

# Cadmium and inorganic cadmium compounds

Health-based recommendation on occupational exposure limits

To: the State Secretary of Social Affairs en Employment  
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Health Council of the Netherlands



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# samenvatting

In 2013 heeft de Gezondheidsraad een advies uitgebracht over beroepsmatige blootstelling aan cadmium en anorganische cadmium-verbindingen. In dat advies heeft de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) toen aangegeven zich aan te sluiten bij de aanbevelingen die de Scientific Committee on Occupational Exposure Limits (SCOEL) eerder in 2010 heeft gedaan. In 2017 heeft de SCOEL opnieuw een advieswaarde afgeleid. De Commissie GBBS heeft die nieuwe advieswaarde beoordeeld en komt tot de conclusie dat deze wetenschappelijk onvoldoende onderbouwd is. Ze adviseert de staatssecretaris van SZW om uit te blijven gaan van van de Gezondheidsraad.

## **Gezondheidsrisico's cadmium en anorganische cadmiumverbindingen**

Cadmium en anorganische cadmium-verbindingen zijn schadelijk voor de gezondheid. Mensen die op hun werk worden blootgesteld aan cadmium in de lucht kunnen daar ziek van worden. Na inademing hoopt de stof zich op in het lichaam en beschadigt daar onder andere nieren en botten. Ook het eten van met cadmium verontreinigd voedsel en roken draagt bij aan de blootstelling. Daarnaast kan het inademen van cadmium op de werkplek leiden tot longemfyseem en mogelijk tot longkanker.

## **Advieswaarden SCOEL 2010**

In 2010 stelde de SCOEL voor om een biologische limietwaarde te hanteren om te beschermen tegen nierschade als gevolg van het cadmium dat mensen binnen kunnen krijgen (zowel beroepsmatig als niet-beroepsmatig). De SCOEL adviseerde een waarde van 2 micro-

gram ( $\mu\text{g}$ ) cadmium per gram creatinine in de urine.

Daarnaast adviseerde de SCOEL om specifiek ter bescherming tegen de nadelige effecten op de longen, ook een gezondheidkundige advieswaarde voor beroepsmatige blootstelling in de lucht in acht te nemen. De SCOEL ging daarbij uit van de *respirabele fractie*, dat wil zeggen het deel van de in lucht aanwezige deeltjes cadmium dat na inademing kan doordringen tot in de longblaasjes. De gezondheidkundige advieswaarde die de SCOEL daarvoor afleidde is 4 microgram ( $\mu\text{g}$ ) cadmium per kubieke meter ( $\text{m}^3$ ) lucht. Het is de bedoeling dat beide advieswaarden in combinatie met elkaar gebruikt worden.

In 2013 publiceerde de Gezondheidsraad een advies over beroepsmatige blootstelling aan cadmium en anorganische cadmium-verbindingen. De Commissie GBBS van de Gezondheidsraad concludeerde dat de aanbevolen advieswaarden van de SCOEL wetenschappelijk voldoende onderbouwd zijn.



**Advieswaarde SCOEL 2017**

In 2017 heeft de SCOEL opnieuw een advies uitgebracht over cadmium en anorganische cadmiumverbindingen. In dit advies stelt de SCOEL een gezondheidskundige advieswaarde voor van 1 µg cadmium per m<sup>3</sup> lucht. Die waarde geldt voor de *inhaleerbare fractie*, dat wil zeggen het geheel van het in lucht aanwezige cadmium dat kan worden ingeademd via mond en/of neus. Deze nieuwe waarde beschermt volgens de SCOEL ook tegen de nadelige effecten op de nieren en daardoor hoeft deze niet in combinatie met de eerder voorgestelde biologische advieswaarde te worden toegepast. De SCOEL concludeert daarnaast dat een huidnotatie niet nodig is.

**Beoordeling Commissie GBBS**

De Commissie GBBS van de Gezondheidsraad heeft de nieuwe gezondheidskundige advieswaarde van de SCOEL voor cadmium en anorganische cadmiumverbindingen van 1 µg cadmium/m<sup>3</sup> (inhaleerbare fractie) beoordeeld.

Zij komt tot de conclusie dat die wetenschappelijk onvoldoende onderbouwd is. De onderzoeken waar de SCOEL de nieuwe waarde op baseert zijn onderling niet goed te vergelijken en kennen methodologische beperkingen. Zo is nierschade op verschillende manieren gedefinieerd, is het in sommige onderzoeken niet duidelijk welke stoffractie is gemeten en is het aantal onderzochte deelnemers erg beperkt. De commissie benadrukt dat het eerdere advies luidde om een biologische limietwaarde te gebruiken in combinatie met een advieswaarde voor de concentratie in de lucht. Door die combinatie te adviseren wordt er rekening mee gehouden dat mensen ook buiten hun werk blootgesteld kunnen worden. Dit is van belang omdat cadmium zich ophoopt in het lichaam. Het cadmium waar mensen in hun vrije tijd aan zijn blootgesteld is het lichaam nog niet uit als ze weer naar hun werk gaan.

Volgens de commissie zijn er geen aanwijzingen dat cadmium makkelijk kan worden opgenomen via de huid en zo substantieel kan bijdragen aan de totale inwendige blootstelling. Daarom kan de

commissie zich wel vinden in de conclusie van de SCOEL dat een huidnotatie niet nodig is.

**Advies aan de staatssecretaris**

De commissie adviseert om het eerdere advies van de Gezondheidsraad aan te houden, dat uitgaat van een biologische advieswaarde in de urine van 2 µg cadmium/g creatinine in combinatie met een gezondheidskundige advieswaarde in de lucht van 4 µg cadmium/m<sup>3</sup> (respirabele fractie).



# executive summary

In 2013, the Health Council of the Netherlands published an advisory report on occupational exposure to cadmium and inorganic cadmium compounds. In this advisory report, the Dutch Expert Committee on Occupational Safety (DECOS) supported the recommendations that were derived by the Scientific Committee on Occupational Exposure Limits (SCOEL) in 2010. In 2017, the SCOEL derived a new advisory value. The Committee has evaluated this value and concludes that it is scientifically insufficiently substantiated. The Committee therefore recommends the State Secretary to maintain the previous advisory values.

## Cadmium and inorganic cadmium compounds and health risks

Cadmium and inorganic cadmium compounds are harmful to health. Occupational exposure to cadmium in the air can lead to adverse health effects. After inhalation, the substance accumu-

lates in the body and can subsequently damage, amongst others, kidneys and bones. Also, the ingestion of cadmium-contaminated food and smoking contributes to the exposure. In addition, inhaling cadmium in the workplace can lead to emphysema and possibly lung cancer.

### Advisory values of SCOEL 2010

The SCOEL recommended in 2010 to maintain a biological limit value to protect against kidney damage due to exposure to cadmium (both occupational as well as non-occupational). The SCOEL recommended a value of 2 microgram ( $\mu\text{g}$ ) cadmium per gram creatinine in the urine. In addition, the SCOEL recommended a health-based advisory value for occupational exposure in air to specifically protect against adverse effects of the lung. The SCOEL based this value on the *respirable fraction*, which means the fraction of the substance in air that can penetrate into the alveoli. The advisory value derived

by SCOEL is 4 microgram ( $\mu\text{g}$ ) cadmium per cubic metre ( $\text{m}^3$ ) air. Both advisory values should be used combined.

In 2013, the Health Council of the Netherlands published an advisory letter on occupational exposure to cadmium and inorganic cadmium compounds. The Committee concluded that the advisory values proposed by the SCOEL in 2010 were scientifically sufficiently substantiated.

### Advisory values of SCOEL 2017

In 2017, the SCOEL again drafted an advisory report on cadmium and its inorganic compounds. In this report, the SCOEL proposed a health-based advisory value of 1  $\mu\text{g}$  cadmium per  $\text{m}^3$  air. That value relates to the *inhalable fraction*, which is the fraction of the substance in air that can be inhaled through the nose and/or mouth. According to the SCOEL, this value protects also against adverse effects on the kidneys and therefore does not have to be applied in combination with the earlier proposed biological limit value.



In addition, the SCOEL concluded that a skin notation is not warranted.

### **Evaluation of the DECOS**

The DECOS of the Health Council of the Netherlands has evaluated the new SCOEL health-based advisory value of 1 µg cadmium/m<sup>3</sup> (inhalable fraction) for cadmium and inorganic cadmium compounds. This Committee concludes that this value is scientifically insufficiently substantiated. The studies used by the SCOEL for derivation are poorly mutually comparable and have methodological limitations. For instance, damage to the kidneys is defined in different ways, in several studies it is not clear which fraction of cadmium in air was measured, and the number of individuals examined is very limited. The Committee emphasizes that the previous recommendation (a biological limit value in combination with an advisory value in air) takes into account that people can also be exposed non-occupationally to cadmium. This is important as cadmium accumulates in the body.

The Committee notes that there is no indication for a substantial contribution of dermal uptake to systemic exposure to cadmium, and therefore supports the conclusion of the SCOEL that a skin notation is not warranted.

### **Recommendation to the State Secretary**

The Committee recommends to maintain the previous recommendation of the Health Council of the Netherlands, which consists of a biological limit value in the urine of 2 µg cadmium/g creatinine combined with a health-based advisory value in air of 4 µg cadmium/m<sup>3</sup> (respirable fraction).



# 01 scope

## 1.1 Background

At the request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations of the toxicity and carcinogenicity of substances to which man can be exposed in the workplace. The purpose of these evaluations is to recommend on health-based occupational exposure limits. These recommendations serve as a basis in setting legally binding limit values by the Minister.

In this advisory report, a recommendation is made for cadmium and inorganic cadmium compounds. The Committee has previously evaluated the consequences of exposure to cadmium and inorganic cadmium compounds.<sup>1</sup> The Committee based that evaluation on an opinion published in 2010 by the Scientific Committee on Occupational Exposure Limits (SCOEL).<sup>2</sup> Recently, the SCOEL published another report on cadmium and inorganic cadmium compounds.<sup>3</sup> In the present advisory report, the Committee evaluates the most recent SCOEL recommendation.

## 1.2 Committee and procedure

The present document contains the evaluation of the DECOS, hereafter called the Committee. The members of the Committee are listed at the end of this report.

In 2018, the president of the Health Council released a draft of the report for public review. No comments were received.

## 1.3 Data

The Committee's recommendations are based on scientific data, which are publicly available. The Committee evaluated the SCOEL opinion<sup>3</sup> adopted in February 2017, taking into account the references used and those used in the previous evaluations of the SCOEL (2010)<sup>2</sup> and the Health Council (2013)<sup>1</sup>. No additional literature search was performed.

# 02 previous evaluations

In this Chapter, the Committee provides a short summary of its previous advisory letter and the previous evaluations of the SCOEL on cadmium and organic cadmium compounds.<sup>1-3</sup> More details can be found in the respective documents.



## 2.1 Recommendation by the SCOEL (2010)

For its recommendation in 2010<sup>2</sup>, the SCOEL concluded that the kidney is the organ most susceptible to systemic cadmium toxicity following workplace exposure. As cadmium has a very long half-life (10-20 years), the accumulated cadmium body burden rather than the cadmium concentration in the air determines the development of systemic effects. The SCOEL considered cadmium levels in the urine (Cd-U) to be the best parameter for the quantification of the body burden, and the concentration of cadmium in ambient air as a measure for local exposure of the lungs. The SCOEL used dose-response relationships between body burden and systemic effects derived from a large number of epidemiological. Based on these assessments, the SCOEL recommended a biological limit value (BLV) of 2 µg cadmium/g creatinine in the urine to protect workers against systemic cadmium toxicity, particularly effects on kidneys and bones. The SCOEL was of the opinion that this BLV provided insufficient protection against local toxicity resulting from long-term inhalation of cadmium-containing dust and vapours, which can lead to local lung effects such as lung emphysema and potentially lung cancer. Therefore, the SCOEL recommended an additional occupational exposure limit (OEL) for the cadmium concentration in the ambient air. Existing epidemiological studies examining the relationship between cadmium and lung cancer were considered not suitable for derivation of a recommended OEL. The SCOEL considered a study on factory workers exposed to cadmium and the effects on lung function<sup>4</sup> suitable for quantitative hazard assessment,

and derived a recommended OEL of 4 µg Cd/m<sup>3</sup> (respirable fraction). The SCOEL indicated that a health-based OEL of 4 µg cadmium/m<sup>3</sup> would also prevent genotoxicity and potential carcinogenic effects caused by cadmium exposure.

The necessity of a skin notation was not discussed by the SCOEL.

## 2.2 Advisory letter of the Health Council (2013)

In an advisory letter<sup>1</sup>, the Committee has indicated that it supported the approach that was described by the SCOEL in 2010<sup>2</sup> 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 2 µg 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 4 µg cadmium/m<sup>3</sup> 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.





In this advisory letter, the necessity of a skin notation was not discussed by the Committee.

### 2.3 Recommendation by the SCOEL (2017)

In 2017, the European Commission published another recommendation by the SCOEL for cadmium and inorganic cadmium compounds.<sup>3</sup> In this report, the SCOEL argued that the previously recommended OEL of 4 µg cadmium/m<sup>3</sup> (respirable fraction) does not sufficiently protect against nephrotoxicity. The SCOEL referred to evaluations of the World Health Organisation (WHO)<sup>5</sup> and the *Bundesanstalt für Arbeitsschutz und Arbeitsmedizin* (BAuA)<sup>6</sup>, that in turn, referred to a study by Thun et al. (1991)<sup>7</sup>. The SCOEL concluded that nephrotoxicity can occur at a cumulative (lifetime) lowest-effect exposure of 100-400 µg/m<sup>3</sup> x years (which is equivalent to a daily mean exposure of 2.5-10 µg/m<sup>3</sup>, for a 40-year working exposure). The SCOEL also noted that the *Ausschuss für Gefahrstoffe* (AGS) of BAuA<sup>6</sup> deduced from the data of Thun et al. (1991)<sup>7</sup> that after exposure to 4 µg cadmium/m<sup>3</sup> for 40 years, nephrotoxicity could arise in about 1% of the exposed workers (the SCOEL does not specify which fraction this value relates to). The SCOEL subsequently recommended a health-based OEL of 1 µg cadmium/m<sup>3</sup> (inhalable fraction), and noted that this value is independent from biological monitoring.

In addition, the SCOEL stated that a skin notation is not indicated.

## 03 recommendation and conclusion by the Committee

### 3.1 Health-based recommended occupational exposure limit

In 2010, the SCOEL has recommended a BLV in urine of 2 µg cadmium/g creatinine to protect workers against systemic cadmium toxicity, in combination with a recommended OEL in the air of 4 µg cadmium/m<sup>3</sup> (respirable fraction) to protect against local effects in the lungs.<sup>2</sup> The Committee has agreed with this recommendation, as was outlined in an advisory letter in 2013.<sup>1</sup> 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 1 µg cadmium/m<sup>3</sup> (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 1 µg cadmium/m<sup>3</sup> (inhalable fraction).

SCOEL has based its recommended OEL of 1 µg/m<sup>3</sup> (inhalable fraction) on a publication of Thun et al. (1991)<sup>7</sup>, in which publications on adverse health effects after occupational exposure to cadmium are reviewed. With



respect to the most critical effect (i.e., the induction of kidney dysfunction), Thun et al. (1991)<sup>7</sup> summarises data on the prevalence of tubular proteinuria and the exposure to cadmium from several occupational cohorts (Kjellstrom (1977)<sup>8</sup>; Jarup et al (1988)<sup>9</sup>; Elinder et al. (1985)<sup>10</sup>; Falck et al. (1983)<sup>11</sup>; Thun et al. (1989)<sup>12</sup>; Mason et al. (1988)<sup>13</sup>; Ellis et al. (1985)<sup>14</sup>). 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 500  $\mu\text{g}/\text{m}^3\cdot\text{year}$ ; 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)<sup>7</sup> is not a suitable starting point for deriving an advisory value.

The Committee therefore recommends to maintain the previously recommended values, i.e., a health-based BLV in urine of 2  $\mu\text{g}$  cadmium/g creatinine to protect workers against systemic cadmium toxicity, in combination with a health-based advisory value in the air of 4  $\mu\text{g}$

cadmium/ $\text{m}^3$  (respirable fraction) to protect against local effects in the lung. The Committee emphasizes that the previous recommendation takes into account that people can also be non-occupationally exposed to cadmium. This is important as cadmium accumulates in the body.

### 3.2 Skin notation

The SCOEL concludes that for cadmium and its inorganic compounds, a skin notation is not indicated.

Limited data on skin absorption of cadmium are available. The only study allowing quantitative assessment is the in vitro percutaneous absorption study by Wester et al. (1992), using human skin.<sup>15</sup> In this study, 0.5-0.6% of an environmental dose of  $58 \cdot 10^{-5} \mu\text{g}/\text{cm}^2\text{a}$  was absorbed into plasma in 16 hours.

The Committee considers a skin notation warranted when exposure of 2,000  $\text{cm}^2$  of skin (both hands and forearms) to the substance during one hour could result in an absorbed amount exceeding 10% of the amount that can be absorbed via the lungs, on exposure for eight hours to the occupational exposure limit.<sup>16</sup> Considering the limited absorption reported by Wester et al. 1992)<sup>15</sup>, and considering the physico-chemical properties of cadmium, the Committee concludes that a skin notation is not indicated.

<sup>a</sup>  $11.6 \cdot 10^{-2} \mu\text{g}/\text{mL}$  (116 ppb) x 5  $\mu\text{L}$



### 3.3 Conclusions

The Committee recommends the previously proposed a health-based biological limit value in urine of 2 µg cadmium/g creatinine, in combination with a health-based advisory value in the air of 4 µg cadmium/m<sup>3</sup> (respirable fraction).

The Committee further concludes that a skin notation is not indicated.

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## The Committee

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