European Commission

SCOEL/OPIN/336 Cadmium and its inorganic compounds

Opinion from the
Scientific Committee on Occupational Exposure Limits

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Directorate-General for Employment, Social Affairs and Inclusion
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8-hour TWA:	1 µg/m^3 (inhalable fraction)
STEL:	None
BLV:	2 µg Cd/g creatinine in urine (sampling time not critical)
Additional categorisation:	SCOEL Carcinogen group C (Genotoxic carcinogen for which a mode of action-based threshold is supported and a health-based OEL is proposed)
Notations:	None

The present Opinion was adopted by SCOEL on 8th of February 2017.

This literature update was based on existing compilations by ATSDR (2012), IARC (2012), Hartwig (2013a), BAuA (2014), NTP (2016) and on a literature search by SCOEL in January 2017. The core database relevant for grouping of Cd as a carcinogen and for OEL setting (8h-TWA and BLV) has not significantly changed since the time of the SCOEL Recommendation in 2010.

OPINION EXECUTIVE SUMMARY

Outcome Considerations

Evaluation and Recommendations

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

IARC considers Cd and Cd compounds to be carcinogenic to humans (IARC Group 1), based on *sufficient* evidence in humans for the carcinogenicity of cadmium and cadmium compounds. Cadmium and cadmium compounds cause cancer of the lung. Also, positive associations have been observed between exposure to cadmium and cadmium compounds and cancer of the kidney and of the prostate, whilst there is also *sufficient* evidence in experimental animals for the carcinogenicity of cadmium compounds (IARC 2012).

As explained in chapter 8.9, different and a priori non-mutually exclusive mechanisms for the carcinogenicity of Cd have been identified, including oxidative DNA damage, induction of oxidative stress (generation of reactive oxygen species), inhibition of DNA repair and deregulation of cell proliferation. All these mechanisms are non-stochastic and are characterised by a threshold below which no effect is expected. Cd is therefore considered by SCOEL as a **Category C carcinogen**, *i.e.* a genotoxic carcinogen for which a mode of action-based threshold can be identified, also called 'practical threshold' (Bolt and Huici-Montagud, 2008). In consequence, a set of OELs (8h-TWA and BLV) will be protective that avoids toxicity in workers at the relevant targets for carcinogenity, *i.e.* locally at the airways and systemically at the kidneys.

Derived Occupational Exposure Limit (OEL) Values

Biological Monitoring

The kidneys (and possibly bone) are the most sensitive target of systemic Cd toxicity following occupational exposure (critical target organs). Cd is a cumulative toxicant; the systemic manifestations associated with chronic exposure are related to the body burden of the element (liver and kidney content). Biological markers such as Cd-U (cadmium excretion in urine) allow the assessment of 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 researchers to document reliable dose-effect/response relationhips. A biological limit value will thus protect workers against systemic toxicity of Cd, mainly renal and bone effects.

In workers exposed to cadmium, a Cd body burden corresponding to a Cd-U (cadmium concentration in urine) of 5 µg/g creatinine is a LOAEL based on the occurrence of LMW (low molecular weight) proteinuria (see 8.1.5). There is general 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. Links between kidney and bone effects induced by Cd strengthen the health significance of these effects.

Based on recent studies, it appears 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 continuing 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 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.

The following considerations are integrated to derive an acceptable biological limit (BLV) 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 health hazard of Cd have been extensively and quite reliably documented in a number of 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 Cd/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 (5 µg Cd/g creatinine) is a LOAEL for renal effects (chapters 8.1.5, *Table 2*; 8.3.1, *Table 3*).
- 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 3 µg Cd/g creatinine as a LOAEL 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 SCOEL group C carcinogens, and it is seems prudent to recommend limiting the body burden of the workforce to a minimum.

Therefore, a **BLV of 2 µg Cd/g creatinine** is proposed. As explained in 8.1.5, the sampling time is not critical.

Setting an 8h-TWA

Besides a biological limit (BLV, see above), setting an 8h-TWA limit is necessary to protect workers against long-term local effects of airborne Cd (and its inorganic compounds) at the respiratory system. 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).
- Insufficient epidemiological evidence exists in humans to perform a working-life risk assessment for the cancer risk for exposure to Cd alone. When an increased risk was observed in Cd exposed populations, 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, non-genotoxic events such as interactions with DNA repair processes and genotoxic events mediated by indirect mechanisms (e.g. oxidative stress), for which a threshold can be identified (Category C, Bolt and Huici-Montagud, 2008).

- A threshold of 1000 µg/m³ x years (or 25 µg/m³ over 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 x years, corresponding to 40 years exposure at a level of 12.5 µg Cd/m³ (LOAEL). Applying an extrapolation factor of 3 (LOAEL to NOAEL; Leung, 2002) leads to a value of 4 µg Cd/m³.

An 8h-TWA (8h time-weighted average) of 4 µg/m³ (respirable fraction), based on non-cancer respiratory effects, can therefore be considered as being protective for workers against local respiratory effects of Cd exposure. Such a 8h-TWA value of 4 µg Cd/m^3 (as derived by SCOEL in 2010) must be seen in close conjunction with the derived BLV, as both refer to and are protective for different toxicity endpoints of relevance (local and systemic). Thus, implementation of both elements of the OEL- TWA and BLV- are of critical importance.

However, an isolated OEL (8-h TWA) of 4 µg/m^3 (not linked with a BLV) would not appear being equally protective against the systemic nephrotoxixity of Cd. Evaluations by both WHO (2000) and the German AGS (*Ausschuß für Gefahrstoffe*; BAuA 2014) of published data (primarily by Thun et al 1991) have pointed, for nephrotoxicity, to a cumulative (life-time) lowest-effect exposure of 100-400 µg/m^3 x years. For working-life exposure of 40 years, this equals an LOAEC range of 2.5 – 10 µg/m^3. AGS (BAuA 2014) has deduced that nephrotoxic effects could arise in about 1% of the workforce after 40 years of airborne exposure to 4 µg Cd/m^3. Accordingly, an OEL (8h-TWA, not connected with biological monitoring) for Cd and its inorganic compounds should be 1 µg/m^3.

In this case, an **OEL (8h TWA) of 1 µg Cd/m^3 (inhalable fraction)** can be proposed.

Measurement systems

Analytical measurement systems exist to determine the recommended levels in the respective matrix with an appropriate level of precision and accuracy.

There is no database to support a STEL (short-term exposure limit).

Notations

There is no need to apply a skin notation.
Cd and its compounds are not considered as sensitisers or reproductive toxicants.

OPINION FROM THE SCIENTIFIC COMMITTEE ON OCCUPATIONAL EXPOSURE LIMITS FOR CADMIUM AND ITS INORGANIC COMPOUNDS

OPINION REPORT

1. CHEMICAL AGENT IDENTIFICATION AND PHYSICO-CHEMICAL PROPERTIES

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. There is a great variety of inorganic cadmium compounds. For the identification of physical and chemical properties, reference can be made to ATSDR (2012 - Table 4-2). Characteristics of the most common inorganic Cd compounds are given in **Table 1a**.

Table 1a: Identification and physico-chemical properties of relevant Cd compounds

	Cd metal	**CdO**	**$CdCl_2$**	**CdSO4**	**CdS**
EC No	231-152-8	215-146-2	233-296-7	233-331-6	215-147-8
CAS No	7440-43-9	1306-19-0	10108-64-2	10124-36-4	1306-23-6
MW	112.41	128.41	183.32	208.47	144.48
Physical form	White silvery solid	Brown powder	White crystals	Colorless crystals	Yellow-orange-brown crystals
Water solubility	Insoluble	Practically insoluble	1400 g/L@ 20°C	755 g/L@ 0°C	1.3 mg/L@ 18°C

	Yellow Pigments Cd(1-x)ZnxS	Red Pigments CdS(1-x)Sex
EC No	232-466-8	261-218-1
CAS No	8048-07-5	58339-34-7
MW	variable depending on Zn/Se content	
Physical form	Bright yellow powder	Brightly coloured powder (from yellow-orange, through red to deep maroon
Water solubility	Practically insoluble	Practically insoluble

2. EU HARMONISED CLASSIFICATION AND LABELLING

Information about the EU harmonised classification and labelling for cadmium and some of its inorganic comounds is included in *Table 1b below*. Cd and most of the Cd containing substances are classified as Carc. 2 or even Carc. 1B (GHS), leading to H351 and H351, respectively.

Table 1b: Harmonised Classification according to CLP Regulation (EC) No 1272/2008 of a number of selected compounds (ECHA, 2017).

	Cd	**CdO**	**$CdCl_2$**	**$CdSO_4$**	**CdS**
EC No	231-152-8	215-146-2	233-296-7	233-331-6	215-147-8
CAS No	7440-43-9	1306-19-0	10108-64-2	10124-36-4	1306-23-6
Harmonised classification	Acute Tox. 2; H330 Muta. 2; H341 Carc. 1B; H350 STOT RE 1; H372 Repr. 2; H361fd *		Acute Tox. 3; H301 # Acute Tox. 2; H330 ## Muta. 1B; H340 Carc. 1B; H350 STOT RE 1; H372 Repr. 1B; H360FD **		Acute Tox. 4; H302 & Muta. 2; H341 Carc. 1B; H350 STOT RE 1; H372 Repr. 2; H361fd *

Cadmium zinc sulfide yellow **C.I. 77205 $**	**Cadmium sulfoselenide red** **C.I. 77202 $**
232-466-8	261-218-1
8048-07-5	58339-34-7
Harmonised classification: Not classified under CLP Regulation.	

* Suspected of damaging fertility. Suspected of damaging the unborn child; ** May damage fertility. May damage the unborn child; # Toxic if swallowed; ## Toxic if inhaled; & Harmful if swallowed; $ Colour Index Constitution Number.

ECHA (2017) European Chemicals Agency. C&L Inventory. https://echa.europa.eu/information-on-chemicals/cl-inventory-database . Accessed 2017-01-24.

3. Chemical Agent and Scope of Legislation

Cadmium and its inorganic compounds are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and fall within the scope of this legislation.

Cadmium and its inorganic compounds are also carcinogens or mutagens for humans in accordance with Article 2(a) and (b) of Directive 2004/37/EC and fall within the scope of this legislation.

4. Existing Occupational Exposure Limits

Occupational exposure limits for cadmium and its inorganic compounds exist in a number of countries. At EU level, no OEL has been adopted for cadmium and inorganic cadmium compounds. As described in chapter 2, cadmium and many cadmium-containing compounds are classified as carcinogen (Carc. 2 or even Carc. 1B) in the CLP Regulation (EC) No 1272/2008.

The most important OELs with respect to verifiability and relevance (only respirable Cd and Cd compounds aerosols because of the recommendation in the executive summary) globally are presented in **Table 2a**. In Germany, official carcinogenic risk figures have been derived by the *Ausschuß für Gefahrstoffe* (BAuA 2014 ; see 7.7.3).

Biological limit values (BLVs) have not been found for cadmium, only biological guidance values (BGVs). An overview is presented in Table 4b.

In Germany, a BGV (BAR value) was set at 1 µg/l blood and 0.8 µg/l urine (DE-DFG 2016). Switserland set a BGV at 5 µg/g creatinin or 5,03 nmol/mmol creatinine (**Table 2b**).

It is noted that the urinary BLV at EU level and in Switserland ares expressed in µg/g creatinine, whereas the German is expressed in µg/l.

Table 2a: Overview of existing OELs for cadmium and inorganic compounds in airborne particulates (aerosols)

EU	TWA (8 hrs)	Specifications	References
	mg/m³		
Ireland	0.002	Respirable	HSA (2016)
Spain	0.002	Respirable	INSHT (2016)
Sweden	0.005	Respirable dust	SWEA (2011)
Non-EU			
Canada (Ontario)	0.002	Respirable	ML (2013)
Switzerland	0.004	Respirable dust	SUVA (2016)
US (OSHA)	0.005	Applies to all Cd compounds. Cadmium dust (as Cd)	NIOSH (2016)

Table 2b: Overview of existing BLVs and reference values for the general population (not occupationally exposed) for cadmium and inorganic compounds

EU	Blood	Urine	Specifications	References
Germany	1 µg/l	0.8 µg/l	BAR* sampling time not fixed	DFG (2016)
Switzerland		5 µg/g creatinine 5,03 nmol/mmol creatinine		SUVA (2016)

**Reference value orientated at the upper 95th percentile of the general population*

5. OCCURRENCE, USE AND OCCUPATIONAL EXPOSURE

5.1. Occurrence

Cadmium occurs in nature mainly associated with zinc, but also with lead and copper (generally as Cd sulfidesulfide).

The general population may be exposed through consumption of food and drinking water, inhalation of cadmium-containing particles from ambient air or cigarette smoke, or ingestion of contaminated soil and dust. Tobacco smokers are exposed to an estimated 1.7 µg of cadmium per cigarette. Food is the major non-occupational source of cadmium exposure for nonsmokers; average cadmium levels in the U.S. food supply range from 2 to 40 ppb. The daily dietary Cd intake for an adult in European countries has been estimated at 0.10-0.50 µg/kg body weight (European Commission, 1996). In the US, The daily adult intake of cadmium is estimated to be approximately 30 µg, with the largest contribution from grain cereal products, potatoes, and other vegetables (NTP 2016). Exposures through drinking water or ambient air typically are very low (NTP 2016).

5.2. Production and use information

Cadmium is recovered as a by-product during the refining of zinc, lead and copper. 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).

Industrial uses of Cd are for the production of:
- active electrode materials in batteries (79 % of its uses in the Western world in 2003, mainly CdO),
- pigments in ceramics, plastics and glasses (11%, $Cd_{(1-x)}$ Zn_xS and $CdS_{(1-x)}Se_{x)}$),
- stabilisers 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).

The primary use of cadmium, in the form of cadmium hydroxide, is in electrodes for Ni-Cd batteries. Cadmium sulfide compounds are used as pigmernts in a wide variety of applications, including engineering plastics, glass, glazes, ceramics, rubber, enamels, artists' colours, and fireworks. Cadmium and cadmium alloys are used as engineered or electroplated coatings on iron, steel alumimium, and other non-ferrous metals. Cadmium salts of organic acids were widely used in the past as heat and light stabilisers for flexible vinyl chloride polymers and other plastics (IARC 2012, NTP 2016).

5.3. Occupational exposure

Workers in a wide variety of occupations are exposed to cadmium and inorganic cadmium compounds (IARC 1993). Occupations with the highest potential levels of exposure include smelting zinc and lead ores, welding or remelting cadmium-coated steel, working with solders that contain cadmium, and producing, processing, and handling cadmium powders. Recycling of scrap metal and Ni-Cd batteries may also involve some exposure.

The major routes of occupational exposure are inhalation of dust and fumes and incidental ingestion of dust from contaminated hands, cigarettes, or food (NTP 2016).

In industrial settings, airborne exposure levels typically have been reported to range from 5 to 50 µg/m³; with extreme values up to 400 µg/m³ (European Chemical Bureau, 2007).

5.4. Routes of exposure and uptake

In humans, uptake of Cd occurs occupationally *via* inhalation of Cd-containing dusts and fumes in industrial settings (occupational exposure), and for the general population *via* the gastrointestinal route through contaminated food (environmental exposure).
An additional source of cadmium exposure is tobacco smoke. Each cigarette contains about 2 µg of Cd, the amount varying considerably with the origin of tobacco leaves.

6. MONITORING EXPOSURE

6.1 External exposure (airborne) monitoring

Cadmium and its inorganic compounds as contained in particulates can be monitored in the workplace air using a number of official methods.

Only one method (UK-HSE MDHS91/2) requires the use of either an inhalable or a respirable dust sampler upstream of the sampling on a filter, according to UK-MDHS14 (UK - HSE, 2014b). This is in order to distinguish between inhalable and respirable particulates.

The DFG method (DE-DFG 1999a), clearly indicates a limit of quantification (LOQ) that would allow enforcement of the proposed OEL, *i.e.* 4 µg/m^3 (see 'RECOMMENDATION EXECUTIVE SUMMARY').

The DFG method is based on full digestion of the air sample on the filter and elemental analysis by (graphite) furnace atomic absorption spectroscopy (GFAAS or FAAS). The UK-

HSE method is based on direct analysis of the loaded filter by X-ray fluorescence spectroscopy (XRFS). This means for both methods that any cadmium species will be detected and quantified be it atomic, ionic, inorganic or organic cadmium.

It is noted that both methods available have a problem (either no separation into respirable fraction or the LOQ is not low enough). The US-OSHA and US-NIOSH methods that have been retrieved all lack separation into respirable fraction.

Both methods are suited for background and for personal sampling. See **Table 3** for an overview.

Table 3: Overview of sampling and analytical methods for monitoring cadmium and cadmium compounds (as cadmium) in workplace air based on digestion of the loaded filter*

Method	Sampling	Filters	Analysis	LOD/LOQ	Working range	Flow rate / sample volume / time	Refs
DE-DFG	Personal and stationary sampling	Particle filter CEM	GFAAS FAAS	LOQ 0.10 µg/m^3 LOQ 0.17 µg/m^3		420 L 45000 L	DFG (1999a)
UK-HSE MDHS 91/2	Particulates trapped on a filter mounted in an inhalable or respirable dust sampler Background and personal sampling	MCE filter	XRFS	LOD: 1 µg (Kα X-ray line) 0.005 µg (Lα X-ray line) LOQ: 4 µg (KαX-ray line) 0.02 µg (LαX-ray line)	Target values: 25 µg/m^3 (Kα) 25 µg/m^3 (Lα)	Long-term: max. 8 hours (960 L) Short-term: 15 minutes (60 L) 2 L/min	HSE (2014a)

CEM – Cellulose Ester Membrane; FAAS –furnace atomic absorption spectrometry; GFAAS – graphite furnace atomic absorption spectrometry; LOD - Limit of Detection (for the overall procedure); LOQ - Limit of Quantification; MCE – Mixed Cellulose Ester; XRFS - X-ray fluorescence spectroscopy

** Digestion preparation suitable for most of the industrially used cadmium compounds, e.g. cadmium (metal), cadmium chloride, cadmium iodide, cadmium nitrate, cadmium oxide, cadmium sulphide, cadmium stearate and cadmium sulphate.*

6.2 Internal exposure/biomonitoring of exposure

Biomonitoring of exposures to cadmium and cadmium compounds in the workplace can be carried out by the measurement of total cadmium in blood and urine (**Table 4**). The level can be quantitated either by atomic absorption spectroscopy (AAS) or by inductively coupled plasma quadrupole mass spectrometry (Q-ICP-MS). For none of the three methods a limit of quantification (LOQ) was presented, only a limit of detection (LOD).

Table 4: Overview of the available methods for biomonitoring of occupational exposures to cadmium and cadmium compounds*

Method	Matrix	Analysis	Within series imprecision	Between-day imprecision	Various	Detection limit	References
DE-DFG 1981	Blood	Flameless AAS	0.65-5.5 µg/L: *s*=12.3–5.5% *u*=27.8–12.3%	5.5-31.9 µg/L: *s*=8.4-6.6% *u*=18.1-14.7%	0.7-2.0 µg/L: *s*=16-8% ***	0.2 µg/L	DFG (1981)
DE-DFG 1984	Urine	Electro-thermal AAS	2.6-5.5 µg/L: *s*=3.7–4.0% *u*=8.1–9.5%	2.9-41.2 µg/L: *s*=10.5-6.8% *u*=22.0–14.1%	*r* = 106% **	0.2 µg/L	DFG (1984)
DE-DFG 1998	Urine	Q-ICP-MS	0.21 or 2 µg/L: *s*=4.8 or 0.9% *u*=9.0 or 1.5 %	1 µg/L: *s*=2.4% *u*=4.2%	*r* = 95% **	0.020 µg/L	DFG (1999b)

* *s* = standard deviation (rel); *u* = prognostic range; *r* = recovery rate; AAS = atomic absorption spectroscopy; Q-ICP-MS = inductively coupled plasma quadrupole mass spectrometry

** Inaccuracy; recovery rate

*** Between-laboratory imprecision

7. HEALTH EFFECTS

7.1. Toxicokinetics (absorption, distribution, metabolism, excretion)

7.1.1. Human data

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. However, while protecting from acute toxicity, metallothionein binding may promote chronic toxicity in the kidney: Due to a very long half-life of Cd in

the kidney of several decades, gradual release of cadmium ions during storage may contribute to the particular susceptibility of this organ towards cadmium.

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).

In humans, average Cd concentrations in liver and kidney are near zero at birth, and rise roughly linearly with age to peak values of around 40-50 mg/kg in the kidney between ages 50 and 60 (after which kidney levels plateau or decline), and 1-2 mg/kg in the liver by age 20-25 (and increase only slowly thereafter). After "normal" exposure to background Cd levels, about 50% of the Cd body burden is found in the kidneys, about 15% in the liver, and about 20% in the muscles (ATSDR 2012). Kjellström (1979) describes that after long-term low level exposure, about half the Cd body burden is stored in the liver and kidneys.where the major part is located in the cortex (). 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.

Cd can cross the placenta, but at a low rate (Lauwerys *et al.* 1978; Lagerkvist *et al.* 1992). The placenta is therefore only a partial barrier to foetal exposure (Baars *et al*. 2001).

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 and Hoet, 2001). Smokers excrete more Cd than non-smokers, and their Cd-U is on average 1.5-fold higher than in non-smokers (ATSDR 2012).

7.1.2. Animal data

Most estimates of cadmium absorption in animals are somewhat lower than the values found from human studies, particularly after prolonged exposure. In mice, 0.27–3.2% of an oral dose of cadmium chloride was retained after 3–5 days (Bhattacharyya *et al*. 1981; Engström and Nordberg 1979), and in rats, 2–3% of a single oral dose of cadmium chloride was retained (Moore *et al*. 1973; Schäfer *et al*. 1990). Following 30 days of oral exposure, 0.2–0.3% of an administered dose was retained in rats (Müller *et al*. 1986). After 4 weeks of dietary exposure to cadmium, absorption of cadmium was reduced to one-third the absorption of rats without pre-exposure to cadmium (Schäfer *et al*. 1990). Cadmium pigments (cadmium sulfide and cadmium sulfoselenide) appear to be absorbed

much less than cadmium chloride in rats (ATSDR 2012). Increases in Cd absorption have been observed during gestation and lactation, 0.37 and 0.35% of cadmium administered via gavage was absorbed in mice on gestation days 8 and 15 and 0.56, 0.60, and 0.30% on lactation days 10, 17, and 24, as compared to 0.27% in nonpregnant controls; absorption was only significantly different from nonpregnant controls on lactation days 10 and 17 (Bhattacharyya *et al*. 1981). Similar findings were observed in mice continuously exposed to cadmium during pregnancy and/or lactation (Bhattacharyya *et al*. 1981, 1986). For details of these studies, see ATSDR (2012).

7.1.3. *In vitro* data

Wester *et al*. (1992) evaluated the percutaneous absorption of cadmium ($^{109}CdCl_2$) from water and soil into and through human skin using *in vitro* skin cells. Dermal absorption was very low.

7.1.4. Toxicokinetic modelling

Several models have been reported to describe the kinetics of cadmium in mammalian systems. Of these models, the Shank *et al.* (1977) and Matsubara-Khan (1974) models provide insights into the absorption, distribution, and compartmentalization of cadmium in laboratory animals. The Nordberg-Kjellström model (Kjellström and Nordberg 1978; Nordberg and Kjellström 1979) has been used for cadmium risk assessment in humans. Although the Nordberg-Kjellström model has its limitations, it is considered to provide the best overall description of cadmium toxicokinetics, as it is largely based on human data. For details and a critical comparison of the modellings, reference can be made to ATSDR 2012).

7.1.5. Biological monitoring

Blood cadmium levels are principally indicative of recent exposure(s) to cadmium rather than of whole body-burden. In workers occupationally exposed to cadmium by inhalation blood cadmium levels ranging up to 50 µg/L have been noted (Roels *et al.* 1981). By constrast, urine cadmium levels primarily reflect the total body burden of cadmium, although urine levels do respond somewhat to recent exposure. Therefore, the sampling time is largely non-critical (DFG 2008). When the critical level for renal damage has been reached, urinary cadmium levels rise sharply because of the release of intra-renal cadmium along with decreased renal reabsorption of cadmium (Roels *et al.* 1981). In environmentally-exposed individuals, Buchet *et al.* (1990) report that abnormal values of various biomarkers are found in 5% of the population with urinary excretion of cadmium above the 2–4 µg Cd/24 hour level (approximately 1–3 µg/g creatinine). Significant correlations between total cadmium exposure, urinary cadmium levels and renal effects have been found in environmentally exposed populations. Data of relevant studies are shown in **Table 5**.

Liver and kidney tissues preferentially accumulate cadmium. In workers exposed to cadmium by inhalation, values up to 300 µg/g wet weight in kidney and 100 µg/g wet weight in liver can be found (Roels *et al.* 1981). Because kidney cadmium content begins to decline after the onset of cadmium-induced renal dysfunction, liver cadmium may be a better indicator of cadmium exposure than kidney cadmium, and it has been suggested that kidney dysfunction is likely to appear at liver cadmium concentrations between 30 and 60 µg/g wet weight (Roels *et al.* 1981). Studies in cadmium workers suggest that metallothionein levels may also be a biomarker of cadmium exposure. Elevated levels of metallothionein gene expression were observed in peripheral blood lymphocytes in highly exposed workers. The level of metallothionein gene expression was significantly correlated with blood and urinary cadmium levels (Lu *et al.* 2001). Urinary metallothionein correlates with cadmium concentrations in liver, kidney, and urine (Shaikh *et al.* 1987). Relatively strong correlations have been found between urinary metallothionein and urinary cadmium levels in exposed humans (Kawada *et al*. 1989),

and a dose-related increase in urinary metallothionein was found in rats exposed to cadmium in drinking water for up to 2 years (Shaikh *et al.* 1989).
Excess urinary excretion of low-molecular-weight proteins and solutes is associated with decreased tubular reabsorption (Hoet et al 2012). Increased excretion of high-molecular-weight proteins or decreased serum clearance of creatinine reflects glomerular dysfunction, which is generally associated with progressive renal damage (Roels *et al.* 1989).
Urinary β_2-microglobulin, a low molecular weight protein, has been widely used as an indicator of tubular renal dysfunction. However, tubular renal dysfunction can be caused by exposures and diseases other than cadmium, so β_2-microglobulin is not a specific marker of cadmium-induced effects. Practical considerations in using urinary β_2-microglobulin as a marker of tubular renal dysfunction include the need to control the pH of samples to prevent the rapid degradation that occurs at pH values below 5.5 (Shaikh and Smith 1984), and the fact that urinary β_2-microglobulin excretion normally rises with age (Roels *et al.* 1989).
Urinary retinol-binding protein is also considered to be a sensitive indicator of decreased tubular reabsorption, but it also is not specific for cadmium-induced damage in the kidney (Shaikh and Smith 1984; Topping *et al.* 1986). Retinol-binding protein is more stable in urine than β_2-microglobulin (Bernard and Lauwerys 1981) and appears to be of approximately equal sensitivity and specificity for detecting tubular proteinuria in cadmium-exposed populations (Topping *et al.* 1986). Levels of both proteins fluctuate over time, so regular, repeated sampling may be necessary to establish abnormal levels (Ormos *et al.* 1985).
Human complex-forming glycoprotein (pHC, also referred to as α1-microglobulin) is another sensitive marker of tubular renal dysfunction (Moriguchi *et al*. 2005). As with retinol binding protein, pHC is more stable in urine than β_2-microglobulin at room temperature and low urinary pH levels.
Urinary N-acetyl-β-D-glucosaminidase (NAG), a lysosomal enzyme present in high concentrations in the proximal tubule, has been shown to correlate with urinary cadmium levels in occupationally and environmentally exposed subjects and has a better correlation with urinary cadmium levels than does β_2-microglobulin at low cadmium exposure levels (urinary cadmium <10 µg/g creatinine). However, increased urinary NAG activity can result from effects other than nephrotoxicity (Bernard and Lauwerys 1989).
There is no single biological indicator for cadmium toxicity that is entirely adequate when considered alone. Measurement of cadmium levels in various biological materials can provide an indication of recent or total cadmium exposure, but the probability of adverse effects cannot be reliably predicted except at high exposure levels. Measurement of a variety of markers of renal dysfunction can provide a sensitive measure of early kidney toxicity, but cannot establish whether cadmium exposure was the cause (ATSDR 2012).

Table 2 gives a compilation of relevant studies showing renal adverse effects of cadmium exposure in humans, related to biological Cd exposure parameters.

Table 5: Dose-effect relationships between biological parameters of 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*. 1999 Järup et al. 2000
	5.6 – 8.4	O	glomerular damage (reduced GFR)	Roels *et al*. 1989, Roels *et al*. 1991, Järup and Elinder 1994
> 4	> 6.7	O	kidney stones	Järup and Elinder 1993

E : environmental; O : occupational exposure

7.2. Acute toxicity

7.2.1. Human data

Cadmium fumes (mainly consisting of CdO) when inhaled at a sufficiently high 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 such as chills, fever, and muscle pains). When exposure is sufficiently intense, evidence of pneumonitis and pulmonary edema develops within 1 or 2 days, which can be fatal in severely affected victims. The diagnosis of acute Cd poisoning can be confirmed by the measurement of Cd-U (Ando *et al.*, 1995). The dose that is sufficient to cause pulmonary oedema 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).

7.2.2. Animal data

Acute inhalation of cadmium oxide fumes led to death in rats, mice, rabbits, guinea pigs, dogs, and monkeys, with the mortality rate apparently being directly proportional to the product of the duration of exposure and the concentration of inhaled cadmium (Barrett *et al.* 1947). The most reliable LC_{50} (after 7 days) established by this study was 500 minute-mg cadmium oxide/m^3 for rats, equivalent to a 15-minute exposure to 30 mg Cd/m^3 (Barrett *et al.* 1947). Rusch *et al.* (1986) demonstrated high mortality rates in the Sprague-Dawley rat from a 2-hour exposure to cadmium fumes at 112 mg Cd/m^3 (25 of 32 died within 1 week). A 2-hour exposure to a different form of cadmium, cadmium carbonate, at 132 mg Cd/m^3 resulted in considerably lower mortality (3 of 22 died by day 30). No deaths resulted from a 2-hour exposure to cadmium sulfide at 99 mg Cd/m^3 or cadmium selenium sulfide (cadmium red pigment) at 97 mg Cd/m^3. Grose *et al.* (1987) reported 2 out of 36 rats died from a 2-hour, nose-only inhalation exposure to only 0.45 mg Cd/m^3 of cadmium oxide dusts, but the statistical significance of this low rate of mortality was not reported. A 3-day, 1-hour/day exposure to cadmium chloride aerosol at 61 mg Cd/m^3 resulted in the death of 17 of 18 rats exposed (Snider *et al.* 1973). In another study, no deaths were observed in rats from a cadmium yellow (cadmium sulfide) pigment exposure 6 hours/day for 10 days at 6.29 mg Cd/m^3 (Klimisch 1993). Thus, it appears that in acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium carbonate compounds are more toxic than the relatively less soluble cadmium sulfide compounds (Klimisch 1993; Rusch *et al.* 1986). Rusch *et al.* (1986) attribute this difference to higher lung absorption and retention times for the more soluble compounds, and greater mucociliary clearance for the less-soluble pigments. Glaser *et al.* (1986), however, demonstrated that toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide in biological fluids may be greater than its solubility in water. In hamsters, Henderson *et al.* (1979) reported that a 30-minute exposure to 10.1 mg Cd/m^3 from cadmium chloride resulted in the death of 3

of 30 animals by day 6 postexposure. In rabbits, Friberg (1950) reported an LC_{50} (by day 14) from a 4-hour exposure to cadmium metal dusts at 28.4 mg Cd/m^3. Barrett and coworkers (Barrett and Card 1947; Barrett *et al.* 1947) reported LC_{50} values for cadmium oxide fume of 940 mg Cd/m^3 for a 14-minute exposure in the monkey, 46.7 mg/m3 for a 15-minute exposure in the mouse, 204 mg Cd/m^3 for a 15-minute exposure in the guinea pig, and 230 mg Cd/m^3 for a 15-minute exposure in the dog. However, the authors noted that these LC_{50} values are only approximations because of insufficiencies in the data or the small numbers of animals used (ATSDR 2012).

7.3. Specific Target Organ Toxicity/Repeated Exposure

7.3.1. Human data

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 locally 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 and Crabtree, 1961). A 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 and Campbell, 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 and Kazantzis, 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/m^3** (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, 2007).

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, $ß_2$-microglobulin ($ß_2$M) and/or retinol-binding protein (RBP), but also calcium and amino-acids (Lauwerys *et al.*, 1979a,b; 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; Hoet *et al*., 2012 ; Hambach *et al.*, 2013a,b). 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 6**. 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 6: Thresholds for renal effects in recent studies in occupational settings.

	Type of industry	n	Glomerular effect	Tubular effect	Threshold
Lauwerys *et al.* 1979b	Electronic workshop Ni-Cd storage battery factory Cd-producing plants	-	HMW proteins β2M-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 β2M	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.* 1992	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.*, 1993) 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 occupationallyexposed 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.*, 1998). Others, however, 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.

Mortality studies were not able to detect an excess of end-stage renal diseases in populations environmentally exposed to cadmium compounds. This was recently confirmed by a qualitative systematic review, which did not support the contention that human exposure to Cd leads to progressive chronic kidney disease (Byber *et al.* 2016). However, 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; Åkesson *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 and Elinder, 1993).

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 and Lundholm, 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 an understanding of 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 review, see Friberg *et al.*, 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 *etal.,* 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 (Åkesson *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 (Järup *et al.* 1998a). 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 environmental exposure 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.

7.3.2. Animal data

7.3.2.1. Inhalation

Early animal studies confirm that renal damage occurs following inhalation exposure to cadmium. Rabbits developed proteinuria after a 4-month inhalation exposure to cadmium metal dust at 4 mg/m^3 for 3 hours/day, 21 days/month; histologic lesions were found after an additional 3–4 months of exposure (Friberg 1950). Friberg (1950) noted that the degree of proteinuria was not especially pronounced. Most subsequent studies using inhalation exposure have not found proteinuria primarily because the levels of exposure and durations of follow up (*e.g.*, 1–5 mg/m^3 for intermediate exposures; 0.2–2 mg/m^3 for chronic exposures) that produce serious respiratory effects have not been sufficient to produce a critical concentration of cadmium in the kidney (ATSDR 2012).

Studies in animals are in accordance with human experience that inhalation exposure to cadmium can lead to respiratory injury (ATSDR 2012). Single acute exposures in rats to 5–10 mg Cd/m^3 as cadmium oxide dust, cadmium oxide fume, or cadmium chloride for 1–5 hours resulted in moderate to severe, multifocal interstitial pneumonitis, diffuse alveolitis with hemorrhage, increased lung weight, inhibition of macrophages, focal interstitial thickening, oedema, and necrosis of alveolar type 1 cells leading to type 2 cell hyperplasia and fibroblasts (Boudreau *et al.* 1989; Buckley and Bassett 1987; Bus *et al.* 1978; Grose *et al.* 1987; Hart *et al.* 1989; NTP 1995). Similar results (*i.e.,* severe pneumonitis) were seen in hamsters exposed to cadmium chloride at 10 mg/m^3 for 30 minutes (Henderson *et al.* 1979) and in rabbits exposed to cadmium oxide dusts at 4.5 mg/m^3 for 2 hours (Grose *et al.* 1987). Exposures in rats to cadmium chloride at 6.1 mg Cd/m^3 1 hour/day for 5, 10, or 15 days resulted in emphysema; a 3-day exposure to 61 mg Cd/m^3 for 1 hour/day resulted in pulmonary hemorrhage (Snider *et al.* 1973).

In subchronic inhalation toxicity studies reported by NTP (1995) male and female F344/N rats and B6C3F1 mice were exposed to cadmium oxide aerosol (MMAD=1.1-1.6 mm) for 6 hours per day, 5 days per week, for 2 or 13 weeks. Exposure levels were 0.1 to 10 mg/m^3 for the 2-week studies and 0.025 to 1 mg/m^3 for the 13-week studies. In the 2-week studies, all rats and mice at the highest exposure level (10 mg/m^3) died from respiratory toxicity characterised by inflammation, necrosis, and fibrosis of the lung. Toxicity to the nasal cavity and tracheobronchial lymph nodes was also observed in the 10 mg/m^3 groups. At the lower exposure levels, treatment-related toxic lesions were not life threatening, and all body weights were within 10% of controls. In the 13-week studies, all rats and mice (with the exception of one control mouse) survived to the end of the studies. The final mean body weight of rats in the highest exposure groups (1 mg/m^3) was 93% of the control value. For all other exposed rat and mouse groups, final mean body weights corresponded to those of the respective controls. For rats and mice in the 13-week studies, the major toxicity was to the respiratory system. Treatment-related lesions were observed in the lung, tracheobronchial lymph node, larynx, and nose. The no-observed-adverse-effect concentration (NOAEC) in the lungs was 0.025 mg/m^3 for rats. A NOAEC was not found in the lungs or larynx of mice or in the larynx of rats. At the 0.025 and 0.05 mg/m^3 levels in mice, lung lesions were minimal and not considered life threatening. A NOAEL in the nasal cavity was 0.05 mg/m^3 for rats and mice (NTP 1995).

7.3.2.2. Oral exposure

Numerous oral studies indicate that the kidney is the primary target organ of cadmium toxicity following extended oral exposure, with effects similar to those seen following inhalation exposure. A notion that a critical concentration of approximately 200 µg/g in the renal cortex must be reached before proteinuria develops is generally supported by the available animal data (for details, see ATSDR 2012).

7.3.2.3. Dermal exposure

No relevant data on dermal exposure were retrieved.

7.3.3. *In vitro* data

In vitro studies regarding to the chronic toxicity of cadmium were primarily focussed on the mode of action of of carcinogenicity (see 8.9). At the cellular level, cadmium affects cell proliferation, differentiation, apoptosis and other cellular activities. Current evidence suggests that exposure to cadmium induces genomic instability through complex and multifactorial mechanisms. Most important seems to be cadmium interaction with DNA repair mechanism, generation of reactive oxygen species and induction of apoptosis. For details, reference can be made to reviews by Hartwig (2013a,b) and Rani *et al.* (2014).

7.4. Irritancy and corrosivity

7.4.1. Human data

Dermal or ocular toxicity does not appear to be a significant effect of inhalation exposure to cadmium. Studies of workers occupationally exposed to cadmium have not reported dermal or ocular effects following acute or chronic exposure (ATSDR 2012).

Routine patch tests on patients with dermatitis and eczema yielded evidence of skin irritation after application of 2 % cadmium chloride solutions (European Chemical Bureau 2007, DFG 2006).

7.4.2. Animal data

7.4.2.1. Skin

No study was located that specifically examined dermal toxicity in animals following inhalation exposure to cadmium (ATSDR 2012).

7.4.2.2. Eyes

No study was located that specifically examined ocular toxicity in animals following inhalation exposure to cadmium (ATSDR 2012).

7.4.3. *In vitro* data

No relevant studies were retrieved.

7.5. Sensitisation

7.5.1. Human data

Regarding skin sensitisation, some studies report on positive patch tests with 1-2% Cd chloride or sulfate preparations. However, the clinical relevance is questionable, and an involvement of irritation is uncertain (see 8.4.1). For details, it may be referred to DFG (2006). There are no data available for sensitization of the respiratory tract in humans caused by cadmium and its inorganic compounds (DFG 2006).

7.5.2. Animal data

No relevant data were retrieved.

7.5.3. In vitro data

No relevant data were retrieved.

7.6. Genotoxicity

In the first IARC Monograph (1993), the genotoxicity core data on cadmium and its compounds, published up to 1992, were comprehensively presented. The data on the genotoxicity of cadmium published up to 2002 have been summarized and evaluated by Verougstrate *et al.* (2002) and in the report of the European Commission (European Chemical Bureau 2007). Data up to 2012 were compiled by ATSDR (2012). For details, reference can be made to these exhaustive compilations.

7.6.1. Human data

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 informative 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 aberrations was recorded only in the subgroup of workers with the highest cumulative exposure to Cd (>1000 µg/m³ x years, **Table 7a**, or Cd-U>10 µg/L, **Table 7b**).

Table 7a*: 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/m^3.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 7b: 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 the identification of 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).

7.6.2. Animal data

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 reported. Cadmium oxide did not induce micronuclei in erythrocytes of mice exposed by inhalation for 13 weeks (NTP 1995).

7.6.3. In vitro

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. Cadmium oxide was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537, with or without exogenous metabolic activation (NTP 1995).

7.7. Carcinogenicity

7.7.1. Human data

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 and Waterhouse, 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 and Waterhouse, 1983; Thun *et al.*, 1985; Kazantzis *et al.*, 1988) failed to confirm this hypothesis.
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 and Katzantzis, 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 evaluation by IARC (1993) 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 uptated by Stayner et al. (1992) and Park *et al.* (2012) 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 and Lancashire, 1997; Sorahan and Esmen 2012). In two .cohorts of workers from a nickel-cadmium battery plant (where arsenic was 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 and Esmen, 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=116-446) 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; IARC, 2012).

Some epidemiological studies suggest an association between occupational exposure to Cd and the occurrence of renal cancer (reviewed by Il'yasova and Schwartz, 2005) and urothelial cancer (reviewed by Feki-Tounsi and Hamza-Chaffai, 2014).

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 .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) (Åkesson *et al.* 2008).

7.7.2. Animal data

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).

For details of these studies, see IARC (1993, 2012).

7.7.3. Carcinogenic risk assessment

Based on mechanistic evidence (see 8.9.) the mode of carcinogenic action of Cd and its inorganic compounds comprises genotoxic and non-genotoxic elements. The non-genotoxic elements are non-stochastic and characterised by a threshold below which no carcinogenic effect is expected. In consequence, SCOEL proposes OELs (8h-TWA and BLV, as outlined in chapter 1).

Others have performed linear linear risk extrapolations from experimental (Takenaka *et al* 1983) or epidemiological (Thun et al 1985; Park et al 2012) data. Data from the inhalation carcinogenicity bioassay with $CdCl_2$ by Tanaka et al (1983) were considered by EPA (1994) and by the *Ausschuß für Gefahrstoffe* (BauA 2014). Related to working lifetime exposure, an additional cancer risk of 1:1000 resulted from the EPA procedure at 1 µg Cd/m^3, and of 4:1000 at 1.6 µg Cd/m^3 by the Ausschuß für Gefahrstoffe (BauA 2014). Based on epidemiological data [Park *et al.* (2012) update of the Thun *et al*. (1985) cohort], Haney (2016) estimated an excess risk level of 1:100000 for a lifetime air concentration of 0.02 µg Cd/m^3 (continous environmental exposure, corresponding to 1:1000 at 2 µg Cd/m^3) for the general population in the State of Texas.

7.8. Reproductive toxicity

7.8.1. Human data

Epidemiological studies do not indicate 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, 2007).

7.8.2. Animal data

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 understand the possible effect of low doses of Cd on the developing brain suggested in experimental animals.

In studies by NTP (1995), sperm-positive Sprague-Dawley rats and Swiss (CD-1(R)) mice were exposed to 0, 0.05, 0.5, or 2 mg/m^3 cadmium oxide 6 hours per day, 7 days per week, on gestation day 4 through 19 (rats) or gestation day 4 through 17 (mice). Maternal toxicity was observed in Sprague-Dawley rats exposed to 2 mg/m^3 cadmium oxide for 16 days and included body weights lower than those of the controls and clinical signs of toxicity (dyspnea and hypoactivity). There was no evidence of embryolethality in rats at any exposure level. However, in rats exposed to 2 mg/m^3, developmental toxicity was evidenced by lower fetal weights and a significant increase in the incidence of reduced skeletal ossifications. Maternal toxicity was also observed in Swiss (CD-1(R)) mice exposed to 2 mg/m^3 cadmium oxide for 14 days. Clinical signs were dyspnea, hypoactivity, lower body weight, and a lower pregnancy rate (30% vs. 97% in the control group). The total number of resorptions per litter was increased at the 2 mg/m^3 level. Developmental toxicity was evidenced by lower fetal weights in the 0.5 and 2 mg/m^3 groups and an increase in the incidence of reduced sternebral ossification in the 2 mg/m^3 group. Reproductive toxicity was observed in the 1 mg/m^3 groups of rats and was evidenced by a reduced number of spermatids per testis and an increase in the length of the estrous cycle. Reproductive toxicity was not observed at any exposure level in mice (NTP 1995).

7.8.3. In vitro data

No relevant in vitro data on reproductive toxicity were retrieved.

7.9. Mode of action and adverse outcome pathway considerations

Cadmium is an established human and animal carcinogen. Most evidence is available for elevated risk for lung cancer after occupational exposure; however, associations between cadmium exposure and tumors at other locations including kidney, breast, and prostate may be relevant as well. Furthermore, enhanced cancer risk may not be restricted to comparatively high occupational exposure, but may also occur via environmental exposure, for example in areas in close proximity to zinc smelters. The underlying mechanisms are still a matter of manifold research activities. While direct interactions with DNA appear to be of minor importance, there is interference with distinct cellular signalling pathways (Bishak *et al.*, 2015; Fischer *et al.,* 2016). Thus, elevated levels of reactive oxygen species (ROS) have been detected in diverse experimental systems, presumably due to an inactivation of detoxifying enzymes. Also, the interference with proteins involved in the cellular response to DNA damage, the deregulation of cell growth as well as resistance to apoptosis appears to be involved in cadmium-induced carcinogenicity. Within this context, cadmium has been shown to disturb nucleotide excision repair, base excision repair, and mismatch repair. Particularly sensitive targets appear to be proteins with zinc binding structures, present in DNA repair proteins such as

XPA, PARP-1 as well as in the tumor suppressor protein p53. Whether or not these interactions are due to displacement of zinc or due to reactions with thiol groups involved in zinc complexation or in other critical positions under realistic exposure conditions remains to be elucidated. Further potential mechanisms relate to the interference with cellular redox regulation, either by enhanced generation of ROS or by reaction with thiol groups involved in the regulation of signaling pathways. Particularly the combination of these multiple mechanisms may give rise to a high degree of genomic instability evident in cadmium-adapted cells, relevant not only for tumor initiation, but also for later steps in tumor development (for details, see Hartwig 2013a).

In essence, 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 and Hartwig 2008). All these mechanisms are non-stochastic and characterised by a threshold below which no effect is expected. Cd can 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). In consequence, a set of OELs (8h-TWA, BLV) should be protective that prevents toxicity in workers, both locally with regard to the airways and systemically with regard to the kidneys.

7.10. Lack of specific scientific information

Cadmium and its inorganic compounds have been well investigated. This refers to studies both in occupationally-exposed workforce and in experimental systems. There is no lack of specific scientific information for occupational standard setting.

Nevertheless, regarding cadmium-related carcinogenicity in different target organs under low exposure conditions, future research should have a focus on the relevance of underlying mechanisms in experimental animals and in exposed humans (Hartwig 2013a).

8. GROUPS AT EXTRA RISK

Distinct groups of persons at extra risk related to Cd have not been clearly identified in epidemiological studies. However, based on the established systemic effects of Cd in humans (see 8.3.1), persons with pre-existing renal disease or diabetes could be more susceptible than others. This should be taken into account in the medical surveillance of Cd-exposed workforce.

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