SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1306-19-0 & 7440-43-9
Chemical Name	Cadmium oxide & Cadmium metal
Structural Formula	CdO & Cd

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The main reason for treating Cadmium (i.e. cadmium metal) and Cadmium oxide together stems from consideration of similar physico-chemical properties, in particular their relatively low solubility in water and from consideration of the conditions of exposure. Indeed, in occupational settings, workers are mainly exposed to cadmium oxide fumes and dust, produced when the metal is heated. The general population is exposed mainly by the oral route via food or water to cadmium (not necessarily CdO/Cd metal). However, both compounds release the biologically active form, i.e. ionic Cd^{2+} in the environment and biological tissues and so the effects can generally be treated together.

The objective of the study was not to be complete in reviewing the data on cadmium compounds but rather to focus on critical studies and endpoints. Reviews have been used in retrieving critical studies.

Human Health

While the toxicological database for cadmium (generic) is in general considerable, most of the experimental data have been produced with soluble cadmium compounds and, in human studies, the exact species involved is seldom well defined. As a consequence, incomplete data are available when specifically dealing with the fate and hazards of cadmium metal and cadmium oxide. Therefore, when necessary, use has been made of data for cadmium compounds in general.

The gastro-intestinal absorption of cadmium (generic, not specifically Cd metal or CdO) is low and subject to variations according to the source of Cd, the presence of Zn in the diet and its composition, age and physiological status of the individual: generally below 5 % (average 3%) when iron stores are adequate and may increase up to 10% when iron stores are depleted. Absorption rates after inhalation of CdO derived from animal studies range from 50 (fumes) to max. 30 % (dust, depending on particle size). In humans, figures of 10-30 % absorption rate according to particle size are derived for CdO dust. No data are available for Cd metal. From experimental studies performed with soluble Cd salts it can be deduced that percutaneous absorption is likely to be significantly less than 1 % (elemental Cd).

Cd is widely distributed and retained in the body where it accumulates throughout life. Hence, the body burden increases upon continuous exposure and the element has a biological half-life of about 10-20 years. After long-term low-level exposure, about half the body burden of cadmium is localised in the kidneys and liver, a third of the total being in the kidneys with the major part located in the cortex. In non-occupationally exposed subjects the cadmium concentration in the renal cortex is estimated between 10 and 50 ppm (2-3 fold increase in smokers). Only a small part of cadmium absorbed from long-term low level exposure is excreted: daily excretion which takes place via faeces and urine represents only 0.005-0.02% of the total body burden of the element The placenta provides a relative barrier protecting the foetus against cadmium exposure. There is some build up of cadmium in the placenta and levels are significantly higher in smokers than in non-smokers. Cadmium is found in human breast milk at low concentrations (< 1 µg/l).

The whole blood Cd (Cd-B) concentration, is a useful indicator of exposure over the last few months. After long-term high Cd exposure, an increasing proportion of blood Cd will, however, also be related to body burden. Therefore, in non-smokers and after cessation of long-term high exposure, Cd-B may also reflect body burden.

Cd urinary excretion (Cd-U, expressed as µg Cd/l, as µg Cd/g creatinine, as nmol Cd/mmol creatinine or µg Cd/ 24 h) is correlated with the body burden and has been extensively used as a biomarker of long-term exposure in human studies. Several studies have shown that in the general population, Cd-U increases with age and this increase coincides with an increased body burden. At the group level, there is a close relationship between Cd-U and kidney cortex content of the element; a Cd-U of 2.5 µg/g creatinine corresponds, at the group level, to about 50 ppm in the kidneys cortex.

Orally, LD50 values (rat and mouse) range between 72 and 296 mg/kg bw for CdO and from 890 to 2330 mg/kg for Cd metal. Acute inhalation exposure to CdO was found to produce pulmonary inflammation and oedema in experimental rats. The lowest dose (LOAEL) reported to cause mild pulmonary damage (hypercellularity indicative of hyperplasia) in experimental animals was a 3-hour exposure to 0.5 mg/m^3 CdO fumes (MMAD: 0.26-0.33 µm). In humans, it has been estimated that an 8-hour exposure to 5 mg/m^3 may be lethal and an 8- hour exposure to 1 mg/m^3 immediately dangerous for life. LC_{50} and/or CT_{50} values are available for several animal species. CT_{50} expresses the concentration x time, causing death in 50% of a defined experimental animal population. The most reliable data are on rat where the CT_{50}-values of 1 962 and 13 770 mg x min/m^3 were obtained. These results allow to conclude to the high acute toxicity of Cd(O) via inhalation in animals. Human data support this finding. A N(L)OAEL for acute dermal exposure could not be derived. However, acute effects via the dermal route are not expected to be significant as uptake appears to be very low (cf. toxicokinetics).

No specific data were located regarding the irritation potential of CdO or Cd metal on the skin, eye or respiratory tract neither in animals nor in humans. Based on the effects observed after acute and repeated inhalation exposure, it seems, however, possible that CdO (as fumes or dusts) is irritant for the respiratory tract.

A substantial body of information is available indicating that the lung, kidney and bone are the main target organs upon repeated exposure to CdO/Cd metal in occupational settings (mainly by inhalation). Environmental exposure to Cd (generic, not specifically CdO/Cd metal), mainly by the oral route, is associated with bone and kidney toxicity.

NOAELs identified from long-term inhalation tests are 0.025 mg CdO/m^3 in F344/N rats and < 0.025 mg CdO/m^3 in $B6C3F_1$ mice, exposed for 13 weeks. No study specifically using Cd metal dust or powder was located. In humans, long term inhalation of CdO fumes or dusts leads to reduced lung function and emphysema. A LOAEL equivalent to a Cd-U of 3.1 µg Cd/l is derived for CdO fume exposure. No human data are available for Cd metal dust.

Experimental and epidemiological studies indicate that the bone tissue is another target for Cd toxicity, but the mechanism is not fully understood yet. A LOAEL of 3 nmol Cd/mmol creatinine for bone effects was suggested from epidemiological studies conducted in populations exposed to Cd via the diet.

Numerous studies in several experimental species have indicated that exposure to cadmium compounds administered orally or by inhalation causes kidney damage and functional changes (reduced glomerular filtration rate, proteinuria). In workers occupationally exposed to cadmium, a Cd body burden corresponding to a Cd-U of 5 µg/g creatinine constitutes a LOAEL based on the occurrence of Low Molecular Weight proteinuria. In the general population (mainly exposed by the oral route), the most recent studies conducted in Europe indicate that renal effects can be detected for Cd body burdens below 5 µg Cd/g creatinine. The LOAEL of 2 µg/day (Cd-U) derived for increased calciuria is consistent with the view that bone and kidney effects of Cd are probably interrelated.

Cardiovascular and liver effects are not critical endpoints for CdO/Cd metal toxicity.

Evidence from experimental systems indicates a potential neurotoxic hazard for cadmium (not CdO or Cd metal specifically) in adult rats. In humans, heavy occupational exposure to cadmium dust has been associated with olfactory impairments and studies performed on a limited number of occupationally-exposed subjects are suggestive of an effect of Cd on the peripheral and central nervous systems but these findings should be confirmed. In the young age, there is some experimental indication that Cd exposure (not specifically CdO or Cd metal) can affect the

developing brain but this should be further investigated.

In bacterial systems, cadmium compounds generally fail to induce point mutations. A well conducted study on four *S. thyphimurium* strains did not show mutagenic effect of CdO. In mammalian systems, cytotoxic concentrations of cadmium compounds have been shown to cause chromosomal damage *in vitro*. Chromosomal aberrations and micronuclei in bone marrow cells have been reported after exposure of rodents to soluble Cd compounds. However, inhalation exposure to CdO (up to 1 mg CdO/m^3) did not induce micronuclei in peripheral erythrocytes in mouse. With regard to human exposure, data are conflicting but seem to indicate a genotoxic potential of Cd compounds, at least in occupational settings. Studies performed in environmentally exposed populations have suggested that cadmium compounds might exert genotoxic effects. Overall, it cannot be excluded, based on the available data, that cadmium compounds (including Cd metal and CdO) might exert genotoxic effects.

CdO induced lung tumours in rat inhalation studies. Cd metal produced local tumours when injected in experimental animals. In humans, the possibility that cadmium dust or fumes (including CdO) might cause a risk of lung cancer by inhalation is reported in several epidemiological studies but the possible contribution of confounding factors (mainly co-exposure to other carcinogens) could not be clearly defined. No study was specifically conducted with Cd metal in animals exposed by inhalation or in humans. Overall, the weight of evidence collected in genotoxicity tests, long-term animal experiments and epidemiological studies leads to conclude that CdO/Cd have to be considered at least as suspected human carcinogens (lung cancer) upon inhalation exposure. There is no indication or evidence that CdO/Cd act as carcinogens in the general population exposed by the oral route.

Effects on reproductive organs and fertility have been noted in experimental studies after exposure to CdO and Cd compounds-. The lowest values were derived in rats exposed by the oral route to $CdCl_2$ (NOAEL 1 mg Cd/kg/day) and by inhalation to CdO (NOAEL 0.1 mg CdO/m^3). Epidemiological studies do not point to an association between exposure to CdO/Cd metal and relevant effects on fertility or reproductive organs.

Regarding developmental toxicity, cadmium compounds have been reported to induce malformations primarily of the skeleton, neurobehavioral alterations and reduced body weight in offspring of animals exposed via the oral route (gavage or diet) or by inhalation, both at doses that generally produced maternal toxicity. In well conducted inhalation studies with CdO (MMAD: 1.1-1.6 µm) the NOAEL was 0.05 mg CdO/m^3 in mouse and 0.5 mg CdO/m^3 in rat. Neither the mechanism nor the critical period of cadmium-induced adverse effects in offspring due to maternal exposure are completely elucidated.

Further information is needed to better document the possible effect of low doses of Cd/CdO on the developing brain suggested in experimental animals. Based on the human data available, there is no indication of a potential developmental effect of CdO or Cd metal.

Environment

Both substances are solids. Cadmium metal exists in virtually all forms, shapes and particle sizes. CdO is commercialized as powder. Water solubilities are low: in the range of 0.19 mg Cd/L – 0.227 mg CdO/L. Vapour pressure for cadmium metal is 1 mmHg (at 394°C), for cadmium oxide: 1 mmHg (at 1000°C). Octanol-water partition coefficients are not relevant for this type of substances.

The database on the effects of soluble cadmium compounds to aquatic organisms is in general extensive. Limited data are available on cadmium oxide specifically and again far less on cadmium metal.
Besides the available limited number of standard tests on the substances, data from other soluble salts are used as well in the derivation of ecotoxicological thresholds.

The median acute LC50 values are 166 µg L^{-1} for freshwater invertebrates and 1500 µg L^{-1} for fish and amphibians (all values expressed as concentrations of cadmium ion). The median EC50 for primary producers (algae and aquatic plants) is 59 µg/l.

The lowest adverse effect concentrations of Cd in chronic studies with freshwater species range from 0.3 to >100 µg Cd L^{-1} with a tendency to find the lowest toxic thresholds for invertebrates in soft waters. The $PNEC_{water}$ of Cd was

derived with statistical extrapolation from 44 chronic NOEC values. The HC5 of this distribution is 0.38 µg/l. A safety factor of 2 is applied to reach the PNEC of 0.19 µg Cd L^{-1} (dissolved fraction). A US EPA hardness correction is applied to derive a PNEC for waters with a hardness of 100 to 40 mg $CaCO_3$/l: 0.08 µg/l. Mesocosm data indicate that this corrected PNEC is also protective down to a hardness of approximately 10 mg $CaCO_3$/l. There are no data available to correct the PNEC at a water hardness below 10 mg $CaCO_3$ L^{-1}. No further correction for bioavailability has been applied.

The lowest adverse effect concentrations in soil for plants, invertebrates or soil micro organisms vary between 2.5 and >1000 mg kg^{-1} with a tendency to find lowest thresholds for plants grown in potted soil applied with Cd^{2+} salts. The $PNEC_{soil}$ of Cd is derived by conducting a species sensitivity distribution of either NOEC values for soil microbial processes (based on soil functions) or for plant and invertebrates (species). The most conservative of these distributions (microbial processes) results in an HC5 of 2.3 mg/kg. An assessment factor of respectively 1 or 2 is applied to reach a $PNEC_{soil}$ of 2.3 to 1.15 mg/kg. The final $PNEC_{soil}$ is 1.15 mg Cd kg^{-1}. The overall database did not reveal significant trends between soil properties (pH, % clay) and Cd toxicity and similar information from studies using multiple soil types was inconsistent.

One chronic study with benthic organisms was found from which a NOEC of 115 mg kg^{-1} is derived. The $PNEC_{sediment}$ was derived applying a safety factor of 50 on this value resulting in a value of 2.3 mg Cd kg^{-1} , because other derivation methods (equilibrium partitioning) did not give satisfactory results. No correction for bioavailability was made.

The median Cd Bioconcentration Factors (BCF, L kg^{-1}_{ww}) decrease in the order algae>invertebrates>vertebrates and the water-fish Cd Bioaccumulation Factors (BAF's) are about 40 L kg^{-1}_{ww} with maximal values around 600 Lkg^{-1}_{ww}. Soil-earthworm BAF values are about 15 (dry weight concentration ratio) with values up to 150. All BCF and BAF values exhibit a pronounced decrease with increasing concentrations in the environment.

Environmental monitoring in wildlife does not suggest biomagnification of Cd. Field data of terrestrial birds (body burden Cd) do not indicate Cd poisoning, even in contaminated areas and in top predators. Pelagic birds have reported kidney Cd concentrations above acceptable values but the assessment of hazards to marine organisms was not made.

The effect of Cd on small terrestrial mammals was assessed based on monitoring data of body burden and an assessment of critical kidney Cd concentrations. A critical soil Cd concentration was derived which is 0.9 mg $kg^{-1}_{dw.}$ This value is triggered by data on moles and shrews (both carnivorous) dwelling in acid soils. This critical soil Cd concentration is below the $PNEC_{soil}$ derived from direct toxicity tests (plants, invertebrates and microbial processes) confirming the general knowledge that Cd is more toxic to mammals than to plants or invertebrates.

Exposure

Cadmium is a naturally occurring element with a ubiquitous distribution in the environment. It is found in high concentrations in zinc ores, also as greenockite (CdS) and otavite ($CdCO_3$). Natural processes e.g. volcanic eruptions are major natural source of cadmium release.

Primary cadmium is produced during the refining of other non-ferrous metals' ores, mainly zinc and to a lesser extent lead and copper. Cadmium as a by-product is here obtained by either pyrometallurgical (high temperature) or hydrometallurgical (electrolytic) production techniques. The final step in the production of high purity cadmium (>99.99%) is vacuum distillation or electrolysis. Cadmium is also increasingly being recovered from the recycling of e.g. NiCd batteries, cadmium-coated products, alloys, etc so as to obtain cadmium - so-called secondary cadmium - with a purity, quality and form that can be utilized again in industrial applications.

Cadmium oxide is produced indirectly from commercial cadmium metal.

The production of cadmium in the EU in 1996 was approximately 5808 tonnes, of which 2536 tonnes (approximately 44%) were subsequently converted into CdO.

The major uses of cadmium and cadmium oxide in the EU are in the manufacture of NiCd batteries (75%), other Cd-containing chemicals e.g. pigments (15%) and stabilizers (5%), in cadmium-plating and alloys (5%) and in miscellaneous uses (<0.01%).

Emissions to the environmental compartments are possible from the production and the use of the substances. However, the quantity of Cd actually present in the EU environment (topsoil, sediments and freshwater) exceeds by orders of magnitude the actual annual emissions. The environmental emission from Cd/CdO producers and processors only form a minor part of the total emissions of Cd in Europe. The major sources of Cd emissions at the continental scale are phosphate fertiliser application, production of iron and steel and oil combustion.

During the production or the use of Cd metal and/or CdO, the main route of potential exposure is inhalation. The potential for consumer exposure due to Cd(O) is generally non-existent or very low. Exposure by ingestion (mainly food, to lesser extent water and beverages) and possibly inhalation from environmental sources (nearby point sources) or from smoking is significant. The dietary Cd intake varies between 7-32 µg Cd day^{-1} in EU and is mainly due to consumptions of leafy vegetables, cereals and potatoes, which take up Cd from soil. Seafood may be an additional source of Cd exposure. Inhalation of Cd and direct Cd deposition onto crops are only major contributor for the general population around point sources with elevated atmospheric emissions (i.e. a minority of the production and processing sites, data resp. from 1996 and 1999). Tobacco smoking is an important source of exposure to Cd compounds that leads to a doubling of the Cd body burden in smokers.

RECOMMENDATION

The chemical is a candidate for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health and Environment:
Hazardous properties have been identified for these substances both for human health (respiratory irritation, kidney and bone toxicity, possible genotoxicity, carcinogenicity and neurotoxicity) and for the environment (increased mortality and reduced growth or reproduction for organisms living in water, sediment and soil; reduced microbial functioning of micro-organisms in soils and sewage treatment plants; kidney damage in mammals and birds). In an assessment performed in the context of the EU Existing Substances Regulation, potential exposure (mainly occupational and environmental exposure) was identified and concern for kidney/bone toxicity was expressed for several sub-populations. Other OECD countries may wish to perform an exposure assessment and if necessary a risk assessment.

Further testing could be considered as a post-SIDS activity:

Human Health
Further experimental and epidemiological information is needed to better document the possible effects of low doses of Cd/CdO on neurobehavioural performances suggested in experimental animals, especially on the developing brain (prenatal and early childhood exposure). Effects on the adult nervous system should also be characterised.

Environment
Ecotoxicity testing in very soft waters (hardness below approximately 10 mg $CaCO_3$/L) needs further clarification. Moreover, more information is required to quantify the bioavailability of Cd in the sediment compartment, i.e. if it is appropriate to apply the concept that the excess simultaneously extractable metals above the free sulphide concentration predict the toxicity of Cd.