrial uses are of the open or semi-sealed type and may be of pocket plate, sintered plate or fiber structured construction. Applications for industrial batteries include railway uses such as locomotive starting, emergency braking, coach lighting and air conditioning, trackside power for signaling and warning lights. Other uses include standby power for alarm systems, emergency lighting, military communications, solar energy storage, navigation equipment, military equipment, hospital operating theatres. Semi-sealed industrial batteries are used in aeronautical applications where they are used to start engines and also to provide stand-by power for aircraft systems when the principal power source fails. After long periods of operation most vented or semi-sealed cells may require electrolyte maintenance by topping up with distilled water.
- **Portable Ni-Cd batteries:** Nickel-cadmium batteries for portable use are of the sealed type and are generally of sintered plate construction. They may be of cylindrical, button or prismatic design. Sealed nickel-cadmium batteries are in use in consumer electronic equipment such as cellular telephones, portable tools, toys, camcorders and other domestic cordless appliances. They are also used for memory back-up in computing equipment, military and civil communications, emergency lighting and many other similar applications. Sealed cells require no maintenance and may be recharged up to 2000 times.

According to information from Industry, the following attributes are unique to industrial Ni-Cd batteries:

- High reliability and ability to withstand mechanical and electrical abuse,
- Large operating temperature range,
- Excellent long service life (12 to 20 years), adequate cycling ability,
- Progressive aging, lends itself to accurate monitoring of aging. This makes predictive maintenance the preferred maintenance strategy. No “sudden death” syndrome,
- Low cadmium metal content (8 to 10%) relative to the standard technology (Pb/acid with 70% Pb),
- Low CO₂ footprint compared to the standard technology.

These unique set of performance characteristics makes this family of products the technology of choice when the safety of large assets and/or human beings is at stake. In such applications, Ni-Cd batteries are entrusted with the function of providing back-up power in case of a malfunction in the power supply (often the electrical grid). This is why industrial Ni-Cd batteries are used in safety critical applications such as power back-up aboard commercial aircrafts and high speed trains, power back-up in networks equipment (i.e., telecom, oil and gas, IT) and power back-up in several highly critical industrial processes.

8.2.2 Use for cadmium coatings (ICdA 2012)

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 give high resistance to corrosion in most conditions and especially in marine and alkaline environments, and reduce 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 industry.

Electroplating accounts for over 90% of all cadmium used in coatings but mechanical metal plating and vacuum or ion deposition have some commercial significance. The coating is normally specified in thickness between 5 and 25 μm depending on the severity of the atmosphere.

Cadmium oxide can be used as a starting material for electroplating. In the process will cadmium electrodeposit on the metal article from an electrolyte solution of cadmium salts in barrels or vats. These electrolyte solutions are nearly always based on the alkaline cyanide system. Other solution types are used, such as those based on fluoroborates, but these have not proved popular as they lack the combination of brightness, covering power, throwing power and wide operating parameters of the alkaline cyanide system. When a current is passed through the electrolyte, cadmium is electrodeposited on the metal article at the cathode and cadmium from the anode goes into solution. Large or delicate articles are attached to racks and vat-plated whilst small components, such as bolts, washers, nuts, springs and clips can be vat-plated in drum cages or plated in a rotating barrel.

8.2.3 Use for cadmium alloys (ICdA 2012)

Cadmium forms many binary and more complex alloys which have useful properties for many commercial applications.

Most commercial alloys containing cadmium fall into two major groups:

- Cadmium **improves some feature** of the alloy
- Cadmium **lowers the melting point** of the alloy (mainly for joining)

The only use in alloys where cadmium oxide is mentioned is in material in switching contacts (see “special feature” below). However, cadmium oxide may also be relevant for other alloys.

Alloys with special features (ICdA 2012)

- Cadmium is widely used by the electrical switching industry in the form of cadmium oxide in metal alloys (primarily silver cadmium oxide, AgCdO) to manufacture high quality power switching contacts (NEMA 2008).
- Copper-cadmium alloys, which have almost double the mechanical strength and wear resistance of pure copper, contain between 0.8 to 1.2% cadmium. Major uses include telephone drop wires, contact wire and catenary strand for railway overhead electrification, tinsel conductor for flexible telephone cords, special cables for military and aerospace uses and electrical components such as contact strips. Copper-cadmium alloys can withstand service temperatures as high as 150°C; as a result they are used in both domestic and automotive radiators and fittings.
- A zinc alloy containing 0.1% cadmium improves the mechanical properties of rolled, drawn or extruded zinc. Zinc alloys containing cadmium in the range 0.025 to 0.15% are used as sacrificial anodes in the corrosion protection of structural steelwork immersed in seawater.
- Lead alloys with up to 0.075% cadmium are sometimes used as sheaths for cables subject to cyclic stress.
- Tin-based white metal bearing alloys with up to 1% cadmium have improved tensile and fatigue strength for use in marine engines and gearboxes.
- Precious metal alloys for jewellery incorporate cadmium for improved hardness and strength. Levels of up to 5% cadmium in gold-silver-copper alloys make Greek gold, a greenish-tinged gold (this use is partly restricted in REACH, Annex XVII, entry 23).
- Silver electric contacts incorporating 10 to 15% cadmium are useful in many heavy duty electrical applications such as relays, switches and thermostats. The presence of cadmium improves resistance to material transfer and electric erosion.
- Silver-indium-cadmium alloys are used in control rods for some pressurised water reactors in nuclear power generation. These rods absorb free neutrons and so control the process. In other nuclear engineering applications, cadmium metal sheet is used for shielding by similar neutron absorption (Wikipedia 2012b).

Joining and fusible alloys (ICdA 2012)

- Intermediate temperature soldering alloys and cadmium alloyed with silver, zinc and/or tin are often used in applications where temperature sensitivity prohibits the use of silver solders with higher tensile strength. Zinc-cadmium alloys are useful for soldering aluminium whilst cadmium-zinc-tin alloys are used for soldering magnesium.
- Cadmium as a component in quaternary silver-brazing alloys (lower temperature range of brazing alloys, together with silver, copper and zinc).
- Fusible alloys: Low temperature fusible alloys containing cadmium employ their low melting points and rapid fusing or solidifying characteristics in a variety of uses. Heat sensitive fusible links in fire safety devices or kilns and ovens can activate control mechanisms when they melt at specific temperatures. Woods metal in water sprinkler valves automatically activates the water supply as it melts.

Proof castings in these alloys can be made from wood, plastic or plaster foundry patterns for short run dies for sheet metal and thermoplastics.

The alloys are used to firmly mount glass lenses during grinding operations. Metal fabrication operations on complex or delicate assemblies are also easy when they are encased in a supporting jacket of metal. This technique also produces wrinkle-free bends in pipes and tubes. Similarly, jet engine turbine blades and vanes are machined whilst held by such low melting point alloys.

8.2.4 Other uses of cadmium oxide

Chemical synthesis of other cadmium compounds: Cadmium oxide is used as an intermediate processing aid in the chemical industry for manufacturing of other cadmium-substances. The following relevant downstream uses are identified: laboratory chemicals, lubricants, greases/release products, pharmaceuticals, cosmetics/personal care products (ICdA 2012).

Use as catalysts: Industrial use of cadmium oxide containing catalysts in manufacture of bulk, large scale chemicals as well as fine chemicals. Cadmium oxide is a constituent of many types of catalysts. It is present for its catalytic activity and its ability to absorb catalyst poisons and as catalyst strength. The following relevant downstream uses are identified: adsorbents, filling agents, putties, plasters, modelling clay and extraction agents (ICdA 2012) and paints for outdoor use (SPR 2010).

Material production/inclusion into polymer-matrices, plastics and related preparations: Cadmium has a low specific resistivity and low negative temperature coefficient of resistivity, which makes it useful act as a high temperature resistor material. Cadmium oxide is therefore used to improve the heat resistance of polymers, e.g. Teflon, nitrile rubber and PVC (Kirk-Othmer 2004). Industrial & professional use of cadmium oxide-containing polymers (ICdA 2012):

- For sheet and cable protecting & isolating coatings.
- For tube & sheet articles: polymer preparations and compounds in vehicles, electrical batteries/accumulators/plastic articles.
- For moulded articles: polymer preparations and compounds in vehicles, electrical batteries/accumulators/plastic articles.

Transparent conductor: Microparticles of cadmium oxide undergo bandgap excitation when exposed to UV-A light. This made it useful as a transparent conductive material in the form of thin films in applications such as photodiodes, phototransistors, photovoltaic cells, transparent electrodes, liquid crystal displays, IR detectors, phosphors and anti-reflection coatings. (Wikipedia 2012).

Raw material for production/inclusion into ceramic/glass: Industrial use of cadmium oxide or cadmium oxide-formulations in manufacturing of glass. Use in ceramic glass (ICdA 2012). Used in selenium ruby glass and in heat-resistant enamels (NTP 1995). Use as a component in enamels for the industry for glass and glass products (SPR 2010). Use for glass colorant (Kirk-Othmer 2004).

Pharmaceutical: Cadmium oxide is use for veterinary biocides as nematocide, vermicide, ascaricide or anthelmintic in svine (Kirk-Othmer 2004).

Plastic coating: Cadmium oxide has been reported to be used for metal coatings of plastics (NTP 1995).

Laboratory reagent: Industrial and professional use of cadmium oxide as active laboratory reagent in aqueous or organic media, for analysis or synthesis (ICdA 2012).

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

The registration of cadmium oxide includes the following uses:

- Cadmium oxide production: wet and indirect
- Cadmium production by pyro-metallurgy
- Component for production of inorganic cadmium compounds
- Component for production of inorganic pigments
- Component for production of organic cadmium compounds
- Laboratory reagent
- Additive for production of frits
- Additive for production of glass
- Additive in the manufacturing of electronic components
- Use of cadmium oxide-containing catalysts
- Electro-galvanizing
- Electroplating
- Cadmium oxide in electro-technical contact material
- Batteries/Fuel cells
- Component for polymer-matrices, plastics and related preparations
- Use of cadmium oxide-containing polymers for cable protecting & isolating coatings
- Use of cadmium oxide-containing polymers for tube & sheet articles
- Use of cadmium oxide-containing polymers for molded articles

8.4 Volumes

The total international cadmium consumption is dominated by the Ni-Cd batteries (Figure 2). Japan is the largest producer of raw material for Ni-Cd-batteries in the world (Kirl-Othmer 2004). Other relevant uses are as pigments and anti-corrosion coatings of metals. A quantification of the cadmium flow in EU⁵ has been made by Lig & Held (2009).

The volume for brazing alloys, for both professional and consumer uses was estimated to be 22 to 35 tonnes 2010 (ECHA 2012). This amount can be expected to fall due to the REACH Annex XVII restriction on cadmium in brazing fillers which entered into force in January 2012 (ECHA 2012).

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).

The final effect of the 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

⁵ The 27 EU member states.

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).

Ni-Cd-batteries may be used in electric vehicles, hybrid electric vehicles and electric buses. However, how this usage would influence the cadmium volumes is unclear since future applications are expected to be recycled. An example of a new potential use is combinations of cadmium, calcium, copper, selenium, strontium, sulphur, and tin that can be used as substitutes for hardening lead (USGS 2012).

8.5 Recycling

In the U.S., cadmium is mainly recovered from used consumer and industrial Ni-Cd batteries. Cadmium can also be recovered from copper-cadmium alloy scrap, some complex nonferrous alloy scrap, and cadmium-containing dust from electric arc furnaces (EAF) (USGS 2012).

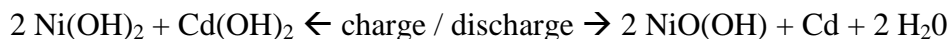
There are recycling systems established for used nickel-cadmium batteries. Today, there are 9 major Ni-Cd battery recycling plants located in the United States, Europe and Japan capable of recycling approximately 20 000 tonnes of industrial and consumer Ni-Cd batteries and their manufacturing scraps (ICdA 2012).

Also the plastic industry has undertaken research to determine the feasibility of recycling cadmium pigments and stabilizers from plastics (Kirk-Othmer 2004).

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

8.6.1 Ni-Cd batteries (ICdA 2012)

Cadmium is incorporated as an active electrode material in a number of rechargeable alkaline batteries or cells. The nickel-cadmium cell, with a potassium hydroxide (alkaline) electrolyte, is the most important and best known application. At the negative electrode (cathode) cadmium oxidizes to cadmium hydroxide whilst the nickel compounds are reduced to nickel hydroxide at the positive electrode (anode) according to the following reaction:



8.6.2 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. In addition to corrosion protection, cadmium coatings provide a low coefficient of friction and therefore good lubricity, predictable torque characteristics, good electrical conductivity, protection from galvanic corrosion (in particular when in contact with aluminum), and easy solderability.

8.6.3 Alloys (ICdA 2012)

Copper-cadmium alloys contain 0.8 to 1.2% cadmium, and have almost double the mechanical strength and wear resistance compared with pure copper. Zinc containing 0.1% cadmium improves the mechanical properties of rolled, drawn or extruded zinc. Lead alloys with up to 0.075% cadmium are sometimes used as sheaths for cables subject to cyclic stress. Silver-indium-cadmium alloys absorb free neutrons and are therefore used to control the nuclear reactions in nuclear power stations. Rods of the silver-indium-cadmium alloy absorb free neutrons and are used to control the process. In other nuclear engineering applications, cadmium metal sheet is used for shielding by similar neutron absorption.

8.6.4 Joining and fusible alloys (ICdA 2012)

Low temperature fusible alloys containing cadmium employ their low melting points (≥ 47 °C) and rapid fusing or solidifying characteristics in a variety of uses (e.g. for soldering aluminum and magnesium).

The main uses of brazing alloys were professional and industrial ones, such as tooling, heat exchangers, refrigeration, plumbing and electrical components. These uses were more widespread in southern European countries such as France, Spain, Italy and Portugal (ECHA 2012).

9 EXPOSURE

Human exposure for cadmium can potentially occur during the whole life-cycle of cadmium oxide. Industrial and professional workers will be exposed during several scenarios where cadmium oxide 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 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 bellows are also shown in the Figure 3 ([..] are use descriptors according to REACH 2010).

1. **Cadmium oxide production – Indirect:** Primary or secondary cadmium is used in the manufacture of cadmium oxide by a pyro metallurgical process (vaporisation + oxidization) and packaging [SU 8, 9], [PC 20], [PROC 2, 3, 8b, 9, 22, 26], [ERC 1].
2. **Cadmium oxide production – Wet:** A Cadmium containing solution is used in the manufacture of cadmium oxide [SU 8, 9; PC 20] by a wet process (purification + precipitation + calcination) and packaging [PROC 2, 3, 8, 9, 22, 26; ERC 1].
3. **Component for production of inorganic cadmium compounds:** Industrial use of Cadmium oxide or cadmium oxide-formulations [SU 8, 9, 10] in the manufacture of other inorganic Cadmium-substances [PC19, 20, 21], [PROC 2, 3, 8b, 9, 15, 21, 22] through different process routes, with potentially drying, calcining and packaging [ERC 1, 2, 6a].
4. **Electro-galvanizing:** Cadmium is deposited from a cadmium-rich solution [SU 15, 17, 0 (Nace C25.26.1: treatment and coating of metals)] as a metallic coating for corrosion inhibition [PC 7, 14] in electrolytic cells [PROC 13, 21] to galvanize effectively steel strips and other articles [AC 2, 7], [ERC 2, 5].
5. **Electroplating:** Cadmium is deposited from a cadmium-rich solution [SU 15, 17, 0(Nace 25.6.1: treatment of metals)] as a metallic coating for corrosion inhibition [PC 7, 14] of the article, during a batch chemical or electrochemical process [PROC 3, 8b, 21], [AC 2, 7], [ERC 2, 5].
6. **Laboratory reagent:** Industrial and professional use [SU 10, 24] of cadmium oxide as active laboratory reagent [PC 19, 21, 28, 39] in aqueous or organic media, for analysis or synthesis [PROC 1, 2, 3, 4, 5, 8b, 9, 15], [ERC 1, 2, 4, 6a, 6b, 8a, 8d].
7. **Cadmium production (pyrometallurgy):** Industrial use of impure or recycled Cadmium oxide in the manufacture of pure cadmium metal [SU 14, 0 (Nace C24.4.5/other non-ferrous metal prod.; E38.3 materials recovery), [PC7]. The smelting process is carried out in a furnace and condenser, with occasional controlled exposure [PROC 2, 8b, 9, 23, 26] [ERC 1].
8. **Component for production of organic cadmium compounds:** Industrial use of cadmium oxide or Cadmium oxide-formulations [SU 8, 9, 10] in the manufacture of organic preparations or organic Cadmium-substances [PC 19, 20, 21, 24, 29, 39] by mixing the starting materials [PROC 1, 2, 3, 4, 8b, 9, 15] in an organic-based matrix, with potentially filtering or casting [ERC 1, 2, 6a].
9. **Component for production of inorganic pigments:** Industrial use of cadmium oxide or cadmium oxide-formulations as component for the manufacture of inorganic pigments [SU 8, 9, 10, 13], [PROC 1, 2, 3, 4, 5, 8b, 9, 22] [PC 9a, 9b, 9c] and others [ERC 1, 2, 5].
10. **Additive for production of frits:** Industrial use of cadmium oxide or cadmium oxide-formulations [PC 19, 0 (UCN R30100-R30200 raw material for synthesis and intermediate

- products/raw material for production of glass and ceramics)], [PROC 2, 3, 4, 5, 8b, 9, 10, 13, 14, 15, 17, 22, 26] in manufacturing of ceramics [SU3, 10, 13], pressing, melting, rapid cooling for production of frits [AC 3, 4, 0 (TARIC 854125: transistors other than photosensitive transistors)] [ERC 1, 2, 3, 5].
11. Additive for production of glass: Industrial use of cadmium oxide or cadmium oxide-formulations [PC19, 20], [PROC 2, 3, 4, 5, 8b, 9, 22] in manufacturing of glass [SU 10, 13, 0 (Nace 23.1 manufacture of glass and glass products)], [AC 4], [ERC 2, 3, 5, 6a].
 12. Additive in the manufacturing of electronic components: Industrial use of cadmium oxide or cadmium oxide-formulations [PC20], [PROC 3, 5, 8b, 9, 14, 22, 24] in manufacturing of electronic components (transistors, diodes) and similar articles [SU 10, 13, 0 (Nace 26.1.1 manufacture of electronic components)], [AC 2, 4], [ERC 2, 5].
 13. cadmium oxide in electro technical contact material: Cadmium oxide can occur [PROC 3, 5, 14] as induced component [SU 13, 14, 16] in electro-technical contact material [PC 7, 14, 19] [AC 2, 4, 7] [ERC 2, 5, 6a].
 14. Batteries/Fuel cells: Industrial use of cadmium oxide or cadmium oxide-formulations [PC14, 19, 20, 21], [PROC 3, 5, 13, 14] in manufacturing of electrode compartments for batteries [16, 0 (Nace C27.2 manufacture of batteries and accumulators)] [AC 3] [ERC 2, 5].
 15. Component for polymer-matrices, plastics and related preparations: Industrial use of cadmium oxide or cadmium oxide-formulations [PC 19, 20, 32, 33], [PROC 2, 3, 5, 6, 8b, 9, 10, 13, 14, 21, 24] in manufacturing of polymer matrices and plastic products [SU 10, 12], [AC 1, 2, 3, 13], [ERC 1, 3, 5, 6a].
 16. Use of cadmium oxide-containing polymers for cable protecting & isolating coatings: Industrial & professional use [SU 10, 12, 19] of cadmium oxide-containing polymers for sheet and cable protecting & isolating coatings [PC 32], [AC 1, 3, 13], [PROC 9, 13, 14, 21, 32], [ERC 10a, 11a].
 17. Use of cadmium oxide-containing polymers for tube & sheet articles: Industrial & professional use [SU 10, 12, 19] of cadmium oxide-containing polymers for tube & sheet articles [PC 32], [AC1, 3, 13], [PROC 9, 13, 14, 21], [ERC 10a, 11a].
 18. Use of cadmium oxide-containing polymers for molded articles: Industrial & professional use [SU 1, 10, 12, 17, 19] of cadmium oxide-containing [PC 32], [AC 1, 3, 13] polymers for molded articles [PROC 9, 13, 14, 21, 24] [ERC 10a, 11a].
 19. Use of cadmium oxide-containing catalysts: Industrial use of cadmium oxide [SU 8, 9, 10] containing catalysts [PC 2, 9b, 19, 20, 40]. Cadmium oxide is a constituent of many types of catalysts: it is present for its catalytic activity, its ability to absorb catalyst poisons (a.o. S and Cl) and as catalyst strength [PROC 1, 2, 3, 5, 8b, 9, 14], [ERC 1, 4, 5, 6a, 6b].

9.2 Releases during the service life

Release of cadmium during service life from anthropogenic sources includes products and materials to which cadmium has deliberately been added to impart a specific chemical, mechanical or physical property and products or materials in which cadmium is naturally 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).

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).

9.3 Releases during the waste life stage

The Ni-Cd battery recycling system will not collect 100% of the batteries on the market. It can be expected that Ni-Cd batteries (mainly portable) to some extent end up in landfills or are incinerated which cause releases of cadmium into the environment (ICdA 2012b).

9.4 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 causes 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 all must be combusted to be utilized. The raw materials employed to produce cement and concrete also contain residual amounts of cadmium and are a contributor 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 into 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 fact, in recent years has been to produce these nonferrous metals, their alloys and their compounds with lower and 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. 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. 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 10 (ICdA 2012b).

Table 10: 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

9.5 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 11.

- 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) are 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 $\mu\text{g/L}$) and urine (median 0.52 $\mu\text{g/L}$; density adjusted = 0.67 $\mu\text{g/g}$ 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 11: Summary of the urinary concentrations observed in three Swedish population-based studies

	Age (years)	Urinary cadmium $\mu\text{g/g}$ creatinine			
		Median and (range)	Never-smokers	% >0.5 $\mu\text{g/g}$	% >1.0 $\mu\text{g/g}$
		<i>All</i>	Never-smokers	<i>All / Never-smokers</i>	
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 $\mu\text{g/g}$ 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 cutoffs of 0.5 and 1.0 $\mu\text{g/g}$ 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 $\mu\text{g/g}$ creatinine, respectively. The corresponding proportions for urinary cadmium concentrations above 1.0 $\mu\text{g/g}$ 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.

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 studies published starting in the 1970. 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.

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 analysed 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.

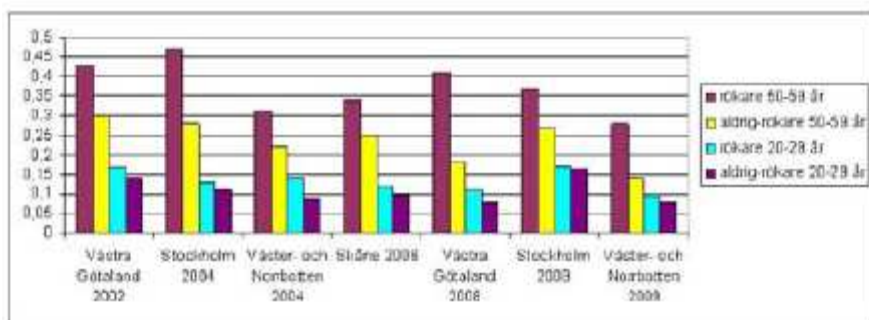


Figure 4: Urinary cadmium ($\mu\text{g/g}$ creatinine) among Swedish woman, 20-29 years and 50-59 years of age, presented as the median.

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.

9.6 Worker exposure to cadmium

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).

In the registration dossier of the lead registrant exposure assessments of the various work tasks involving cadmium oxide are mainly from the EU RAR (ECB 2007). In addition, a few recent air measurements and urinary concentrations of exposed workers are given.

9.7 Consumer exposure

According to the EU RAR, the consumer uses of cadmium oxide and metal fall into five categories corresponding to at least 5 scenarios of exposure: Active electrode material in nickel-cadmium 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 lead registration dossier, no consumer use is given and therefore also no exposure assessments. It is, however, mentioned that one new use (small in quantity) has been emerging: i.e. the use of cadmium substances in the production of photovoltaic cells. This application does not result in any direct consumer exposure.

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 oxide it cannot be completely ruled out that some consumer exposure from articles containing cadmium may still take place.

10 ALTERNATIVES

10.1 Batteries

The information below has been obtained from the battery industry:

Pb/acid batteries: The Pb/acid technology fulfils approximately 90-95% of the industrial storage market needs. However the relatively short service life (3 to 5 years), the limited ability to withstand harsh temperature conditions and the different aging behaviour of lead (Pb/acid) batteries (sudden death syndrome) do not match the performance of industrial Ni-Cd batteries. They are therefore widely used as stationary and motive power batteries when reliability expectations are less severe and are usually selected due to price consideration when their performance is deemed sufficient. The ability of the Pb/acid technology to replace industrial Ni-Cd batteries is therefore considered quite limited.

Li-ion batteries: The set of characteristics of Li-ion batteries relative to Ni-Cd batteries are their high energy and power (volumetric and weight) density, as well as superior ability to cycle many thousands of times. These advantages come with a much higher price tag (2 to 3 times that of Ni-Cd) and such batteries need to be driven and monitored with advanced electronics, as they do not have the same intrinsic stability and ability to withstand abuse as industrial Ni-Cd batteries. These batteries have a good fit for cycling applications, especially when weight limitations are important, volumes are high, and the intrinsic price difference of this technology along with the cost of the required battery management system can be justified. They are not a good candidate for industrial floating uses.

Ni/MH batteries: This chemistry has not been able to show clear benefits for the industrial market.

Na-S batteries: Sodium-sulphur batteries have a high energy (but low power) density making them suitable for some grid storage uses (e.g. linked to wind and solar power) as well as some other stationary applications where cycling is needed. This technology is mainly found in Japan where it fulfils a niche of the stationary market. Use in other fields has been explored, but there is very limited potential for this technology. Indeed there are several technical issues to be solved as these batteries operate at high temperatures (requiring bulky insulation) and the corrosive nature of the sodium polysulfide gives rise to limited shelf life. Currently production has been stopped due to fire incidents, pending resolution. Thus, this technology is focusing on grid related stationary uses and

holds no potential to replace mission critical power back-up uses.

10.2 Metal coating

Except where the surface characteristics of a coating are critical (e.g. fasteners for aircraft), coatings of zinc or vapor-deposited aluminum can be substituted for cadmium in many plating applications (USGS 2012).

10.2.1 Anti-corrosion metal coating

Technical alternatives to cadmium electroplating have been identified for electroplated cadmium. The following alternatives was identified in a study from US 1994: electroplating (alternative materials), chromate conversion coating, electroless plating, ion coating, mechanical plating, metallic-ceramic coating, organic coating, surface hardening, and thermal spraying (NDCEE 1994).

Electroplated aluminium has been mentioned as an alternative to cadmium plating. It is commercially available high purity aluminium plating for corrosion control. The coating can be applied via a wet but non-aqueous process to any conductive substrate, from carbon steel to aluminium beryllium alloys and even graphite. High purity aluminium has high corrosion resistance properties, even as a thin coating. It is also highly ductile, nonembrittling, mitigates galvanic corrosion and can be used in applications up to 1,000 °F. The coating is especially useful in the aerospace industry (Vallejo 2003).

An alternative for the cadmium plating in the aircraft industry has been developed. It is based on a tin-zinc alloy (SIFCO 2012).

10.2.2 Military Electrical Connectors

Alternatives for cadmium in military electrical connectors have been assessed (Mason 2012). According to the abstract are the most promising candidate coating processes to replace cadmium and hexavalent chromium in electrical connector applications are technologies that are already being used on electrical connectors to some extent, or demonstrate both considerable promise for the application and sufficient maturity. These include:

- Electroplated aluminium (AlumiPlate®)
- Electroplated alkaline zinc-nickel (5–15% nickel in the deposit)
- Electroplated tin-zinc (at least 20% zinc in the deposit)

Future efforts will focus on these three most promising candidates. In addition, to support efforts being undertaken by electrical connector manufacturers, two EN-based technologies, both incorporating occluded particles, will also be evaluated. Coatings with both CCCs and TCPs will be considered, as available, and cadmium with CCC will be used as the control. The most promising candidate coating processes from emerging alternatives were also identified. These are technologies that show promise for electrical connector applications, but require further development for the electrical connectors employed by TARDEC. These include:

- Alloys deposited from ionic liquids

- Magnetron sputtered aluminium alloys
- Tin-indium alloys

Future efforts may consider these candidates as the technology matures and becomes more feasible for electrical connectors (Mason 2012).

10.3 Brazing alloys (ECHA 2012)

New specifications for cadmium-free alloys are available on the Internet. ICdA indicates that brazing fillers which do not contain cadmium are now most commonly used in the EU. However, brazing fillers which contain cadmium are still used in the aerospace and military sectors, and in high-speed trains, where safety and security are said to be the main drivers for non-substitution, with the quantity of cadmium involved being less than 25 tonnes per year in Europe. In relation to the identified use in high-speed trains, ICdA noted that cadmium is used in the realisation of 'aluminum cooling systems' for electrical equipment. However, it seems that this application is more relevant to soldering (<450°C) rather than brazing.

11 RISK-RELATED INFORMATION

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

According to the lead registration dossier, worker exposure to dust and fumes is controlled by a general application of local exhaust ventilation at the work place and, in specific cases, personal protection measures. Dermal exposure is prevented by the general use of specialized clothing, including specialized working gloves.

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 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 2012)

The European Food Safety Authority (EFSA) has recently updated their exposure and risk evaluation of cadmium in a scientific report (EFSA 2012), see abstract below.

ABSTRACT: 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 body weight 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 (KemI 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

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, was further explored in humans. 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 percentile 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. In a collaboration project between toxicologists and epidemiologists the possible mechanism of such estrogenic effect was investigated. In a rodent uterotrophic bioassay to transgenic (estrogen-receptor element) ERE-luciferase reporter mice, the animals were exposed to cadmium chloride subcutaneously for four days before puberty. Cadmium was unable to induce uterotrophic response *in vivo* and was unable to induce estrogenic responses via classical estrogen-receptor-signaling through ERE-driven genes. However, luminal epithelium height of the endometrium was significantly increased in a dose dependent manner after cadmium chloride (and estradiol treatment). It was concluded that cadmium can induce estrogen-like responses maybe via non-classical estrogen receptor- signaling pathway and that cadmium may promote tumor development in the uterus. 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 (KemI 2011).

The mechanism of the estrogen-like effects of cadmium has been investigated in transgenic estrogen reporter mice and it was concluded that cadmium acts via a different mechanism from that of steroidal estrogens. Cadmium (chloride) significantly affected kinase phosphorylation and endogenous gene expression at low exposure levels; the lowest effect seen at 0.5 µg /kg bw (Ali et al 2012).

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).

13.4 References

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