Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for cadmium and its inorganic compounds

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8 hour TWA	: 0.004 mg/m³ (respirable fraction)
STEL (15 min)	: -
Notation	: -
BLV	: 2 µg Cd/g creatinine
SCOEL carcinogen group	: C (*genotoxic carcinogen for which a practical threshold is supported and a health –based OEL is proposed)*

Substance identification

Cadmium (Cd) was first isolated in 1817 in Germany. The element has no essential function in humans but causes acute injury to the lungs and cumulative toxicity to the lungs, kidneys and bone.

Metallic Cd is a white silvery metal with a low melting point (321°C). It is soft, malleable, ductile and similar in many respects to zinc. The most common oxidation state of Cd is +2 and the characteristics of the most common inorganic Cd compounds are given in the table below.

	Cd metal	CdO	CdCl2	CdSO4	CdS	Yellow Pigments $Cd_{(1-x)}Zn_xS$	Red Pigments $CdS_{(1-x)}Se_x$
EC No	231-152-8	215-146-2	233-296-7	233-331-6	215-147-8	232-466-8	261-218-1
CAS No	7440-43-9	1306-19-0	10108-64-2	10124-36-4	1306-23-6	8048-07-5	58339-34-7
Classification	Carc. Cat. 2; R45 Muta. Cat. 3; R68 Repr. Cat. 3; R62-63 T; R48/23/25 T+; R26		Carc. Cat. 2; R45 Muta. Cat. 2; R46 Repr. Cat. 2; R60-61 T; R25-48/23/25 T+; R26		Carc. Cat. 2; R45 Muta. Cat. 3; R68 Repr. Cat. 3; R62-63 T; R48/23/25 Xn; R22	Specifically excluded from classification under Directive 67/548/EEC and under Regulation 1272-2008 (GHS) classification and labelling.	
MW	112.41	128.41	183.32	208.47	144.48	variable depending on Zn/Se content	
Physical form	White silvery solid	Brown powder	White crystals	Colorless crystals	Yellow-orange-brown crystals	Bright yellow powder	Brightly coloured powder (from yellow-orange, through red to deep maroon
Water solubility	Insoluble	Practically insoluble	1400 g/L@ 20°C	755 g/L@ 0°C	1.3 mg/L@ 18°C	Practically insoluble	Practically insoluble

1. Occurrence/Uses

Cadmium occurs in nature mainly associated with zinc, but also with lead and copper (generally as Cd sulphide). It is recovered as a byproduct during the refining of these metals. World production of cadmium in 1989 was 21.400 tons but, because of increasing regulations on the presence of Cd in industrial and consumers' products, its uses began to decline in the mid of 1990s to reach 18.700 tons in 2004 (Buckingham *et al.*, 2006). The current industrial uses of Cd are for the production of :

- active electrode materials in batteries (79 % of its uses in Western World in 2003, mainly CdO),
- pigments in ceramics, plastics and glasses (11%, $Cd_{(1-x)}$ Zn_xS and $CdS_{(1-x)}Se_x$),
- stabilizers in PVC and related polymers (2%, mainly organic salts),
- constituents of coating for steel and non-ferrous metals (7%, Cd metal), and
- alloys and other uses (1%, Cd metal) (International Cadmium Association 2005).

Recycling of scrap metal and Ni-Cd batteries may also involve some exposure.

2. Health significance

Human exposure

In humans, uptake of Cd occurs via inhalation of Cd-containing dusts and fumes in industrial settings (occupational exposure) and/or via the gastrointestinal route for the general population exposed through contaminated food (environmental exposure). The daily dietary Cd intake for an adult is estimated at 0.10-0.50 µg/kg body weight in European countries (European Commission, 1996). An additional source of cadmium exposure is tobacco smoke. Each cigarette contains on average 2 µg of Cd, the amount varying considerably with the origin of tobacco leaves.
In industrial settings, airborne exposure levels typically range from 5 to 50 µg/m³, with extreme values up to 400 µg/m³ (European Chemical Bureau, 2003).

Metabolism - Toxicokinetics

Cadmium is absorbed by the respiratory route at rates varying between 2 and 50% depending on the Cd compound involved (water soluble or insoluble), the size of the particles (dusts or fumes), the deposition pattern in the respiratory tract and the ventilation rate. The gastrointestinal absorption of Cd is usually less than 5% but varies with the composition of the diet (e.g. absence of Zn in rice increases Cd GI absorption; (Chaney *et al.*, 2004)), and the individual iron and/or calcium status. High GI absorption rates (up to 20%) have been observed in women with lowered iron stores (serum ferritin <20 µg/l) (Flanagan *et al.*, 1978; Berglund *et al.*, 1994).
Cadmium is a cumulative toxicant. It is transported from its absorption site (lungs or gut) to the liver, where it induces the synthesis of metallothionein which sequestrates Cd. The cadmium-metallothionein complex is then slowly released from the liver and transported in the blood to the kidneys, filtrated through the glomerulus, and reabsorbed in the proximal tubule where it may dissociate intracellularly (Chan *et al.*, 1993). There, free Cd again induces the synthesis of metallothionein, which protects against cellular toxicity until saturation.
In non-occupationally exposed individuals, the Cd concentration in the kidneys is generally between 10 and 50 mg/kg wet weight, with smokers showing 2-5 fold higher values than non-smokers (Nilsson *et al.*, 1995).
After long-term low level exposure, about half the Cd body burden is stored in the liver and kidneys, one third being in the kidney where the major part is located in the cortex (Kjellström, 1979). The ratio between Cd tissue concentrations in the kidney and the liver

decreases with the intensity of exposure and is, for instance, lower in occupationally exposed workers (7-8 fold ratio (Ellis *et al.*, 1981;Roels *et al.*, 1981)) than in the general population (10-30 fold ratio (Elinder, 1985)). The distribution of Cd in the kidney is of particular importance as this organ is one of the critical targets after long-term exposure.
Most of the absorbed Cd is excreted very slowly, with urinary and fecal excretion being approximately equal in quantity (<0.02% of the total body burden per day) (Kjellström *et al.*, 1985). The biologic half-life of cadmium has been estimated to be between 10-30 years in kidney and between 5-10 years in liver (Ellis *et al.*, 1985). The half-life in both organs, particularly the kidneys, is markedly reduced with the onset of renal toxicity when tubule loss of cadmium is accelerated.
The placenta provides a relative barrier protecting the foetus against cadmium exposure. Cd can cross the placenta but at a low rate (Lauwerys *et al.* 1978; Lagerkvist *et al.* 1992).
In blood, most Cd is localised in erythrocytes (90%) and values measured in adult subjects with no occupational exposure are generally lower than 1 µg/l in non-smokers. Blood Cd (Cd-B) values are 2-5 fold higher in smokers than in non-smokers (Staessen *et al.*, 1990; Järup *et al.*, 1998b). In the absence of occupational exposure, the mean urinary Cd concentration (Cd-U) is generally below 1 µg/g creatinine in adults. In one of the most robust and extensive European database (GerES-III, 1998), the 98th percentile for Cd-U was 1.08 µg/g creatinine for the population aged 18-69-year, including smokers. While Cd-B is influenced by both recent exposure and Cd body burden, Cd-U is mainly related to the body burden (Lauwerys *et al.*, 2001). Smokers excrete more Cd than non-smokers and their Cd-U is on average 1.5-fold higher than in non-smokers.

Biomonitoring of exposure

Biomonitoring methods, using either Cd-B or Cd-U, offer advantages compared to airborne measurements because they integrate all possible sources of occupational and environmental exposures (digestive exposure at the workplace, tobacco smoking, dietary exposure). In addition, since Cd is a cumulative toxicant, a measure of the body burden (i.e. Cd-U) is the most appropriate exposure parameter for conducting risk assessments. The biological half-life of Cd-U being very long (10-20 years), the sampling time is indifferent.
While the measurement of urinary Cd (Cd-U) reflects the body burden of the element and predicts the health risk, the measurement of blood Cd (Cd-B) may provide complementary information to detect recent exposures and evaluate the impact of preventive measures to control exposure.

In workers with substantial Cd exposure (i.e. Cd-U>3 µg/g creatinine), the relationship between Cd-U and integrated airborne exposure can be described by the following equation :

$$\ln(\text{Cd-U}, \mu g/g\ creat) = 0.38 * \ln(\text{integrated air Cd}, \mu g/m^3 * years) - 1.7$$

meaning that a 30 years exposure to 50 µg/m³ of Cd would lead to a Cd-µU of 3 µg/g creatinine. It should, however, be emphasised that the value of this equation at lower exposure levels (Cd-U<3 µg/g creatinine) is uncertain (Criteria Group for Occupational Standards, 2003).

Acute Effects on the Lungs

Cadmium fumes (mainly consisting of CdO) when inhaled at a sufficient concentration are toxic to the epithelial and endothelial cells of the alveoli and cause acute pulmonary edema. Compared to elements with which it is found, such as zinc, and with which it is alloyed, such as copper, the boiling point of cadmium (765°C) is low. Cadmium oxide fumes are therefore generated in potentially toxic concentrations in

- the smelting, melting, and refining of metals that contain cadmium,

- in cadmium alloy production and welding,
- during oxyacetylene cutting of cadmium-coated steel and rivets.

In these occupational settings, the presence of CdO fumes is often unsuspected. Moreover, the acute effects induced by cadmium fumes on the lungs do not appear before a delay of 4-10 hours, and the toxicity usually remains unrecognized by those exposed, who therefore can accumulate increasing doses. Early symptoms are predominantly respiratory and similar to those of metal fume fever (shortness of breath, chest tightness, and cough that can be associated with flu-like symptoms of chills, fever, and muscle pains). When exposure is sufficiently intense, evidence of pneumonitis and pulmonary edema develops within 1 or 2 days, which is fatal in the most severely affected victims. The diagnosis of acute Cd poisoning can be confirmed by the measurement of Cd-U (Ando *et al.*, 1995). The dose sufficient to cause pulmonary edema is not exactly known. In one fatal case, the average airborne concentration was estimated to be 8.6 mg/m³ during 5 hours, or approximately an 8-hour time-weighted average (TWA) of 5 mg/m³ (Barrett *et al.*, 1947). This estimate was based on lung Cd content at postmortem examination, which may have been greater than the dose necessary to cause death, and the atmospheric concentration necessary to cause pneumonitis may therefore be considerably less. It has been estimated that an 8- hour exposure to 1 mg/m³ is immediately dangerous for life (Friberg *et al.*, 1986).

Chronic effects

Chronic toxicity of Cd, both at work and in the general environment, includes effects on the kidneys (in particular tubular function), and on bone. In occupational settings, inhalation exposure may also affect the respiratory system.

Respiratory system

Early reports indicated that anosmia was a common finding in workers often exposed to high airborne Cd levels (Friberg, 1950; Adams *et al.*, 1961). A recent study in workers exposed to lower levels (mean Cd-B, 3.7 µg/L and Cd-U, 4.4 µg/g creatinine) has confirmed that olfactory neurons are sensitive to Cd, as demonstrated by an elevation of the olfactory threshold in these workers (Mascagni *et al.*, 2003). Similar olfactory alterations have been reported among Polish workers from a nickel-cadmium production plant, although with much higher exposure (mean Cd-B, 35 µg/l and Cd-U, 86 µg/g creatinine) (Rydzewski *et al.*, 1998).

Long-term inhalation exposure to cadmium and cadmium compounds may also affect lung function and is associated with the development of emphysema. Surveys of workforces exposed to cadmium published in the 1950s already indicated that protracted occupational exposure to cadmium could cause emphysema (Friberg, 1950; Lane *et al.*, 1954). Mortality studies in cadmium workers in the United Kingdom found that those who had experienced high exposure had an increased mortality rate from "bronchitis" (Armstrong *et al.*, 1983). In copper-cadmium alloy producers, a marked excess of deaths from chronic non-malignant respiratory diseases has also been found related to cadmium exposure (Sorahan *et al.*, 1995). The respiratory impact of occupational Cd exposure has also been reported in more recent studies able to collect detailed lung function measurements, good exposure assessment and to control for confounding such as other industrial exposures and tobacco smoking. In a copper-cadmium alloy factory, it was found that the cadmium-exposed workforce had evidence of airflow limitation (reduced FEV_1 and Tiffeneau ratio), hyperinflated lungs (increased RV and TLC), and reduced gas transfer (reduced DL_{CO} and KCO), an overall pattern of functional abnormalities consistent with emphysema. Regression analysis identified a significant relationship between the reduction in FEV_1, FEV_1/FVC ratio, DL_{CO}, and KCO, and both estimated cumulative cadmium exposure (years* µg/m³), and liver Cd content measured by neutron activation

analysis (Davison *et al.*, 1988). A moderate increase in residual volume (+7% compared to controls matched for smoking habits) has also been reported in workers exposed to cadmium fumes in a factory producing silver-cadmium-copper alloys for brazing, already at cumulative exposure levels below **500 years*µg Cd/m³** (mean **Cd-U, 3 µg Cd/l**) (Cortona *et al.*, 1992). Other studies, however, have shown no cadmium-related impairment of respiratory function (Stanescu *et al.*, 1977; Edling *et al.*, 1986) presumably because of differences in the intensity of exposure, the species of Cd involved, variable diagnostic criteria or incomplete control for confounding factors, including tobacco smoking.

Kidneys

Numerous studies in rats, mice, rhesus monkeys and rabbits have indicated that exposure to cadmium compounds administered orally or by inhalation causes kidney damage including modifications of relative kidney weight, histological (necrosis of the proximal tubules, interstitial fibrosis) and functional changes (reduced glomerular filtration rate, proteinuria) (European Chemical Bureau, 2003).

The first manifestation of cadmium nephrotoxicity in occupationally exposed subjects is usually a tubular dysfunction resulting in a reabsorption defect and, hence, an increased urinary excretion of low molecular weight (LMW) proteins such as the human complex protein (HC) also called α1-microglobulin, ß2-microglobulin (ß2M) and/or retinol-binding protein (RBP), but also calcium and amino-acids (Lauwerys et al., 1979; Elinder et al., 1985b; Jakubowski et al., 1987; Mason et al., 1988; Chia et al., 1989; Roels et al., 1993; Järup et al., 1994). Other biomarkers of tubular toxicity such as urinary alanine aminopeptidase (AAP), gamma-glutamyltranspeptidase (γGT), and the lysosomal enzyme N-acetyl-beta-D-glucosaminidase (NAG) have been used to demonstrate the tubular effects associated with occupational exposure to Cd (Mueller et al., 1989; Bernard et al., 1995). A Cd body burden corresponding to a urinary excretion (Cd-U) of **5-10 µg Cd/g creatinine** constitutes a threshold at or above which these tubular effects have been observed (LOEL).

The most recent and relevant studies having examined the dose-response relationship between Cd-U and renal effects in workers are summarised in Table 1. Some of these cross-sectional studies may have underestimated the true LOEL because of the inclusion of aged workers with previously much higher exposure having probably lost a significant portion of their Cd kidney burden when the study was conducted, resulting in a left shift of the dose-response relationship (Bernard et al., 1997).

Table 1. : Thresholds for renal effects in recent studies in occupational settings.

	Type of industry	n	Glomerular effect	Tubular effect	Threshold
Lauwerys et al. 1979	Electronic workshop Ni-Cd storage battery factory Cd-producing plants	-	HMW proteins ß2M-S creatinine-S	ß2M-U	Cd-U : 10 µg/g creatinine (G and T)
Jakubowski et al 1987	alkaline battery factory	102		ß2M, RBP	Cd-U : 10-15 µg/g creat
Shaikh et al. 1987	Cd smelter	53		ß2M	Cd-U : 13.3 µg/g creat
Verschoor et al. 1987	secondary Cd users	26		ß2M, RBP, NAG	Cd-U : 5.6 µg/L
Kawada et al. 1989	Cd pigment factory	29		ß2M, NAG	Cd-U : < 10 µg/g creat (NAG)
Bernard et al. 1990	non-ferrous smelter	58	albumin, transferrin, serum ß2M	ß2M, RBP, protein-1, NAG	Cd-U : 10 µg/g creat
Roels et al. 1991	Zn-Cd smelter	108	GFR decline		Cd-U : 10 µg/g creat
Toffoletto et al, 1992	Cd alloy factory	105		ß2M	Cd-U : 10 µg/g creat
Roels et al. 1993	Zn-Cd smelter	37	albumin, transferrin	ß2M, RBP and other markers	Cd-U : 4 µg/g creat (G) Cd-U : 10 µg/g creat (T)
van Sittert et al. 1993	Zn-Cd refinery	14		ß2M	Cd-U : 7 µg/g creat
Järup and Elinder 1994	battery factory	561		ß2M	Cd-U : 1.5 µg/g creat (>60 y) Cd-U : 5 µg/g creat (<60 y)

G :glomerular effects, T : tubular effects

Tubular changes observed above this value are generally irreversible (Roels et al., 1997; Trzcinka-Ochocka et al., 2002) and the association with further renal alteration, including a reduction of the glomerular filtration rate (GFR) (Roels et al., 1989; Roels et al., 1991; Järup et al., 1993b) support the health significance of this threshold (LOAEL).

An effect on the glomerulus may also be observed in cadmium-exposed workers, as indicated by increased urinary excretion of high molecular weight (HMW) proteins including albumin, immunoglobulins G or transferrin (Bernard *et al.*, 1990; Roels *et al*, 1993).

On the basis of the most recent studies conducted in Europe (Buchet *et al.*, 1990; Hotz *et al.*, 1999; Järup *et al.*, 2000), United States (Noonan *et al.*, 2002) and Asia (Jin *et al.*, 2002), it appears that renal effects can be detected in the general population for Cd-U below 5 µg Cd/g creatinine and even from **2 µg Cd/g creatinine or below**. These studies detected associations between Cd-U and markers of tubular effect (including urinary calcium excretion and its possible relationship with bone effects (see below)). The largest studies were conducted in Belgium (Cadmibel study) in a population exclusively exposed via the environment (n=1700; geometric mean Cd-U, 0.84 µg/24 h) (Buchet *et al.*, 1990) and in Sweden (OSCAR study) in subjects with environmental and/or occupational exposure (n=1021; Cd-U, 0.18-1.8 µg/g creatinine) (Järup *et al.*, 2000). Both studies had a cross-sectional design and it may therefore not be excluded that some of the tubular effects observed in these cohorts are the results of previous much higher exposures (particularly in occupationally exposed subjects included in the OSCAR study), which may have contributed to shift the dose-effect/response relationship to the left. In the Cadmibel study, it was found that, after adjustment for age, gender, smoking, use of medications and urinary tract disease, tubular effects (mainly increased urinary calcium excretion) occurred in the general population at Cd-U levels ≥ 2 µg/24 h (roughly equivalent to 2 µg/g creatinine). The association between renal parameters and Cd exposure has been further confirmed in a follow-up study in the most exposed subgroup of the Cadmibel study (Pheecad study) (Hotz *et al.*, 1999). In the OSCAR study, excretion of protein HC was found associated with Cd-U (0.18-1.8 µg/g creatinine) and the prevalence of elevated values (>95th percentile in a Swedish reference population) increased with Cd-U. The exact health significance of tubular changes observed at Cd-U levels < 5µg/ g creatinine is, however, uncertain and subject to contrasting scientific opinions. Some authors believe that these changes represent the earliest dysfunction of the renal tubular cells and should be considered as an adverse effect because the aim of public health is to detect and prevent effects at their earliest stage in the most sensitive groups of the population (Järup *et al.*, 1998b). Others believe that these changes most likely reflect benign, non-adverse responses (Hotz *et al.*, 1999; Bernard, 2004). The main arguments to support the latter interpretation are that

- variations of tubular parameters observed at these Cd-U levels remain within a normal range,
- statistical associations with Cd-U remain weak (r^2 <10 %), and
- similar associations are observed with other non-nephrotoxic metals in urine (e.g. Cu) (Ikeda *et al.*, 2007),
- variations of this amplitude are reversible when exposure decreases timely, and
- such changes are not predictive of an alteration of the renal function.

While mortality studies were not able to detect an excess of end-stage renal diseases in populations environmentally exposed to cadmium compounds, an ecological study conducted in Sweden indicated that cadmium exposure was a determinant of the incidence of renal replacement therapy in a population with occupational/environmental exposure to Cd (Hellström *et al.*, 2001).
Several studies have also suggested that **diabetics** may represent a population with an increased susceptibility to the renal effects of Cd (Buchet *et al.*, 1990; Hellström *et al.*, 2001; Hotz *et al.*, 1999; Akesson *et al.*, 2005), but this hypothesis needs confirmation.
An additional effect on the kidney seen in workers with high Cd exposures is an increased frequency of kidney stone formation (Friberg, 1950; Scott *et al.*, 1978; Kazantzis, 1979; Falck *et al.*, 1983; Elinder *et al.*, 1985a; Thun *et al.*, 1989; Järup *et al.*, 1993a).

Bone

The bone tissue is another target organ for populations exposed occupationally and/or environmentally to cadmium compounds. *In vitro* studies have demonstrated that cadmium compounds exert a direct effect on bone metabolism, affecting both bone

resorption and formation, and inducing calcium release (Miyahara *et al.*, 1988; Wilson *et al.*, 1996; Litchfield *et al.*, 1998; Romare *et al.*, 1999). In animals, cadmium has been shown to affect bone metabolism, manifested as osteomalacia and/or osteoporosis (Brzoska *et al.*, 2004; Brzoska *et al.*, 2005a; Brzoska *et al.*, 2005b; Brzoska *et al.*, 2005c). In most experimental studies, bone effects were accompanied or preceded by renal damage induced by Cd-treatment; these studies do therefore not allow to know whether Cd bone toxicity occurs in parallel to or as a consequence of nephrotoxicity. Young age (growing bones), gestation, lactation, and ovariectomy (used as an animal model of menopause) appeared to exacerbate Cd-induced bone toxicity.

In humans, the mechanism of bone toxicity is not fully elucidated and types of bone lesions associated with Cd exposure are not clearly identified. One likely mechanism is direct disturbance of bone metabolism but another explanation is that Cd-induced kidney damage and/or hypercalciuria might promote osteoporosis and osteoporotic fractures. The most severe form of bone disease caused by cadmium intoxication is Itai-Itai disease which was associated with kidney and bone lesions in aged Japanese women in the past (for a review see Friberg et al.*, 1986, 1986; Tsuchiya, 1992).*

A follow-up of the population examined in the Cadmibel study (mean Cd-U, approx. 0.5 and 0.8 µg/g creatinine in men and women, respectively) has shown that Cd-U was associated with an increased risk of fracture in women and, possibly, an increased risk of height loss in men. The decline of bone mineral density in postmenopausal women was significantly aggravated by Cd exposure (Staessen et al., 1999). In the Oscar study, bone mineral density (g/cm² and Z-score values) has been measured in the forearm of more than 1000 individuals with occupational (Cd-U, 0.06-4.7 µg/g creatinine) and/or environmental (Cd-U, 0.06-3.7 µg/g creatinine) exposure to Cd. An association between Cd-U and decreased bone mineral density was found in older men, and an increased risk of osteoporosis was noted in men >60 years with a similar tendency in women >60 years. The threshold for these effects was about ***3 µg/g creatinine*** *(Alfven et al., 2000). It has also been shown in the Oscar cohort that Cd exposure was associated with an increased risk of forearm fractures in people over 50 years of age (Alfven et al., 2004). The association between Cd exposure, tubular effects and osteoporosis has been confirmed in a large cross-sectional study in a Chinese population with environmental exposure to Cd (mean Cd-U in the group with the highest exposure, 11 µg/g creatinine) (Jin et al., 2004). In a population-based health survey conducted in southern Sweden among women with no known historical cadmium contamination (Women's Health in the Lund Area (WHILA)), negative effects of low-level cadmium exposure (median 0.67 µg/g creatinine) on bone, possibly exerted via increased bone resorption, seemed to be intensified after menopause (Akesson et al. 2006).*

In workers exposed to cadmium compounds, clinical bone disease has been described but the number of cases is limited. One cross-sectional study reported results compatible with a role of cadmium in the genesis of osteoporosis in exposed workers who were also included in the OSCAR study mentioned above (Jarüp et al. 1998). The dose-effect/response relationship between Cd body burden and bone effects has not been defined.

A possible effect of long-term Cd exposure to promote the occurrence of polyneuropathy in exposed workers has been suggested (Viaene et al. 1999).

While some studies reported an association between environmentalexposure to Cd and increased risks of cardio-vascular diseases (Everett and Frithsen 2008; Schutte et al. 2008; Tellez-Plaza et al. 2008), other studies did not detect such an increased risk (Staessen et al. 1991). Studies on the cardiovascular effects of occupational exposure were not located.

Genotoxicity and Carcinogenicity

Experimental studies indicate that cadmium, in certain forms, has genotoxic properties (Filipic et al. 2006). In experimental systems (in vitro and in vivo) increased DNA damage, chromosomal aberrations, micronuclei, as well as gene mutations have been recorded. In bacterial systems Cd, like several other metals, does not induce genotoxicity. Cd does not induce DNA damage in cell extracts or on isolated DNA, indicating that its genotoxic activity is mediated by indirect mechanisms. With regard to human exposure to Cd and compounds, data are conflicting but seem to indicate a genotoxic potential, at least in occupational settings, but it is unclear whether these effects are solely attributable to Cd. The most contributive human study was conducted by Forni et al. 1992 in a group of 40 cadmium workers with a wide range of cumulative exposure and 40 controls. An increase in chromosome-type aberrartions was recorded only in the subgroup of workers with the highest cumulative exposure to Cd (>1000 µg/m³xyears, Table 2 or Cd-U>10 µg/L, Table 3).

Table2 : Rates of abnormal metaphases (excluding gaps) and of cells with chromosome-type aberrations in cadmium workers, subdivided by Cd cumulative exposure index, and in the matched controls (Forni et al.,1992)

cumulative exposure index	**% abnormal metaphases**		**% chromosome-type aberrations**	
(µg/m³.y)	**Cd workers**	**Controls**	**Cd workers**	**Controls**
< 100	1.80	1.60	0.8	0.7
101 – 500	2.61	1.54	0.76	0.15
501 – 1000	2.44	2.33	1.00	0.55
> 1000	3.75	1.37	2.37*	0.50

*different from the other subgroups (p<0.01; Wilcoxon matched pair test)

Table 3 : Chromosome-type aberrations in relation to Cd-U (mean values of the last 4 years) (Forni et al., 1992)

Cd workers		**Controls**		
Cd-U (µg/l)	% Chrom. Aberr.	Cd-U (µg/l)	% Chrom.Aberr.	
< 10 (N=18)	0.67	nr	0.50	N.S
> 10 (N=20)	1.55	nr	0.41	P < 0.005

N.S: not statistically significant
nr : not reported

Studies performed in environmentally exposed populations do not allow to identify the type of cadmium compound(s) to which subjects were exposed but it cannot be excluded, based on the available data, that cadmium might exert genotoxic effects in populations exposed via the oral route (Verougstraete et al. 2002).

The concern that Cd might cause cancer in humans was raised in the 1960s, before any experimental evidence of carcinogenicity in laboratory animals was available. The first suspicion started with four men who had worked in a factory of cadmium-nickel battery in UK who were reported to have died from prostate cancer although, compared to national rates, less than one case would have been expected (Potts, 1965). Subsequently, three additional studies conducted in small cohorts of workers employed in the production of batteries (Kipling *et al.*, 1967), alloys (Kjellström *et al.*, 1979), and Cd metal (Lemen *et al.*, 1976) reported an association between Cd exposure and an increased mortality from

prostate cancer. However, later studies (Sorahan *et al.*, 1983; Thun *et al.*, 1985; Kazantzis *et al.*, 1988) failed to confirm this hypothesis.

Subsequently, experimental studies have indicated that several cadmium compounds ($CdCl_2$, $CdSO_4$, CdS and CdO) caused lung cancer (mainly adenocarcinomas) in long-term inhalation experiments in the rat (Takenaka *et al.*, 1983; Glaser *et al.*, 1990), but not in other species (Heinrich *et al.*, 1989; Kazantzis *et al.*, 1992). The lowest concentration inducing primary lung carcinoma in rats (15 versus 0 % in controls) was 12.5 µg Cd/m³ (23 h/day, 7 days per week for 18 months exposure to $CdCl_2$ aerosols with a mean mass aerodynamic diameter of 0.55 µm) (Takenaka *et al.* 1983). In a subsequent experiment, no lung tumors were induced when the rats were exposed continuously for 18 months to CdO fumes at a concentration of 10 µg Cd/m³, whereas 21 % of the animals developed tumors when exposed to 30 µg Cd/m³ (Glaser *et al.* 1990). While these studies indicate that lung tumors can be induced at very low Cd concentrations in the rat, it should be considered that tumours were induced under an unusual exposure regimen (23 h/day, 7 days per week).

In humans, a statistically significant increase in mortality from lung cancer has initially been reported in studies involving Cd recovery (Lemen *et al.*, 1976; Thun *et al.*, 1985), nickel-cadmium battery (Sorahan, 1987) and Cd processing workers (Ades *et al.*, 1988; Kazantzis *et al.*, 1992). Based on these studies, IARC (1993) concluded that there was sufficient evidence to classify cadmium and its compounds as human carcinogens (category 1). However, the epidemiological data that have been used to support this classification have been criticised because of the lack of control for confounding exposures (mainly arsenic) and smoking habits. Studies conducted after this IARC evaluation have tried to address these difficulties. In particular, the dose-response relationship between Cd exposure and lung cancer mortality rates, previously reported by Thun et al. (1985) and Stayner et al. 1992, has not been confirmed with a refined exposure assessment methodology. A significant positive trend between cumulative exposure to Cd and mortality from lung cancer was found after adjustment for age, year of hiring and ethnicity but only in the presence of concomitant exposure to arsenic (Sorahan *et al.*, 1997). In two recent cohorts of workers from a nickel-cadmium battery plant (where arsenic is not a confounder), a globally increased mortality from lung cancer was observed but the dose-response relationships were not consistent with a causal role of Cd (Järup *et al.*, 1998a; Sorahan *et al.*, 2004). In the latter cohort, 926 male workers from a Ni-Cd battery factory were followed up for a very long period of time (1947-2000). Significantly increased mortality was observed for pharynx cancer, diseases of respiratory system and diseases of genitourinary system. For lung cancer, the mortality was modestly increased (SMR=111, 95%CI=81-148) and without any definite pattern or trend by time variables and cumulative exposure to Cd. Interestingly, indications exist in this cohort of increased risks from other known adverse effects associated with exposure to Cd compounds, specifically, a significantly increased mortality (although without dose-response trend) from non-malignant respiratory diseases (SMR=142, 9%CI=109-182), and an increase of diseases of the genitourinary system (SMR=243, 9%CI=1116-446) possibly reflecting late effects of kidney toxicity. These studies indicate that, in the absence of As co-exposure, Cd does not seem to induce an excess of lung cancers at exposure levels, however, sufficient to cause renal and respiratory toxicity.
In a cohort of copper-cadmium alloy workers for whom individual cumulative exposure indexes were estimated, a non significant negative trend between cumulative cadmium exposure and risks of lung cancer was reported. The dose-response trend was, however, significant for non-malignant diseases of the respiratory system (Sorahan et al. 1995).
These recent studies do, therefore, not support the hypothesis that Cd compounds act as lung carcinogens in humans (Verougstraete *et al.*, 2003). In a recent review, which integrates the latest epidemiological studies, IARC has, however, reaffirmed its previous

assessment and confirmed the group 1 classifiation of cadmium and its compounds as "human carcinogens for the lung" (Straif *et al.*, 2009).

Some epidemiological studies suggest an association between occupational exposure to Cd and the occurrence of renal cancer (reviewed by Il'yasova and Schwartz, 2005).

Studies conducted in environmentally-exposed populations (i.e. via the diet) do not provide strong arguments for an increased risk of cancer (Verougstraete et al., 2003). A recent prospective study conducted in a region of Belgium with historical industrial pollution by heavy metals found an excess of lung cancer cases. The risk of lung cancer was positively associated with Cd-U measured during the Cadmibel study (1985-89), suggesting a possible impact of inhalation exposure to Cd, but the role of other associated pollutants cannot be excluded (Nawrot et al., 2006). A statistically significant association between dietary Cd intake (calculated from a food frequency questionnaire) and the risk of endometrial cancer has been reported in a cohort of post-menopausal women in Sweden followed during 16.0 years (484,274 person-years) (Akesson et al. 2008).

Different and a priori non-mutually exclusive mechanisms for the carcinogenicity of Cd have been identified (Joseph, 2009), including oxidative DNA damage (Filipic and Hei 2004), induction of oxidative stress (Liu *et al.*, 2009), inhibition of DNA repair (Hartwig et al. 2002, Kopera et al. 2004) and deregulation of cell proliferation (Beyersmann *et al.*, 2008). All these mechanisms are non-stochastic and characterised by a threshold below which no effect is expected. Cd should therefore be considered as a Category C carcinogen, i. e. a genotoxic carcinogen for which a practical threshold can be identified (Bolt and Huici-Montagud, 2008).

Reprotoxicity

While effects on reproductive organs and fertility have been noted in experimental studies at high doses of Cd compounds (oral LOAEL 1 mg/kg/d, effect on seminiferous tubules in rats, and inhalation NOAEL 0.1 mg/m³, increased length of oestrus cycle), further information is needed to better document the possible effect of low doses of Cd on the developing brain suggested in experimental animals.

Epidemiological studies do not speak for an association between exposure to Cd and relevant effects on fertility or reproductive organs. Based on the human data available, there is no indication of a potential developmental effect of Cd (European Chemical Bureau, 2003).

Recommendations

In exposed workers, inhalation is the main route of exposure. Additional uptake can also occur through the consumption of contaminated food and/or tobacco smoking.

Setting a BLV

The kidneys (and possibly bone) represent the most sensitive targets of systemic Cd toxicity upon occupational exposure (critical target organs). Cd being a cumulative toxicant, the systemic manifestations associated with chronic exposure are related with the body burden of the element (liver and kidney content). Biological markers such as Cd-U allow to assess this body burden, and to integrate all sources of Cd exposure, including contaminated food and smoking. The use of such biomarkers of exposure in most epidemiological studies conducted in occupational settings has allowed to document quite reliable dose-effect/response relationhips. A biological limit value will mainly protect workers against systemic toxicity of Cd, mainly renal and bone effects.

Table 4 : Dose-effect relationships between cadmium exposure and effects on kidneys.

Dose measure		Exposure	Effect	Reference
Cd-U (µg/g creat)	Cd-B (µg/l)			
≤1		E	increased urinary N-acetylglucosaminidase and alanine aminopeptidase activity	Noonan et al. 2002
1 – 3		E	renal tubular effects (microproteinuria)	Buchet et al. 1990, Hotz et al. 1998, Jarup et al. 2000
	5.6 – 8.4	O	glomerular damage (reduced GFR)	Roels et al. 1989, Roels et al. 1991, Jarup et al. 1995
> 4	> 6.7	O	kidney stones	Jarup et al. 1993a

E : environmental; O : occupational exposure

In workers exposed to cadmium, a Cd body burden corresponding to a Cd-U of 5 µg/g creatinine is a LOAEL based on the occurrence of LMW proteinuria. There is consensus on the health significance of this threshold because of the frequent observation of irreversible tubular changes above this value and in view of its association with further renal alteration. The possible links between kidney and bone effects induced by Cd strengthen the health significance of these effects.

Based on the most recent studies, it seems that renal effects can be detected in the general European population (mainly exposed by the oral route) for Cd body burdens at or even below 2 µg Cd/g creatinine (LOAEL). There is, however, a lingering scientific debate about the health significance of these early changes. This lower LOAEL in the general population compared to that identified in workers is thought to reflect, among other parameters, an interaction of Cd exposure with pre-existing, concurrent or subsequent renal diseases (mainly renal complications of diabetes) that are less prevalent

in healthy young individuals in occupational settings. As workers exposed to Cd may, however, suffer from such diseases during or, most often, after their occupational career, and considering the long half-life of Cd in humans and its accumulation with age, it may be prudent to provide a sufficient degree of protection in this respect.
Cd and its compounds are not considered as sensitisers or reproductive toxicants.

The following considerations should be integrated to derive an acceptable exposure level for Cd and its inorganic compounds :

- there is an abundant database on the health effects of Cd and its compounds,
- the mechanisms of the systemic toxicity of Cd are relatively well understood,
- the available dose-effect/response relationships characterising the hazard of Cd have been extensively and quite reliably documented in several human studies,
- mean Cd-U in European individuals with no occupational exposure to Cd or living in an area with no specific Cd pollution is generally below 1µg/g creatinine.
- the critical systemic effect selected to define the point of departure in epidemiological studies (urinary excretion of LMW proteins reflecting tubular dysfunction) is a relatively early sign occurring before the onset of overt clinical manifestations of kidney disease,
- the point of departure identified from human studies in occupational settings (5µg Cd/g creatinine) is a LOAEL for renal effects.
- the point of departure identified from human studies in the general population (2 µg Cd/g creatinine) is a LOAEL for renal effects which is relevant for protecting workers after their occupational career
- other points of departure for systemic effects are 3µg Cd/g creatinine as a LOEAL for respiratory effects in workers and 3 µg/ g creatinine as a LOAEL for bone effects in the general population.
- Cd and its compounds are considered as Cat C carcinogens and it is seems prudent to recommend limiting the body burden of the working force to a strict minimum.

It is, therefore, proposed to recommend a **BLV of 2 µg Cd/g creatinine.**

Setting an OEL

Beside a BLV, an OEL is necessary to protect workers against long-term local effects. Chronic inhalation of Cd-containing dusts and fumes is associated with the development of local respiratory effects, including lung emphysema and cancer. Cd is considered as a lung carcinogen in experimental animals and upon occupational exposure.

- experimental studies have reported the induction of tumours in rats exposed to low concentrations of Cd (12.5 µg/m³).
- in humans, no sufficiently valid epidemiological data exist to perform a working-life risk assessment for the cancer risk when exposure is to Cd alone. When an increased risk was observed, co-exposures did appear to play a central role
- the mechanism of the carcinogenic activity of Cd is not exactly known, but involves, at least in part, genotoxic events mediated by indirect mechanisms for which a threshold can be identified (Category C, Bolt and Huici-Montagud, 2008)
- a threshold of 1000 µg/m³x years (or 25 µg/m³ during 40 years) has been reported for genotoxic effects in workers exposed to Cd by inhalation
- there is also some epidemiological evidence that Cd does not seem to induce an excess of lung cancers at exposure levels sufficient to cause renal and respiratory toxicity (Sorahan and Esmen, 2004).

Human data have shown that changes in residual volume of the lung occur for a cumulative exposure to CdO fumes of 500 µg Cd/m³*years, corresponding to 40 years exposure at a level of 12.5 µg Cd/m³ (LOAEL). Applying a default extrapolation factor of 3 (LOAEL to NOAEL,Leung, 2002) leads to a value of 4 µg Cd/m³.

An OEL of 4 µg/m³ (respirable fraction), based on non-cancer respiratory effects, is therefore recommended to protect workers against local respiratory effects of Cd exposure.

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