Biological Exposure Index (BEI) review

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

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New Zealand Government

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1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers changes to the Biological Exposure Indices (**BEI**) for cadmium and cadmium compounds (as **Cd**).

Biological monitoring is an assessment of overall systemic exposure to chemicals by measurement of the chemicals, their metabolites, or conjugates in blood, urine or breath.

The review considers BEIs from other jurisdictions/organisations around the world and includes a recommendation to change the WorkSafe BEI for cadmium and cadmium compounds (as Cd), which is currently set at BEIs of 5**µg/L** (blood) and 5**µg/g** (creatinine), as published in the special guide *Workplace Exposure Standards and Biological Exposure Indices*, 11th Edition (WorkSafe, 2019).

It is noted that only the BEIs which have a documented rationale for why they have been set at that level have been considered for this review. The BEIs considered are from the:

- American Conference of Governmental Industrial Hygienists (**ACGIH**®)
- Scientific Committee on Occupational Exposure Limits (**SCOEL**) of Europe
- Dutch Expert Committee on Occupational Standards (**DECOS**) of The Netherlands, and
- Deutsche Forschungsgemeinschaft (**DFG**) of Germany.

It should be noted that WorkSafe is proposing to:

1. Adopt a WES-TWA for airborne cadmium and cadmium compounds of 0.004**mg** cadmium/m^3 [**respirable fraction**] to be assessed in conjunction with a BEI of 2**µg** cadmium/g creatinine in the urine.

Discussion on cadmium exposures in New Zealand and the health effects of cadmium are described in the WorkSafe Workplace Exposure Standards review of cadmium and cadmium compounds (2020) included in this consultation period.

Cadmium in blood and urine can be analysed in either New Zealand or Australia.

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

2.0 Exposure standards

IN THIS SECTION:

The WorkSafe BEI for cadmium has remained unchanged since 2002.

Table 1 below shows the current WorkSafe, ACGIH®, DECOS, DFG and SCOEL BEI values for cadmium.

JURISDICTION OR ADVISORY BODY	BEI VALUE
WorkSafe New Zealand (2001)	5µg/L (blood) 5µg/g (creatinine)
ACGIH® (2016)	5µg/L (blood) 5µg/g (creatinine)
DECOS (2019)	2µg/g (creatinine)
DFG (2016)	1µg/L (blood) 0.8µg/L (urine)
SCOEL (2017)	2µg/g (creatinine in urine)

TABLE 1:
BEI values adopted by WorkSafe, ACGIH®, DECOS, DFG and SCOEL

2.1 ACGIH®

The ACGIH® 2016 review of cadmium and inorganic compounds recommended BEIs® of 5µg/g creatinine and 5µg/L in blood. They state that:

- The BEI® for cadmium is health-based.
- The urine BEI® intends to protect against renal dysfunction in nearly all workers.
- Most studies have indicated an increase in excretion of specific proteins in urine when the cadmium excretion exceeded the BEI® for **Cd-U** of 5µg/g of creatinine. Although these changes were subclinical and often within the range of normal values, there was evidence that they may have been followed by deterioration of renal function (tubular proteinuria) that may have persisted after cessation of exposure.
- An exposed worker's Cd levels may take weeks, months or years to approach steady state. Health professionals should note that if sequential blood and urine samples taken early in a worker's exposure career show a marked increase, an over exposure situation might be developing and must be addressed despite the values being below the BEI®.
- Measurement of cadmium in urine is the most widely used biological measure of chronic exposure to cadmium.
- Once the BEI® of Cd-U of 5µg Cd/g creatinine has been reached. The exposure should be drastically reduced or ceased and reduction in Cd-U concentration should be closely monitored. As this stage, kidney dysfunction should also be monitored.

2.2 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). 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). Their rationale states:

> "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 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."
>
> "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 (5µg 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 (2µg Cd/g creatinine) is a LOAEL for renal effects which is relevant for protecting workers after their occupational career.

- Other points of departure for systemic effects are 3µg Cd/g creatinine as a LOAEL for respiratory effects in workers and 3µg/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.

In addition SCOEL say: "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 50µg/L have been noted (Roels *et al*. 1981). By contrast, 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)".

"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 2–4µg Cd/24 hour level (approximately 1–3µg/g creatinine). Significant correlations between total cadmium exposure, urinary cadmium levels and renal effects have been found in environmentally exposed populations." (SCOEL, 2017).

2.3 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 4**µg/m³** [respirable fraction], as an eight-hour weighed average concentration (DECOS, 2019).

The DECOS Committee indicated that: "it supported the approach that was described by the SCOEL in 2010 for deriving health based advisory values for cadmium and inorganic compounds. The Committee noted that the kidneys are the most critical target organs for cadmium-induced toxicity, that is related to the systemic cadmium burden. After evaluation of the available data, the Committee supported the BLV of 2µg cadmium/g creatinine in the urine that was recommended by SCOEL. The Committee also acknowledged that the BLV did not provide sufficient protection for local effects after exposure by inhalation, necessitating the derivation of an advisory value in air. In line with SCOEL, the Committee considered the reported lung function effects as the most suitable starting point and concluded that a health-based recommended occupational exposure limit (HBROEL) of 4µg cadmium/m³ was appropriate (Note: the Committee did not specify that this value related to the respirable fraction). The Committee confirmed that this HBROEL would also prevent genotoxic and potential carcinogenic effects" (DECOS, 2019).

2.4 DFG

In its 2016 addendum to *Cadmium and its inorganic compounds*, the DFG established a **BAR** of 1µg/L cadmium in blood, and 0.8µg/L cadmium in urine. Both values are for non-smokers. The BAR describes the background level for persons of working age who are not occupationally exposed to cadmium. The DFG state in their review that:

Cadmium in blood

"In accordance with the BAR concept, the evaluation uses the results for the non-smoking population of working age not occupationally exposed to chemical substances. The 95th percentile of this sub-collective (in the case of sufficient data if possible the upper limit of the **95% confidence interval**) serves as the basis for the BAR. The Human Biomonitoring Commission evaluated a reference value for cadmium of 1.0µg/l blood for adults (non-smokers, 25–69 years old) using the database of the environmental survey from 1990/92 (Becker *et al*. 2002 b; Krause *et al*. 1996) (UBA 1998). In the re-evaluation of this value using the database of the environmental survey from 1998 (Becker *et al*. 2002 a, b) noticeable changes in the cadmium levels in blood compared with in the environmental survey from 1990–1992 were not found, so that the reference value of the Human Biomonitoring Commission for cadmium of 1.0µg/l blood for adults (non-smokers, now 18–69 years old) has been retained (UBA 2003; Wilhelm *et al*. 2004).

"On this basis a BAR has been set for the non-smoking population of 1µg cadmium/l blood for adults. This value covers also the slightly higher concentrations of cadmium in blood, compared with the concentrations found in men, of women who have never smoked.

"The sampling time is not fixed.

"As described above, the cadmium concentrations in the blood of smokers are markedly higher than in non-smokers. In the environmental survey from 1998 (Becker *et al*. 2002 a, b) a median cadmium concentration of 1.17µg/l blood and a 95th percentile of 3.32µg/l blood were found in smokers. In heavy smokers (>20 cigarettes/day) these values are increased to 1.68µg and 4.09µg cadmium/l blood." (References cited in DFG, 2016).

Cadmium in urine

"In accordance with the conditions described in Section 19.2.2 that also apply for the BAR concept, the Human Biomonitoring Commission evaluated an initial reference value for cadmium of 1.5µg/l urine for adults (non-smokers, 25–69 years old) (UBA 1998) using the database of the environmental survey from 1990/92 (Becker *et al*. 2002 b; Krause *et al*. 1996). In the re-evaluation of this value using the database of the environmental survey from 1998 (Becker *et al*. 2002 b, 2003) the reference value was lowered to 0.8µg/l urine for adults (non-smokers, now 18–69 years old) as a result of the above-mentioned decrease in exposure (UBA 2003; Wilhelm *et al*. 2004). The data available from the two German Environmental Surveys from 1990–1992 and 1998 (Becker *et al*. 2002 b, 2003; Krause *et al*. 1996) suggest that when the first reference value was set, much greater analytical uncertainties were assumed and taken into consideration than in the re-evaluation. It cannot, therefore, be deduced from the data with certainty that the background exposure in the period of time covered was really reduced by almost half.

"Whether and to what extent the reduction in the levels of cadmium in urine visible between 1990–1992 and 1998 continued after 1998 cannot be answered as there are insufficient data. There is, however, no reason to doubt a dramatic reduction, as the exposure in 1998 in Germany, compared with that in the USA in 2001–2002, had already reached a very low level.

"Therefore a BAR has been set for the non-smoking population on the basis of the environmental survey from 1998 (Becker *et al*. 2002 b, 2003) of 0.8µg cadmium/l urine for adults.

"The sampling time is not fixed.

"As described above, the cadmium concentrations in the urine of smokers are higher than in non-smokers. In the environmental survey from 1998 (Becker *et al*. 2002 b, 2003) generally a 95th percentile of 1.2µg cadmium/l urine was found in smokers. In heavy smokers (>20 cigarettes/day) the 95th percentile is as high as 1.39µg cadmium/l." (References cited in DFG, 2016).

Interpretation

"The BAT value relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3.0g/l. In addition, the Commission considers selecting a more restricted target range of 0.5–2.5g/l for urine samples to be useful, as this further improves the validity of the analyses undertaken. As a rule, in urine samples outside the limits cited above, a repetition of the analysis in normally hydrated test persons is recommended (see Documentation 2010, translated)." (References cited in DFG, 2016).

3.0
Discussion

WorkSafe's BEIs for cadmium and cadmium compounds, as Cd have been unchanged since 2002.

Based on the aforementioned documentation, informed by the conclusions of the DECOS, DFG, SCOEL and ACGIH® reviews, WorkSafe considers its current BEI's of 5µg/L (blood) and 5µg/g (creatinine) for cadmium and cadmium compounds, as Cd, to be inadequate to manage health risks from possible workplace exposure:

- DECOS and SCOEL recommended BLVs to protect workers against systemic cadmium toxicity of the kidneys and bones, 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 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 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.

4.0
Recommendations

WorkSafe considers its BEIs of 5µg/L (blood) and 5µg/g (creatinine) for cadmium and cadmium compounds, as Cd, to be inadequate to manage health risks from possible workplace exposure, 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
2. As such, adopt a BEI of 2µg cadmium/g creatinine in the urine to be assessed in conjunction with a WES-TWA for cadmium and cadmium compounds, as Cd, of 0.004mg cadmium/m^3 [respirable fraction].

Noting that the proposed WES and BEI values 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.
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.
BAR	*Biologische Arbeitsstoff-Referenzwerte*. Describes the background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance. The BAR are based on the 95th percentile without regarding effects on health. It must be taken into account that the reference level of the background exposure can be influenced by such factors as age, sex, social status, residential environment, life style and geographical region. Occupational exposure can be assessed by comparing biomonitoring values in occupationally exposed persons with the BAR. A DFG term.
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-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.
EPRS	European Parliamentary Research Service.
HBR-OEL	Health-based recommended exposure limit. European Union term.
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)
LOAEC	Lowest Observed Adverse Effect Concentration.
µg	Microgram or one millionth of a gram.
µg/g	Micrograms of substance per gram.
µg/L	Microgram or one millionth of a gram per litre.
µg/m^3	Micrograms of substance per cubic metre of air.
mg	Milligram or one thousandth of a gram.
OEL	Occupational Exposure Limit (equivalent to a WES).
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)

TERM	MEANING
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.
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.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.
WHO	World Health Organisation, Geneva.

Appendix 2: References

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