# Workplace Exposure Standard (WES) review

***CADMIUM AND CADMIUM COMPOUNDS AS Cd (CADMIUM CAS NO: 7440-43-9)***

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WORKSAFE
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# 1.0
# Introduction

# This WorkSafe New Zealand (WorkSafe) review considers whether the **WES** for cadmium and cadmium compounds (as **Cd**) should be changed.

It considers the potential for exposures to cadmium and cadmium compounds in New Zealand, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring exposures.

The review includes a recommendation to change the WorkSafe WES for cadmium and cadmium compounds (as Cd), which is currently set at a **WES-TWA** of 0.01**mg/m³** for **inhalable fraction** and 0.002mg/m³ for **respirable fraction**, as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Ed., November 2019 (WorkSafe, 2019).

Terms that are **bold** (first occurrence only) are further defined in the Glossary.
Synonyms: Cadmium metal, Cd.

# 2.0 Chemical and physical properties

# Metallic cadmium is an odourless, silver-white, blue-tinged malleable metal or greyish-white powder at room temperature (**SCOEL**, 2017; **NTP RoC**, 2016; **ACGIH®**, 2001).

Almost all cadmium compounds have an oxidation state of +2 and there are a great variety of cadmium compounds with varying chemical and physical properties (SCOEL, 2017; NTP RoC, 2016).

Chemical and physical properties of cadmium and cadmium compounds include:

| SUBSTANCE | CADMIUM METAL | CADMIUM OXIDE | CADMIUM CHLORIDE | CADMIUM SULPHATE | CADMIUM SULPHIDE |
|---|---|---|---|---|---|
| **CAS No.** | 7440-43-9 | 1306-19-0 | 10108-64-2 | 10124-36-4 | 1306-23-6 |
| **Molecular weight** | 112.41g/mol | 128.41g/mol | 183.32g/mol | 208.47g/mol | 144.48g/mol |
| **Formula** | Cd | **CdO** | $CdCl_2$ | $CdSO_4$ | CdS |
| **Physical form** | White silvery solid | Brown powder | White crystals | Colourless crystals | Yellow-orange-brown crystals |
| **Specific gravity** | 8.65g/cm³ at 25°C | 6.95g/cm³ at 20°C | 4.047g/cm³ at 25°C | 4.69g/cm³ at 20°C | 4.5–4.85g/cm³ at 20°C |
| **Melting point** | 321°C | Decomposes at 950°C | 568°C | 1,000°C | 1,750°C |
| **Boiling point** | 765°C | Decomposes at 950°C | 960°C | No data | Sublimes in $N_2$ at 980°C |
| **Vapour pressure** | 1Pa at 257°C | 1mmHg at 1,000°C | 10mmHg at 656°C | No data | No data |
| **Auto flammability** | 250°C | No data | No data | No data | No data |
| **Water solubility** | Insoluble | Practically insoluble | 1400g/L at 20°C | 755g/L at 0°C | 1.3mg/L at 18°C |

SCOEL, 2017; **ATSDR**, 2012; ACGIH®, 2001

**TABLE 1:** Physicochemical properties of cadmium and cadmium compounds

Health-related hazard classifications for cadmium and cadmium compounds:

| SUBSTANCE | CAS NO. | CLASSIFICATION |
|---|---|---|
| **Cadmium metal** | 7440-43-9 | 6.1B (All); 6.1B (O); 6.1C (I); 6.6A; 6.7A; 6.8A; 6.9A (All); 6.9A (O) |
| **Cadmium oxide** | 1306-19-0 | 6.1D (All); 6.1D (O); 6.7A; 6.9A (All); 6.9A (O); 6.9A (I) |
| **Cadmium chloride** | 10108-64-2 | 6.1C (All); 6.1C (O); 6.6A; 6.7A; 6.8A; 6.9A (All); 6.9A (O); 6.9A (I) |
| **Cadmium sulphate** | 10124-36-4 | 6.1C (All); 6.1C (D); 6.7A; 6.9A (All); 6.9A (O); 6.9A (I) |
| **Cadmium sulphide** | 1306-23-6 | 6.1D (All); 6.1D (O); 6.7B; 6.9A (All); 6.9A (O); 6.9A (I) |

**TABLE 2: HSNO** health-related hazard classifications of cadmium and cadmium compounds (EPA, 2019a-e)

For a full listing of all HSNO health-related hazardous substances classification codes and their descriptions, see Appendix 2.

[All] Overall classification for that endpoint.

[O] Oral exposure route.

[D] Dermal exposure route.

[I] Inhalation exposure route.

# 3.0
# Uses

Cadmium compounds are used primarily as active electrode materials in batteries; as pigments in ceramics, plastics and glass; as additives in metal production; and, as stabilisers in PVC and related polymers (SCOEL, 2017).

The various cadmium compounds are favoured in particular industrial roles, for example: cadmium oxide and hydroxide in battery electrodes; cadmium sulphide compounds as pigments; cadmium chloride in electroplating etc (SCOEL, 2017).

Occupational exposure to cadmium can occur during production, storage, transportation and end-use.

Workers can be exposed to cadmium as dust or fumes via inhalation (SCOEL, 2017; **IARC**, 2012).

The number of workers exposed or potentially exposed to cadmium in New Zealand workplaces is unknown.

Statistics New Zealand 2018 data indicate that 36,400 New Zealand workers were working in the areas of:

- primary metal and metal product manufacturing
- fabricated metal product manufacturing
- electrical equipment manufacturing
- waste treatment, disposal and remediation services (NZ.Stat, 2019).

# 4.0
# Health effects

**IN THIS SECTION:**

## 4.1 Non-cancer

### Humans

The SCOEL opinion on cadmium and its inorganic compounds summarised the acute toxicity in exposed humans:

> "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.
>
> "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.
>
> "It has been estimated that an 8-hour exposure to 1mg/m$^3$ is immediately dangerous for life (Friberg et al., 1986)." (References cited in SCOEL, 2017).

The New Zealand EPA classifies cadmium and its inorganic compounds as 6.1B, 6.1C, and 6.1D substances – substances that are acutely toxic (EPA 2019a-e)."

The SCOEL opinion on cadmium and its inorganic compounds summarised the irritation/corrosion potential in humans:

> "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)." (References cited in SCOEL, 2017).

The SCOEL opinion on cadmium and its inorganic compounds summarised the sensitisation potential in humans:

> "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)." (References cited in SCOEL, 2017).

The SCOEL opinion on cadmium and its inorganic compounds summarised the genotoxic potential in humans:

> "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, or **Cd-U**>10**µg/L**)." (References cited in SCOEL, 2017).

The New Zealand EPA classifies cadmium and cadmium chloride as 6.6A substances – substances that are known or presumed mutagens (EPA 2019a, c).

The SCOEL opinion on cadmium and its inorganic compounds summarised the reproductive/developmental toxicity in humans:

> "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)." (Reference cited in SCOEL, 2017).

The New Zealand EPA classifies cadmium and cadmium chloride as 6.8A substances – substances that are known or presumed human reproductive or developmental toxicants (EPA 2019 a, c).

The SCOEL opinion on cadmium and its inorganic compounds summarised the repeated exposure toxicity in humans:

> **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, 3.7µg/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)."
>
> "Long-term inhalation exposure to cadmium and cadmium compounds may also affect lung function and is associated with the development of emphysema.
>
> "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 **DLCO** 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**, DLCO, and KCO, and both estimated cumulative cadmium exposure (years * µg/$m^3$), 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." (References cited in SCOEL, 2017).

### Kidney

"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., 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 (□**GT**), 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**)." (References cited in SCOEL, 2017).

"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)". (References cited in SCOEL, 2017).

"The largest studies were conducted in Belgium (Cadmibel study) in a population exclusively exposed *via* the environment (n=1700; geometric mean Cd-U, 0.84µg/24h) (Buchet et al., 1990) and in Sweden (OSCAR study) in subjects with environmental and/or occupational exposure (n=1021; Cd-U, 0.18–1.8µg/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 ≥ 2µg/24h (roughly equivalent to 2µg/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 (0.18–1.8µg/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 (eg 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)." (References cited in SCOEL, 2017).

**Bone**

"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." (Reference cited in SCOEL, 2017).

The New Zealand EPA classifies cadmium and its inorganic compounds as 6.9A substances – substances that are toxic to human target organs or systems (EPA 2019a-e).

## Animals

The SCOEL opinion on cadmium and its inorganic compounds summarised the acute toxicity in experimental animals:

"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) … 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." (References cited in SCOEL, 2017).

The SCOEL opinion on cadmium and its inorganic compounds summarised the genotoxic potential in experimental animals and *in vitro* test systems:

> "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).
>
> "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)." (References cited in SCOEL, 2017).

The SCOEL opinion on cadmium and its inorganic compounds summarised the reproductive/developmental toxicity in experimental animals:

> "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** 0.1mg/m$^3$, 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 2mg/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 2mg/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 2mg/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 2mg/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 2mg/m$^3$ level. Developmental toxicity was evidenced by lower fetal weights in the 0.5 and 2mg/m$^3$ groups and an increase in the incidence of reduced sternebral ossification in the 2mg/m$^3$ group. Reproductive toxicity was observed in the 1mg/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)." (References cited in SCOEL, 2017).

The SCOEL opinion on cadmium and its inorganic compounds summarised the repeated exposure toxicity in experimental animals:

**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)." (Reference cited in SCOEL, 2017).

**Bone**

"*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." (References cited in SCOEL, 2017).

## 4.2 Cancer

The International Agency for Research on Cancer (IARC) evaluation of cadmium and cadmium compounds concluded that:

There is *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.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cadmium compounds.

There is *limited evidence* in experimental animals for the carcinogenicity of cadmium metal.

With an overall evaluation that:

Cadmium and cadmium compounds are *carcinogenic to humans (Group 1)* (IARC, 2012).

The US National Toxicology Program [NTP] Report on Carcinogens [RoC], Fourteenth Edition concluded that:

"Cadmium and cadmium compounds are known to be human carcinogens based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies." (NTP RoC, 2016).

The New Zealand EPA classifies cadmium metal, cadmium oxide, cadmium chloride and cadmium sulphate as 6.7A – substances known or presumed to be human carcinogens; and cadmium sulphide as 6.7B – a substance suspected to be a human carcinogen (EPA, 2019a-e).

## Humans

The SCOEL opinion on cadmium and its inorganic compounds summarised the data on exposure and carcinogenicity 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 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 updated 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 [sic] 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)." (References cited in SCOEL, 2017).

### Animals

The IARC Monograph on cadmium and cadmium compounds summarised the data on exposure and carcinogenicity in experimental animals:

> "By inhalation, various cadmium compounds induce lung tumours in rats (cadmium chloride, cadmium oxide, cadmium oxide dust, cadmium oxide fumes, cadmium sulphide). Intratracheal administration of cadmium chloride and cadmium sulphide induces lung tumours in rats. In one study, subcutaneous injection of cadmium chloride caused lung tumours in mice. A variety of cadmium compounds and metallic cadmium cause local sarcomas in rats and mice. Administration of various salts of cadmium causes testicular tumours in rats. Cadmium chloride induced prostatic proliferative lesions and testicular tumours in rats after subcutaneous or oral administration." (IARC, 2012).

## 4.3 Absorption, distribution, metabolism and excretion

The SCOEL opinion on cadmium and its inorganic compounds summarised the absorption, distribution, metabolism and excretion (**ADME**) and mechanistic data for carcinogenesis:

> "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 [eg 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 <20µg/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 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 1–2mg/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 1µg/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 1µg/g creatinine in adults. In one of the most robust and extensive European database (GerES-III, 1998), the 98th percentile for Cd-U was 1.08µg/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)." (References cited in SCOEL, 2017).

"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, that is, a genotoxic carcinogen for which a practical threshold can be identified (Bolt and Huici-Montagud, 2008). In consequence, a set of **OEL**s (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." (References cite in SCOEL, 2017).

# 5.0 Exposure standards

**IN THIS SECTION:**

## 5.1 Other exposure standards

Table 3 below shows some of the cadmium and cadmium compounds exposure standards from around the world, as published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (**IFA**, 2019).

| JURISDICTION OR ADVISORY BODY | 8-HOUR LIMIT VALUE[1] | SHORT-TERM LIMIT VALUE[1] |
|---|---|---|
| | mg/m³ | mg/m³ |
| Australia | 0.01[1] | |
| Austria | 0.015[4,11]<br>0.03[4,11] | 0.06[3,4,11]<br>0.12[3,4,11]<br>0.002[5] |
| Belgium | 0.01[1]<br>0.002[5] | |
| Canada – Ontario | 0.01[1]<br>0.002[5] | |
| Canada – Québec | 0.025[1,12] | |
| Denmark | 0.005[1,12] | 0.01[1,12] |
| Finland | 0.004[11] | |
| France | 0.05[1,12] | |
| Germany – **AGS** | 0.001[4,8]<br>0.00016[5,9] | 0.008[3,4,8] |
| Hungary | 0.015[1,12] | 0.015[1,10]<br>0.06[1,12] |
| Ireland | 0.01[1,12]<br>0.002[5,12] | |
| Israel | 0.01[1]<br>0.005[2] | |
| Japan | 0.05[1,12] | |
| Japan – **JSOH** | 0.05[1] | |
| Latvia | 0.01[1] | 0.05[3] |
| New Zealand | 0.01[4]<br>0.002[5] | |
| People's Republic of China | 0.01[1] | 0.02[3] |
| Poland | 0.01[1,15]<br>0.002[5] | |
| Romania | 0.05[1] | |
| Singapore | 0.01[1,12,13]<br>0.002[1,12,14] | |
| South Korea | 0.01[1]<br>0.002[5] | |
| Spain | 0.01[4,12]<br>0.002[5,12] | |
| Sweden | 0.02[1,12]<br>0.005[5] | |
| Switzerland | 0.015[4,11]<br>0.004[5] | |
| USA – **NIOSH** | 0.01[6,7] | |
| USA – **OSHA** | 0.005[1] | |
| UK | 0.025[1,13] | |

**TABLE 3:**
Exposure standards for cadmium and cadmium compounds, as Cd, from around the world

1 Total dust.
2 Women.
3 15 minutes average value.
4 Inhalable aerosol/fraction.
5 Respirable aerosol/fraction.
6 Lowest feasible concentration.
7 Dust and fume.
8 Workplace exposure concentration corresponding to the proposed **tolerable cancer risk**.
9 Workplace exposure concentration corresponding to the proposed preliminary **acceptable cancer risk**.
10 Except CdO, CdCl2, CdF2.
11 **TRK** value (based on technical feasibility).
12 Except CdO fume and CdS pigments.
13 Elemental.
14 Compounds.
15 Inorganic compounds.

It is noted that the only organisations from whom we obtained information as to how and why they set occupational exposures standards on cadmium and cadmium compounds were **DECOS**, European Parliamentary Research Service [**EPRS**], SCOEL, ACGIH® and Safe Work Australia.

## 5.2 DECOS

The Dutch Expert Committee on Occupational Standards [DECOS] review of cadmium and inorganic cadmium compounds recommended a health-based biological limit value [BLV] in urine of 2µg cadmium/g creatinine, in combination with a health-based occupational exposure limit [**HBR-OEL**] for cadmium of 4µg/m$^3$ [respirable fraction], as an eight-hour weighed average concentration (DECOS, 2019). This recommendation is a re-statement of DECOS 2013 advice (DECOS, 2013), and specifically rejects the recommendation in the latest SCOEL opinion for a 'stand-alone' 8-hour TWA of 1µg cadmium/m$^3$ [inhalable fraction] (SCOEL, 2017).

Rationale:

> "In 2010, the SCOEL has recommended a BLV in urine of 2µg cadmium/g creatinine to protect workers against systemic cadmium toxicity, in combination with a recommended OEL in the air of 4µg cadmium/m$^3$ (respirable fraction) to protect against local effects in the lungs (SCOEL, 2010). The Committee has agreed with this recommendation, as was outlined in an advisory letter in 2013 (DECOS, 2013). Recently, the SCOEL has recommended an additional OEL in the air that fundamentally differs from the previous one. This new recommendation involves an advisory value of 1µg cadmium/m$^3$ (inhalable fraction) to protect against systemic effects, which is to be applied independently of the BLV. For its present recommendation, the Committee has only evaluated the most recent evaluation by the SCOEL, involving a value of 1µg cadmium/m$^3$ (inhalable fraction).
>
> "SCOEL has based its recommended OEL of 1µg/m$^3$ (inhalable fraction) on a publication of Thun et al. (1991), in which publications on adverse health effects after occupational exposure to cadmium are reviewed. With respect to the most critical effect (ie the induction of kidney dysfunction), Thun et al. (1991) summarises data on the prevalence of tubular proteinuria and the exposure to cadmium from several occupational cohorts (Kjellstrom (1977); Jarup et al (1988); Elinder et al. (1985); Falck et al. (1983); Thun et al. (1989); Mason et al. (1988); Ellis et al. (1985)). The recommended OEL of the SCOEL is related to both cadmium fumes and cadmium dusts (generally with unknown particle size distribution), as has been reported in the original publications. Since all inhaled cadmium is assumed to contribute to the critical effect, the OEL recommended by the SCOEL relates to the inhalable fraction. The Committee notes that the studies underlying the OEL recommended by the SCOEL show methodological differences and have several limitations. They vary in the criteria used to define kidney dysfunction, have included a limited number of individuals (particularly at exposure levels below 500µg/m$^3$*year; range 125–34) and prevalence cases (2–3/exposure category), and for several studies it is not clear which fraction of cadmium dust was measured. The Committee is therefore of the opinion that the study of Thun et al. (1991) is not a suitable starting point for deriving an advisory value." (References cited in DECOS, 2019).

The DECOS review of cadmium and inorganic cadmium compounds also recommended that a **"skin"** notation was not indicated, due to the low rate of skin absorption reported (DECOS, 2019).

## 5.3 EPRS

The European Parliamentary Research Service [EPRS] appraisal of the European Commission's impact assessment on the proposed amendment to the Carcinogens and Mutagens Directive 2004/37/EC that would establish a Binding OEL [**BOEL**] for cadmium and inorganic cadmium compounds included a review of the SCOEL 2017 recommendations (EPRS, 2018).

The EPRS concluded that the preferred BOEL was an 8-hour TWA of 1µg cadmium/m$^3$ [inhalable dust fraction] to be set after a 7-year transitional period with an OEL of 4µg cadmium/m$^3$ [inhalable dust fraction] (EPRS, 2018).

The EPRS noted that the Swedish Chemicals Agency reported a factor of 2–2.5 had been used to divide a measured inhalable fraction to obtain an estimate for the respirable fraction (**KemI**, 2013, cited in EPRS, 2018), whereas other conversion factors of 4–6 have been proposed (EPRS, 2018). EPRS noted that a BOEL of 1µg cadmium/m$^3$ [inhalable dust fraction] would be equivalent of 0.4µg cadmium/m$^3$ [respirable dust fraction] using a factor of 2.5 [0.2µg cadmium/m$^3$ *respirable dust fraction* using a factor of 5].

## 5.4 SCOEL

The EU Scientific Committee on Occupational Exposure Limits [SCOEL] opinion on cadmium and its inorganic compounds recommended an acceptable biological limit value [BLV] of 2µg cadmium/g creatinine in the urine to protect workers from the systemic toxicity of cadmium, primarily targeting kidneys and bones; and, in conjunction with the BLV an 8-hour TWA concentration of 4µg cadmium/m$^3$ [respirable fraction] to protect workers against local respiratory effects, including emphysema and lung cancer (SCOEL, 2017). In addition, SCOEL also recommended an 8-hour TWA concentration of 1µg cadmium/m$^3$ [inhalable fraction] that would protect workers against local respiratory effects and against systemic effects [nephrotoxicity] if it was not connected to a biological exposure index. SCOEL noted that 4µg cadmium/m$^3$ was estimated to increase the incidence of nephrotoxic effects by 1% over a 40-year working life, while the **LOAEC** was 2.5–10µg cadmium/m$^3$ (SCOEL, 2017).

Rationale:

> "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 (12.5µg/m$^3$).
> - 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 (eg oxidative stress), for which a threshold can be identified (Category C, Bolt and Huici-Montagud, 2008).
> - A threshold of 1000µg/m$^3$ x years (or 25µg/m$^3$ 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 500µg Cd/$m^3$ x years, corresponding to 40 years exposure at a level of 12.5µg Cd/$m^3$ (LOAEL). Applying an extrapolation factor of 3 (LOAEL to NOAEL; Leung, 2002) leads to a value of 4µg Cd/$m^3$.

"An 8h-TWA (8h time-weighted average) of 4µg/$m^3$ (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 4µg 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 4µg/$m^3$ (not linked with a BLV) would not appear being equally protective against the systemic nephrotoxixity [sic] 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 100-400µg/$m^3$ x years. For working-life exposure of 40 years, this equals an LOAEC range of 2.5–10µg/$m^3$. AGS (BAuA 2014) has deduced that nephrotoxic effects could arise in about 1% of the workforce after 40 years of airborne exposure to 4µg Cd/$m^3$. Accordingly, an OEL (8h-TWA, not connected with biological monitoring) for Cd and its inorganic compounds should be 1µg/$m^3$." (References cited in SCOEL, 2017).

The SCOEL opinion on cadmium and its inorganic compounds noted in regards cancer risk, that:

"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 [sic] 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 1µg Cd/$m^3$, and of 4:1000 at 1.6µg 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 0.02µg Cd/$m^3$ (continous [sic] environmental exposure, corresponding to 1:1000 at 2µg Cd/$m^3$) for the general population in the State of Texas." (References cited in SCOEL, 2017).

## 5.5 ACGIH®

The ACGIH® review of cadmium and compounds concluded with recommendations that a **TLV-TWA** of 0.01**mg** cadmium/$m^3$ [total particulate] for occupational exposure to cadmium and its compounds, would minimise the potential for development of preclinical kidney dysfunction [urinary α2-microglobulin excretion]; and, a TLV-TWA of 0.002mg cadmium/$m^3$ [respirable particulate fraction], would minimise the potential for lower respiratory tract accumulation of a cadmium burden that could induce lung cancer. The **TLV®**s should also significantly reduce the potential for metal fume fever in cadmium-exposed workers (ACGIH®, 2001).

The ACGIH® review of cadmium and compounds noted that an A2, Suspected Human Carcinogen, notation was assigned, based on rat inhalation studies of cadmium that produced lung carcinomas and the reports of the occurrence of lung cancer in cadmium workers. Sufficient data were not available to recommend **Skin** or **SEN** notations or a **TLV-STEL**, but **BEI**s had been recommended (ACGIH®, 2001).

## 5.6 Safe Work Australia

Safe Work Australia proposed an 8-h TWA of 1μg/$m^3$ to protect for effects on the kidneys in exposed workers.

In their review, they say, "The critical health effects include systemic long-term effects on the kidneys and lung cancer. Carcinogenic effects were reported in rats after multiple routes of exposure. An epidemiological study found no excess cancer incidence in workers exposed to an estimated cumulative exposure of cadmium corresponding to a 40-year TWA of 21 to 40mg/$m^3$. Cadmium oxide is acutely toxic in rats with a reported inhalation LC50 of 25mg/$m^3$. Acute, high exposures *via* inhalation are reported to be intensely irritating and to result in severe respiratory effects in humans including metal fume fever (ACGIH, 2018; DFG, 2006).

"A study reviewing published data has presented a cumulative life-time lowest-effect exposure of 0.1 to 0.4mg/$m^3$ per year for kidney effects in workers (SCOEL, 2017). This value equates to an LOAEC of 0.0025mg/$m^3$. Applying an uncertainty factor of 2 to account for lack of NOAEC derives a TWA of 1μg/$m^3$. This TWA is considered sufficiently low to protect for adverse effects in kidneys and reduce the risk of cancer in exposed workers (SCOEL, 2017; HCTON, 2013)". (Safe Work Australia, 2019).

# 6.0 Analytical methods for the assessment of airborne cadmium and cadmium compounds

# A common method to measure cadmium exposure is using a modification of NIOSH Method 7303, Issue 1 (NIOSH, 2003).

Using this method, an air sample is collected onto a cellulose ester filter membrane using a sampling train set at a flow rate of 2 litres of air per minute. The sample is analysed by inductively coupled plasma – atomic emission spectroscopy (ICP-AES). The limit of quantitation of this modified method has been quoted as 0.3µg (or 0.0003mg) of cadmium per sample.

Collecting an air sample for 8 hours at a flow rate of 2**L/min** would allow a minimum concentration of less than 0.0003mg of cadmium per cubic metre of air to be measured based on the quoted limit of quantitation.

# 7.0
# Discussion

# WorkSafe's WES for cadmium and cadmium compounds, as Cd have been unchanged since adoption in 1994.

The toxicological database reviewed above indicates that cadmium and cadmium compounds are locally and systemically toxic to humans, causing respiratory tract irritation/corrosion, emphysema, and lung cancer; and systemically, renal dysfunction and bone effects. Cadmium and several cadmium compounds are confirmed human carcinogens.

Based on the aforementioned documentation, informed by the conclusions of the DECOS, EPRS, SCOEL, ACGIH® and Safe Work Australia reviews, and in particular the findings listed below, WorkSafe considers its current WES-TWA of 0.01mg/m$^3$ for inhalable fraction of cadmium and cadmium compounds, as Cd, to be inadequate to manage health risks from possible workplace exposure:

- Cadmium is a cumulative toxicant and potentially exposed workers are also exposed to cadmium through environmental (food, water and air) and lifestyle (eg tobacco) sources. Therefore, measurements of cadmium in biological matrices of potentially exposed workers are essential to assess total body burden and current health status. About 50% of the cadmium body burden is found in the kidneys, particularly the proximal tubules, and tubular dysfunction is the most sensitive marker of cadmium systemic toxicity.
- Cadmium and cadmium compounds cause lung cancer in humans. Positive associations have also been observed for cancer of the kidney and of the prostate (IARC, 2012).
- IARC concluded that there is *convincing* evidence, that cadmium: causes disturbances of DNA-repair and tumour-suppressor proteins, which lead to chromosomal damage and genomic instability; and, changes in DNA-methylation patterns and interactions with signal-transduction processes, which may contribute to the deregulation of cell growth (IARC, 2012).
- Linear risk extrapolations for additional cancers expected from cadmium inhalation have been reported as 1:1000 at 1µg Cd/m$^3$ (US EPA, 1994); as 4:1000 at 1.6µg Cd/m$^3$ (BauA 2014); and, as 1:1000 at 2µg Cd/m$^3$ continuous environmental exposure for the general population in the State of Texas (Haney, 2016) (References cited in SCOEL, 2017).
- DECOS and SCOEL recommended BLVs to protect workers against systemic cadmium toxicity with OELs to protect workers against local respiratory effects, including lung cancer. The DECOS recommendation stated that the BLV and OEL should be used together as they were designed to address different health risks posed by inhaled cadmium.
- DECOS recommended a BLV of 2µg cadmium/g creatinine in urine; and, an 8-hour HBR-OEL of 4µg cadmium/m$^3$ [respirable fraction] (DECOS, 2019). (Note that these recommendations were based on the SCOEL 2010 opinion, not the current SCOEL 2017 opinion.)

- SCOEL in 2017 recommended a BLV of 2µg cadmium/g creatinine in urine as a LOAEL for renal effects which is relevant for protecting workers; and, in conjunction with the BLV an 8-hour TWA of 4µg cadmium/$m^3$ (respirable fraction) to protect workers against local respiratory effects. In addition, SCOEL also recommended an 8-hour TWA of 1µg cadmium/$m^3$ (inhalable fraction) as a 'stand-alone' OEL that would protect workers against local respiratory effects and against nephrotoxicity. SCOEL noted that 4µg cadmium/$m^3$ was estimated to increase the incidence of nephrotoxic effects by 1% over a 40-year working life, while the LOAEC was 2.5–10µg cadmium/$m^3$ (SCOEL, 2017).
- The DECOS 2019 recommendation noted the SCOEL 2017 'stand-alone' OEL, but considered the underlying study (Thun et al., 1991 cited in DECOS, 2019) to be unsuitable for deriving an advisory value (DECOS, 2019).
- Safe Work Australia derived their WES based on a study reviewing published data that presented a cumulative life-time lowest-effect exposure of 0.1 to 0.4mg/$m^3$ per year for kidney effects in workers (SCOEL, 2017). This value equates to an LOAEC of 0.0025mg/$m^3$. Applying an uncertainty factor of 2 to account for lack of NOAEC derives a TWA of 1µg/$m^3$. This TWA is considered sufficiently low to protect for adverse effects in kidneys and reduce the risk of cancer in exposed workers (SCOEL, 2017; HCTON, 2013). (Safe Work Australia, 2019).
- The EPRS noted that some debate exists over the relative merits of biomarker measurements *vs* air measurements to reliably assess the long-term health effects of low-level cadmium exposures (EPRS, 2018). Such considerations indicate the importance of a combined approach using both WES-TWA and BEIs to protect worker health.
- The proposed WES-TWA for respirable fraction of cadmium is intended to protect exposed workers from local toxic effects: irritation, lung cancer and emphysema.
- The proposed WES-TWA for respirable fraction of cadmium is intended to protect exposed workers from systemic effects with the most sensitive endpoint being nephrotoxicity, on the premise that contributions to body burden is likely to be greater from respirable than for the inhalable fraction.
- The WES-TWA for respirable fraction should ideally be supported by a robust BEI to ensure that body burdens of cadmium in workers remain at levels not associated with systemic toxicity from all sources of cadmium exposure.
- A *skin notation* is not justified for cadmium, due to the low rate of dermal absorption reported.
- Available information indicates that cadmium is not a sensitiser, and a ***sen*** *notation* is not warranted.

# 8.0
# Recommendations

# WorkSafe considers its current WES-TWA of 0.01mg/m$^3$ for inhalable fraction of cadmium and cadmium compounds, as Cd to be inadequate to protect workers exposed in the workplace, based on current knowledge.

It is proposed that WorkSafe:

1. Adopt the recommendation by DECOS and SCOEL for assessing exposure to cadmium using both the WES and BEI

– As such, adopt a WES-TWA for cadmium and cadmium compounds of 0.004mg cadmium/m$^3$ (respirable fraction) to be assessed in conjunction with a BEI of 2µg cadmium/g creatinine in the urine.

Noting that the proposed WES-TWAs for inhalable and respirable fractions of cadmium may not eliminate all risk, due to the uncertainty as to the nephrotoxic threshold for cadmium and the potential for non-occupational exposures. Therefore, workplace exposures should be minimised so far as is reasonably practicable.

# Appendices

**IN THIS SECTION:**

## Appendix 1: Glossary

| TERM | MEANING |
|---|---|
| 95%CI | 95% Confidence Interval. |
| AAP | Alanine aminopeptidase. |
| Acceptable (cancer) risk | EU criterion: 4 extra cases in a population of 10,000 until 2013; 4 extra cases in a population of 100,000 after 2013 (see Tolerable risk). |
| ACGIH® | The American Conference of Governmental Industrial Hygienists (ACGIH®) is a member-based organisation, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and work practice guides. |
| ADME | Absorption, Distribution, Metabolism and Excretion. |
| AGS | Ausschuss für Gefahrstoffe (Committee for Hazardous Substances) is a consultative body of the German Federal Ministry of Labour and Social Affairs on issues of the Ordinance on Hazardous Substances. Administered by the BAuA. |
| As | Arsenic. |
| ATSDR | Agency for Toxic Substances and Disease Registry is a federal public health agency of the US Department of Health and Human Services. |
| ß2M | Beta-2-Microglobulin. |
| BAuA/BauA | Bundesanstalt für Arbeitsschtz und Arbeitsmedzinin (German Federal Institute for Occupational Safety and Health). |
| BEI | Biological Exposure Index. |
| BLV | Biological Limit Value. |
| BOEL | Binding Occupational Exposure Limit – EU term. |
| Cd | Cadmium. |
| Cd-B | Cadmium in blood. |
| CdO | Cadmium oxide. |
| Cd-U | Cadmium in urine. |
| DECOS | Dutch Expert Committee on Occupational Standards a Committee [DECOS] of the Health Council of the Netherlands. The latter was established in 1902 as an independent scientific advisory body with a remit: "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act). |
| DFG | Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance. |
| DLCO | Diffusing Capacity of the Lungs for Carbon Monoxide. |
| DNA | Deoxyribonucleic acid. |
| EPA | The New Zealand Environmental Protection Authority. |
| EPRS | European Parliamentary Research Service. |
| FEV1 | Forced expiratory volume in 1 second. |
| FEV1/FVC | Ratio of the forced expiratory volume in 1 second to the full, forced vital capacity. The ratio can be expressed as FEV1%. |
| □GT | Gamma-glutamyltranspeptidase. |
| GI | Gastrointestinal. |
| HBR-OEL | Health-based recommended exposure limit. European Union term. |

| TERM | MEANING |
|---|---|
| HC | Human Complex (protein). |
| HMW | High Molecular Weight. |
| HSNO | Hazardous Substances and New Organisms Act 1996, New Zealand. |
| IARC | The International Agency for Research on Cancer – an agency of the World Health Organisation. |
| IFA | Institut für Arbeitsschutz der Deutschen Gestzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance). |
| Inhalable fraction | Inhalable particulate fraction is that fraction of dust that can be breathed into the nose or mouth. Particulate size: mostly < 100µm, 50% cut point. For sampling purposes the inhalable dust is to be collected according to the method set out in AS 3640-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Inhalable Dust (Standards Australia, 2009b). (*cf.* Respirable fraction) (Also referred to as: inhalable aerosol; inhalable particulate matter) |
| JSOH | Japan Society for Occupational Health. |
| KCO | Carbon monoxide transfer coefficient. (Lung function test). |
| KEMI/KemI | Kemikalieinspektionen (Swedish Chemicals Inspectorate). |
| L/min | Litres per minute. |
| LMW | Low Molecular Weight. |
| LOAEC | Lowest Observed Adverse Effect Concentration. |
| LOAEL | Lowest Observed Adverse Effect Level. |
| LOEL | Lowest Observed Effect Level. |
| µg | Microgram or one millionth of a gram. |
| µg/g | Micrograms of substance per gram. |
| µg/m$^3$ | Micrograms of substance per cubic metre of air. |
| mg | Milligram or one thousandth of a gram. |
| mg/kg | Milligrams per kilogram. |
| mg/kg/d | Milligrams per kilogram per day. |
| mg/m$^3$ | Milligrams of substance per cubic metre of air. |
| Ni-Cd | Nickel-Cadmium. |
| NAG | N-acetyl-beta-D-glucosaminidase. |
| NIOSH | The National Institute for Occupational Safety and Health is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. |
| NOAEL | No Observed Adverse Effect Level. |
| NTP | National Toxicology Program, US Department of Health and Human Services. |
| OEL | Occupational Exposure Limit (equivalent to a WES). |
| OSHA | Occupational Safety and Health Administration, US Department of Labor. |
| PARP-1 | Poly [ADP-ribose] polymerase 1 enzyme. |
| $r^2$/$R^2$ | Coefficient of determination |
| RBP | Retinol-binding protein. |

| TERM | MEANING |
|---|---|
| **Respirable fraction** | Respirable particulate fraction is that fraction of inhaled airborne particles that can penetrate beyond the terminal bronchioles into the gas-exchange region of the lungs (alveoli). Particulate size: mostly <4µm, 50% cut point. For sampling purposes the respirable dust samples are to be collected according to the method set out in the Standards Australia publication AS 2985-2009: Workplace Atmospheres – Method for Sampling and Gravimetric Determination of Respirable Dust (Standards Australia, 2009a). (*cf.* Inhalable fraction) (Also referred to as: respirable aerosol; respirable particulate matter) |
| **RoC** | Report on carcinogens. |
| **ROS** | Reactive Oxygen Species. |
| **RV** | Residual Volume. |
| **SCOEL** | The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive. |
| **sen** | A substance that can 'sensitise' the respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term. |
| **SEN** | A notation indicating the substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term. |
| **skin** | Skin absorption – applicable to a substance that is capable of being significantly absorbed into the body through contact with the skin. A WorkSafe term. |
| **Skin** | A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term. |
| **SMR** | Standardised Mortality Ratio (SMR) is a measure of the strength or association between exposure and mortality; a form of Relative Risk (RR) in which the outcome is death.<br>The SMR is the ratio of the number of deaths (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of deaths that would be expected if the study population had the same rate of mortality as the general population (the standard).<br>By convention, the figure is usually multiplied by 100 (an SMR of 200 corresponds to a RR of 2.0). *A value greater than 100/1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or confounding). (WHEC, 2017). |
| **Tiffeneau ratio** | The Tiffeneau ratio, also called Tiffeneau-Pinelli index or FEV1/FVC ratio (qv), is a calculated ratio used in the diagnosis of obstructive and restrictive lung disease. |
| **TLC** | Total Lung Capacity. |
| **TLV®** | Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term. Please see the Statement of Position Regarding the TLVs® and BEIs® and Policy Statement on the Uses of TLVs® and BEIs® |
| **TLV-STEL** | TLV-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term. |
| **TLV-TWA** | TLV – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term. |
| **Tolerable (cancer) risk** | EU criterion: 4 extra cases in a population of 1,000 (see Acceptable risk). |
| **TRK** | Technische Richtkonzentration (technical guidance concentration level). |
| **WES** | Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term. |

| TERM | MEANING |
|---|---|
| **WES-STEL** | The 15-minute time-weighted average exposure standard. Applies to any 15-minute period in the working day and is designed to protect the worker against adverse effects of irritation, chronic or irreversible tissue change, or narcosis that may increase the likelihood of accidents. The WES-STEL is not an alternative to the WES-TWA; both the short-term and time-weighted average exposures apply. Exposures at concentrations between the WES-TWA and the WES-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range. A WorkSafe term. |
| **WES-TWA** | The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term. |
| **WHO** | World Health Organisation. |
| **XPA** | *Xeroderma pigmentosum* complementation group A protein. |
| **Zn** | Zinc. |

## Appendix 2: HSNO health-related hazardous substance classifications

This is the full list of all health-related hazardous substances classifications that are listed by the NZ EPA, including those that apply to this substance.

| CLASSIFICATION CODE | MEANING |
|---|---|
| **Acutely toxic** | |
| 6.1A | Substances that are acutely toxic – Fatal |
| 6.1B | Substances that are acutely toxic – Fatal |
| 6.1C | Substances that are acutely toxic – Toxic |
| 6.1D | Substances that are acutely toxic – Harmful |
| 6.1E | Substances that are acutely toxic – May be harmful, aspiration hazard |
| **Skin irritant** | |
| 6.3A | Substances that are irritating to the skin |
| 6.3B | Substances that are mildly irritating to the skin |
| **Eye irritant** | |
| 6.4A | Substances that are irritating to the eye |
| **Sensitisation** | |
| 6.5A | Substances that are respiratory sensitisers |
| 6.5B | Substances that are contact sensitisers |
| **Mutagens** | |
| 6.6A | Substances that are known or presumed human mutagens |
| 6.6B | Substances that are suspected human mutagens |
| **Carcinogens** | |
| 6.7A | Substances that are known or presumed human carcinogens |
| 6.7B | Substances that are suspected human carcinogens |
| **Reproductive/developmental toxicants** | |
| 6.8A | Substances that are known or presumed human reproductive or developmental toxicants |
| 6.8B | Substances that are suspected human reproductive or developmental toxicants |
| 6.8C | Substances that produce toxic human reproductive or developmental effects on or via lactation |
| **Target organ toxicants** | |
| 6.9A | Substances that are toxic to human target organs or systems |
| 6.9B | Substances that are harmful to human target organs or systems |
| **Skin corrosive** | |
| 8.2A | Substances that are corrosive to dermal tissue (UN PGI) |
| 8.2B | Substances that are corrosive to dermal tissue (UN PGII) |
| 8.2C | Substances that are corrosive to dermal tissue (UN PGIII) |
| **Eye corrosive** | |
| 8.3A | Substances that are corrosive to ocular tissue |

Source: www.epa.govt.nz/industry-areas/hazardous-substances/rules-for-hazardous-substances/hazardous-substances-classification-codes

## Appendix 3: References

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