Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for

Cadmium and its inorganic compounds

ECHA/RAC/A77-O-0000006982-64-01/F

18 March 2021

18 March 2021

ECHA/RAC/A77-O-0000006982-64-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR CADMIUM AND ITS INORGANIC COMPOUNDS

Commission request

The third amendment of the Carcinogens and Mutagens Directive (Dir 2004/37/EC) was published on 5 June 2019[1] and in Recital (17), included the following statement:

> *" ….the Commission should, no later than three years after the date of entry into force of this Directive, assess the option of amending Directive 2004/37/EC by adding provisions on a combination of an airborne occupational exposure limit and a biological limit value for cadmium and its inorganic compounds".*

The European Commission made a request (on 08/01/2020) to ECHA and its Committee for Risk Assessment (RAC) in accordance with the relevant Service Level Agreement[2], to reevaluate, **Cadmium and its inorganic compounds**.

The European Commission has asked ECHA "*to assess the option of an airborne occupational exposure limit (OEL) and/or a combination of an airborne occupational exposure limit and a biological monitoring value for cadmium and its inorganic compounds based on their possible equal effectiveness in protecting the health of workers*".

The request elaborates further:

- *"the scientific evaluation shall include, where appropriate, review of/or proposals for OEL(s), biological limit value(s), health surveillance measures concerning biomonitoring and/or appropriate notations. The existing scientific evaluations by SCOEL are considered to be up to date, unless new scientific information indicates that this is not the case. The key task shall be a comparison of the effectiveness of the health protection of the combination of an OEL and biomonitoring value as proposed in the SCOEL Opinion 336 (2017) compared to the OEL adopted in Directive 2019/983/EU. It shall report on whether these approaches are equally effective in protecting workers' health and, if not equally effective, to report on the reasons why and to recommend biological monitoring values which could be applied separately or in combination with the OEL.*
- *"The scientific evaluation shall include, where appropriate, review of/or proposals for OEL(s), biological limit value(s), health surveillance measures concerning biomonitoring and/or appropriate notations.*
- *The existing scientific evaluations by SCOEL are considered to be up to date, unless new scientific information indicates that this is not the case.*
- *This task arises from detailed discussions that took place preceding the adoption of Directive 2019/983/EU. DG EMPL shall assist ECHA to engage with key stakeholders*

[1] Directive (EU) 2019/37/EC

[2] Ares (2019)11098

to ensure that scientific and technical concerns raised during the negotiations can be taken into full consideration during the scientific evaluation

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission, RAC is requested to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for cadmium and its inorganic compounds with a deadline of 08/07/2021.

Chemical name(s): Cadmium and its inorganic compounds

In support of the Commission's request, ECHA prepared a scientific report concerning occupational limit values for cadmium and its inorganic compounds at the workplace.

This scientific report was made publically available[3] on **14/09/2020** and interested parties were invited to submit comments by **12/11/2020.**

RAC developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further developed as an Annex to the RAC opinion to ensure alignment.

The RAC opinion includes a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant Occupational Safety and Health legislative procedures.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC are **Bert-Ove Lund** and **Andrea Hartwig.**

The opinion was adopted **by consensus** on **18 March 2021.**

[3] https://echa.europa.eu/oels-pc-on-oel-recommendation

RAC Opinion on the assessment of the scientific relevance of OELs for cadmium and its inorganic compounds

RECOMMENDATION

The opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for cadmium and its inorganic compounds, is set out in the table below and in the following summary of the evaluation, supported by Annex 1.

In relation to the mandate from the EU Commision (see page 1), RAC concluded that **a combination of an airborne exposure limit value and a biomoitoring-based limit value (BLV) would be more effective in protecting the health of workers than either one of them used alone**. In consideration of the data on the effects of cadmium, RAC considered it necessary to set both an 8h-TWA and a biological limit value (BLV), with the former being related to the current working practice at the time of measurement and the latter representing the long-term exposure and the accumulation of cadmium over time.

RAC noted that the binding airborne occupational limit value in the present legislation[4] and supported a final inhalable limit value of 1 µg cadmium/m^3 as explained later in this opinion. RAC noted the BLV proposal in the ECHA scientific report (2 µg cadmium/g creatinine in urine), however, it concluded that a weight of evidence analysis of available data indicated that a fully protective BLV should be set at 1 µg cadmium/g creatinine in urine as explained further in this opinion.

SUMMARY TABLE

The table presents the outcome of the RAC evaluation to derive limit values for cadmium and its inorganic compounds.

Derived Limit Values

OEL as 8 hour TWA (8h-TWA):	0.001 mg cadmium/m^3 (=1 µg cadmium/m^3 (inhalable fraction))
STEL:	--
BLV:	1 µg cadmium/g creatinine
BGV:	**--**

Notations

Notations:	--

[4] 4 µg cadmium/m^3 inhalable fraction to be decreased to 1 µg cadmium/m^3 in 2027: Directive (EU) 2019/983.

RAC OPINION

Background

This opinion concerns cadmium and inorganic cadmium compounds (see section 1 of the Annex).

The SCOEL recommendation (2017) is the basis for the current analysis. This RAC evaluation also takes previous reviews into account, in particular:

- International evaluations such as: EFSA (2009), ATSDR (2012), IARC (2012), NTP (2016), BAuA (2014) and (2021).

Scientific papers published between 2017 and 2020, as well as contributions from the consultation on the ECHA report, are also taken into account.

The mandate given by the European Commission for cadmium and its inorganic compounds (asee page 1), was to assess the option of an airborne occupational exposure limit or a combination of an airborne occupational exposure limit and a biological monitoring value for cadmium and its inorganic compounds based on their possible equal effectiveness in protecting the health of workers. The key task was thus to compare the effectiveness of the health protection of the combination of an OEL and biomonitoring value as proposed in the SCOEL Opinion 336 (2017) compared to the OEL adopted in Directive 2019/983/EU.

Key conclusions of the evaluation

- Cadmium is easily taken up into the body via inhalation. Uptake via ingestion can be also important, depending e.g., on the iron status and food habits of the individual as well as ”hand to mouth contact“from contaminated surfaces. Dermal uptake is negligible.
- Cadmium is mainly distributed to, and accumulated in, the kidney and bone. The half-life is very long, and only biomonitoring (especially in urine) can indicate the long-term exposure relevant for toxicity. The toxic species is the cadmium (2+) ion.
- An air limit value will protect against local toxicity in the lung, including carcinogenicity, but also protects against internal exposure via inhalation and thus organ toxicity.
- Additionally, and most importantly, a biomonitoring-based limit value is needed in order to protect against cadmium accumulated over a longer time period, e.g., from peak air levels and hand-to-mouth contact due to contaminated surfaces, also at an individual level.
- Cadmium is carcinogenic to experimental animals (lung tumours). In humans, evidence for lung carcinogenicity upon inhalation is less evident, mostly due to simultaneous exposure to other carcinogens like inorganic arsenic, but it cannot be ruled out. Furthermore, associations have been suggested in several meta-analyses between cadmium exposure and kidney tumours as well as prostate cancer. Cadmium is not mutagenic, and carcinogenicity is proposed to be due to indirect mechanisms, such as inhibition of DNA repair. While a mode of action-based threshold is likely to exist, it is difficult to define due to limited in vivo data. Based on animal data and an assumed hockey-stick dose-reponse (MoA-based threshold), BAuA has recently calculated that an air level of 0.9 µg cadmium/m^3, which represents a cancer risk of 4:10,000.
- At current industrial exposure levels, only chronic toxicity is of relevance for limit setting.
- Studies of the general population indicate that cadmium may cause renal, bone and reproductive toxicity (decreased birth weight), as well as cardiovascular effects, at exposure levels around 1 µg cadmium/g creatinine in urine.

- Data from occupational settings mainly concerns renal and bone toxicity, with effect levels around or higher than 2 µg cadmium/g creatinine in urine.
- Studies concerning the general population show lower effect levels than studies on workers. Reasons for potentially lower sensitivity of workers than the general population are, for example, that workers are healthier and younger (<65 years of age) than (parts of) the general population. However, older workers (retired), sometimes become less healthy with age and accumulate additional cadmium from the diet. Thus, in considering the cumulative risks of cadmium, RAC was of the opinion that data and effect levels from the general population cannot be ignored when discussing occupational limit values.
- A Biological Limit Value (BLV) is needed since internal cadmium levels are decisive for both chronic toxicity and carcinogenicity. Biological monitoring allows an assessment of the total accumulation of cadmium in the body upon long-term exposure, covering the inhalation route as well as ingestion from contaminated hands (hand to mouth contact) due to contaminated surfaces in the occupational setting.
- An air limit value complementary to the BLV will protect against local effects in the respiratory system, carcinogenicity in the respiratory system and to some extent other systemic effects caused by long-term inhalation exposure. Long term effects caused by accumulation of cadmium, however, can only be prevented sufficiently by a BLV. Thus, air limit value alone will not sufficiently protect from long-term effects caused by accumulation of cadmium, i.e. resulting from exposure to peaks or contaminated surfaces. There is also the possibility of resuspension of the dust settled on the surfaces, resulting in unforeseen inhalation exposure.
- A combination of BLV and air limit value is therefore more protective than only an air limit value. A BLV will also more accurately reflect the long-term exposure to cadmium than an 8h-TWA, which is important as cadmium accumulates in the body (especially in the kidney) resulting in peak internal exposure around 50 years of age and toxicological effects late in life.
- Occupational exposure of women of child-bearing age should be minimized considering that cadmium may affect the birth weight of children. The effect on birth weight in the general population is small (10-100 g in girls, mainly dependent on exposure during early pregnancy), but can be important on a population level. Also, it cannot at present be excluded that cadmium has other effects (than affecting the weight) on the newborns.

Cadmium exposure, toxicity and Mode of action (see section 8 of the Annex for full discussion)

In agreement with, and based on the SCOEL opinion (2017), RAC concludes that inhalation is the main route of exposure for workers, and that additional exposure by ingestion may occur after touching contaminated surfaces or equipment (in a contaminated workplace). Additionally, workers can also be exposed through the consumption of contaminated food and/or tobacco smoking. There is also a general background exposure via food consumption. According to a HBM4EU compilation of biomonitoring data from the general population (with exposure mainly through the diet) in different European countries, the median urinary concentration of cadmium was reported to be 0.21 µg/g creatinine in 21 studies (range 0.16-0.41), and the 95-percentiles to range from 0.29 to 1.26 µg cadmium/g creatinine. When data are analysed per country (the 21 studies represented 12 EU member states), the range of the 95-percentiles was 0.29-0.86 for 11 of the member states, and 1.26 in the study from Poland. RAC acknowledges that the data does not cover the whole EU, but it is the most recent (about 10 years old) and best data available.

Toxicological effects depend mainly on the long-term, accumulated exposure to cadmium, which is best assessed by biomonitoring, i.e., measuring the cadmium concentration in urine (normalised in relation to excretion of creatinine; µg cadmium/g creatinine in urine). Most, if not all, epidemiological studies investigating toxicological effects of cadmium exposure relate effects to the concentration of cadmium in urine, and they have shown that the main target organs are kidney, bone, the cardiovascular system, and the respiratory system. In addition, cadmium may affect the birthweight of children. Cadmium is known to interact with proteins, e.g., by binding to thiol-groups, thereby affecting their structure and function, but the precise mode of action for the effects described above is not completely understood.

Based on animal studies, showing lung tumours in rats after long-term exposure to 12.5 µg/m^3 respirable cadmium, it is suspected that cadmium and cadmium compounds are carcinogenic to humans (IARC Group 1; IARC 2012). Although an unusual exposure regime was used, a high carcinogenic potency is indicated in the rat lung for respirable cadmium. There are also recent epidemiological meta-studies suggesting associations between cadmium exposure in workers and lung tumours (Park et al., 2012, Haney, 2016), kidney tumours (Ju-Kun et al., 2015) as well as prostate tumours (Ju-Kun et al., 2016). Although such associations can be challenged, e.g. based on unclear confounding data from smoking, carcinogenicity in workers cannot be ruled out. Cadmium and some cadmium salts are also classified as carcinogenic in the EU (Carc 1B). Underlying mechanisms include the induction of oxidative stress (generation of reactive oxygen species, most likely via inhibition of antioxidative defence systems), oxidative DNA damage, inhibition of DNA repair and deregulation of cell proliferation. Since all these interactions are mediated by interactions with proteins, the potential carcinogenicity is characterised by a mode of action (MoA)-based practical threshold below which no adverse effect is expected. Indirect genotoxicity was also considered within the most recent risk assessment conducted by BAuA (2021). Based on animal data and an assumed hockey-stick dose-response-relationship for carcinogenicity, an air level of 0.9 µg cadmium/m^3 (respirable fraction) was calculated to represent an additional lung cancer risk of 4:10,000.

Most epidemiological studies are conducted on the general population. Since they are many, conducted at background exposure levels, a WoE assessment of all studies is needed to get an idea of the toxicological profile of cadmium, considering that there are always some negative studies among the many positive studies. Thus, studies on the general population have shown associations between cadmium concentration in urine and effects on kidney, bone, cardiovascular system and birth weights. In addition, studies on occupationally exposed workers have shown respiratory effects after inhalation of cadmium.

Effects on kidney, bone, cardiovascular system and birth weights in the general population have often been seen at exposure levels around 1 µg cadmium/g creatinine, and sometimes even at lower exposure levels (EFSA 2009). The adversity of these effects at this exposure levels can sometimes be discussed, but an overall impression is that cadmium may affect human health in the general population at urine concentrations at 1 µg cadmium/g creatinine. Accordingly, based on an analysis of the association between cadmium exposure in the general population and an adverse level of excretion of beta-2-microglobulin in urine, EFSA concluded that 5% of the exposed population will be affected by kidney toxicity at a urinary concentration of 4 µg cadmium/g creatinine. Applying an uncertainty factor of 4 to account for intra-individual variation, EFSA (2009) concluded that the urinary cadmium level should be kept below 1.0 µg cadmium/g creatinine.

Studies in occupational settings have generally focused on kidney and bone as the most sensitive target of systemic cadmium toxicity. Measuring cadmium excretion in urine shows the body burden as a result of exposure via all sources, including contaminated food and smoking. Some such studies generate reliable dose-effect/response relationships for systemic effects, and the effect levels generally seem to be higher in workers than in the general population. For instance, a cadmium body burden corresponding to a cadmium

concentration in urine of 5 µg/g creatinine in workers is a clear LOAEL based on the occurrence of low molecular weight proteinuria and a general consensus that this effect is adverse (Chaumont et al., 2011). Links between kidney and bone effects induced by cadmium strengthen their health significance. In the general European population, the LOAEL for effects of cadmium on the kidney is at or even below 2 µg cadmium/g creatinine (LOAEL) (e.g. Buchet et al., 1990). This lower LOAEL in the general population compared to that identified in workers is thought to reflect that workers are healthier, and that there are more older people (>65 years of age) in the general population than in the work force.

However, also workers exposed to cadmium get older and may get less healthy after their occupational career and considering the long half-life of cadmium in humans and its accumulation with age (also from the background exposure via food), it may be prudent to provide a sufficient degree of protection in this respect. Also, predispositions like diabetes, slight symptoms of renal damage as well as arterial hypertension are expected to be present also in workers and increase with age.

Derived Limit Values (see section 9 of the Annex for a full discussion)

In the view of RAC, there is a need for both an 8h-TWA and a BLV.

When discussing an acceptable BLV for cadmium and its inorganic compounds it should be noted that:

- Mean urinary cadmium levels in Europeans with no occupational exposure to cadmium or not living in an area with cadmium pollution is generally well below 1 µg cadmium/g creatinine.
- The critical systemic effect selected to define the point of departure in epidemiological studies (urinary excretion of low molecular weight (LMW) proteins reflecting tubular dysfunction) is a relatively early sign occurring before the onset of overt clinical manifestations of kidney disease.
- The point of departure identified from human studies in occupational settings (5 µg cadmium/g creatinine) is a LOAEL for renal effects.
- Effect levels indicated in human studies in the general population (around 1 µg cadmium/g creatinine) need to be considered for protecting workers after their occupational career.
- The effect on birth weight concerns women of fertile age. Women can also be considered extra susceptible in the sense that they absorbed more cadmium due to often suffering from iron deficiency.
- Respiratory effects have been indicated at 3 µg cadmium/L urine in workers.
- Cadmium is a carcinogen in rodents after long-term exposure via inhalation to 12.5 µg/m^3, and there are recent indications of kidney and prostate carcinogenicity in humans. Although the existence of a mode-of-action-based threshold for the carcinogenicity is likely, it seems prudent to recommend limiting the body burden of the workforce to a minimum.

Therefore, in consideration of new data on the effects of cadmium on the general population, RAC considers it necessary to set both an 8h-TWA and a BLV, with the former being related to the current working practise and the latter with the accumulation of cadmium over time.

(i) OEL - 8h-TWA

An 8h-TWA limit is necessary to limit exposure and reduce emissions from current working practises, to protect workers against local effects in the respiratory system as well as other systemic effects of cadmium (and its inorganic compounds), to understand the role of the inhalation route for the total body burden. This exposure limit will also contribute to control

contamination of the workplace and thus limiting exposure by ingestion via contaminated surfaces (hand-to-mouth contact). Chronic inhalation of cadmium-containing dusts and fumes is associated with the development of local respiratory effects, including lung emphysema and cancer. Cadmium is considered as a lung carcinogen in experimental animals and experimental studies have reported tumours in rats chronically exposed to 12.5 µg/m³ respirable fraction of cadmium.

Therefore, in order to protect against local effects in the respiratory system, carcinogenicity in the respiratory system and possibly at other sites (kidney and prostrate) after long-term inhalation exposure, and to avoid contamination of surfaces in the occupational setting potentially resulting in exposure by ingestion, an air limit is needed.

Whether the airborne limit should concern the respirable or inhalable fraction, RAC notes that the respiratory fraction would protect from local respiratory effects and lung carcinogenicity. However, both fractions (respirable and inhalable) will contribute to the total exposure (directly from the respiratory system or indirectly by ingestion), and thus to systemic effects of cadmium, being an argument for focusing on the inhalable fraction.

According to modelling performed by ATSDR (2012), air concentrations of 1.2-2.4 µg cadmium/m^3 inhalable fraction – depending on the actual cadmium compound, but without considering cadmium uptake via food - would result in a urinary concentration of 0.5 µg cadmium/g creatinine. Even though RAC acknowledges the uncertainty inherent to modelling, especially of accumulating compounds, the approach is helpful to correlate urinary cadmium levels with air exposure concentrations. Workers also experience background exposure to cadmium via consumption of contaminated food; the total exposure of these workers would thus already come close to potentially adverse exposure levels at air concentrations of 1-3 µg inhalable cadmium/m^3.

If the air limit value would only refer to the respirable fraction, considerably higher levels of inhalable cadmium could occur, and thus would exceed the levels leading to potentially adverse systemic effects described above.

Altogether, in spite of some remaining uncertainties, RAC supports the value of 0.001 mg/m^3 (=1 µg/m^3) inhalable fraction currently set in the EU (Directive (EU) 2019/983). When SCOEL originally suggested this value, they referred to an estimated LOAEC of 2.5-10 µg cadmium/m^3 for nephrotoxicity after 40 years exposure, a LOAEC of 12.5 µg cadmium/m^3 for carcinogenicity in rats and a LOAEC of 12.5 µg cadmium/m^3 for non-cancer respiratory effects. The current binding 8h-TWA (BOEL of 1 µg/m^3) is also supported by the new information (for example on cardiovascular effects, birth weight, and the BAuA dose-response evaluation) as assessed in this document.

(ii) Short term limit value (STEL)

RAC was of the view that there was no need for a STEL because the key effects of cadmium are related to long term exposure. Cadmium does not cause acute or short term effects used to derive a STEL, so peak exposures rather contributes to the body burden and thereby long-term effects caused by accumulation of cadmium.

(iii) Biological limit value (BLV)

Mean urinary cadmium levels in Europeans with no occupational exposure to cadmium is generally well below 1 µg cadmium/g creatinine as indicated by data from HBM4EU on biomonitoring conducted between 2005 and 2015 in Europe (range of median reported in 21 studies was 0.12-0.41 µg cadmium/g creatinine in urine). Twenty-one studies are reported, representing 12 EU member states. Most studies are about 10 years old, the number of persons participating varies (58-1848 persons) and their occupations are not known. These factors contribute to uncertainty as regards the true background concentration of cadmium in European countries. The data has therefore been analysed per country. The 95-percentiles for 11 of the 12 countries are below 1 (range 0.29-0.86

µg cadmium/g creatinine in urine), while the 95-percentile for 120 samples from Poland in 2011 was 1.26 µg cadmium/g creatinine in urine. The International Cadmium Association (ICdA) reports based on their biomonitoring data that many newly hired workers have Cd-U values at or above 1ug Cd/g creatinine in several EU regions. Whether these workers have had previous occupational exposure to cadmium is not clear. The ICdA guidance recommends monitoring workers before starting a task potentially resulting in cadmium exposure, and RAC supports that in order to be able to avoid further cadmium exposure in persons already having a high previous exposure.

As indicated above, studies on the general population generally indicate lower adverse effect levels than studies on workers, potentially caused by having a younger and healthier population at the workplaces. However, all workers accumulate more cadmium as they get older, also from food consumption, and with time tend to reach a health status more in line with the general population. Thus, RAC was of the view that findings in studies on the general population should not be ignored when setting limit values for cadmium. Based on a large data base it seems that at a urinary concentration of 1 µg cadmium/g creatinine many different adverse effects start to appear, such as effects on bone, kidney and the cardiovascular system.

Thus, on the basis of studies conducted in Europe (Buchet et al., 1990; Hotz et al., 1999; Järup et al., 2000), United States (Noonan et al., 2002) and Asia (Jin et al., 2002), it appears that renal effects can be detected in the general population for urinary cadmium concentrations below 5 µg cadmium/g creatinine and even from 2 µg cadmium/g creatinine or below.

Recent reviews and a meta-analysis have indicated that effects on bone mineral density, osteoporosis, and increased fracture risk may occur at urinary cadmium concentrations as low as 0.5–2 µg cadmium/g creatinine (Akesson et al., 2014, Cheng et al., 2016, Nordberg et al., 2018).

Many reviews and meta-analyses have demonstrated associations between cadmium in blood or urine and atherosclerosis and cardiovascular disease (Tellez-Plaza et al., 2013, Chowdhury et al., 2018, Tinkov et al., 2018). These associations have been demonstrated in the United States, Europe, and Asia and have been reported for many cardiovascular outcomes: myocardial infarction, stroke, atherosclerosis in carotid arteries and legs, and aortic aneurysm. A systematic review and meta-analysis showed an association between cadmium exposure and increased cardiovascular disease mortality (Larsson and Wolk, 2016). Associations have been demonstrated also in never-smokers and suggest increased cardiovascular risk already at cadmium concentrations around 1 µg cadmium/g creatinine in urine or 1 µg cadmium/L in blood.

Two meta-analysis have studied the associations between maternal cadmium exposure and neonatal effects. Based on 11 studies on the general population (urinary cadmium normally < 1 µg/g creatinine), Huang et al. (2019) indicated that a 50% increase of maternal urinary cadmium level would be associated with a decrease in neonatal birth weight. Based on 22 studies, Khoshhali et al. (2019) identified a weak, but still significant association between maternal urinary cadmium levels and birth weight.

In addition, cadmium is a potent lung carcinogen in rats, and human experience indicates a risk for cancer in humans after long-term cadmium exposure. While a mode of action-based threshold is likely to exist, it is difficult to define due to limited in vivo data, therefore minimising all cadmium exposure is recommended.

Setting a BLV will protect workers from systemic toxicity of the kidney toxicity, bone and possibly also cardiovascular effects. A BLV will also more accurately reflect the long-term exposure to cadmium than an 8h-TWA, which is important as cadmium accumulates in the body (especially in the kidney) resulting in peak internal exposure around 50 years of age and toxicological effects late in life. In contrast, air monitoring is conducted using periodic samling, typically once or twice a year as prescribed in monitoring standard EN689 (ICdA,

2020 in the public consultation). Air monitoring is important, especially to ensure good working standards and to understand the role of inhalation for the total cadmium body burden and to understand what further risk management measures are needed, but will be not sufficient to prevent effects caused by the accumulated internal body burden of cadmium.

The previous SCOEL opinion proposed a BLV of 2 µg cadmium/g creatinine, which does not seem sufficiently protective in light of new epidemiological data on e.g. effects on the cardiovascular system and associations between cadmium exposure and an increased mortality in cardiovascular disease or bone toxicity. Another new factor to consider is the meta-studies suggesting that a high exposure to the known animal carcinogen cadmium also may be a risk factor for cancer in occupational populations. Thus, in light of new data, RAC proposes a BLV of 1 µg cadmium/g creatinine.

A further reason for a lower BLV is that reduced birth weights have been observed at exposure levels around 1 µg cadmium/g creatinine. Females in fertile age may absorb more cadmium from food than others because of reduced iron status, and consequently have higher urinary background concentrations of cadmium than males, and can thus be considered a sensitive sub-population. The data are not sufficiently robust for setting a BLV specifically for women, but RAC was of the view that a risk for reduced birth weights (and possibly other effects on the newborns) was a reason for aiming at minimising the occupational exposure to cadmium.

(iv) Assessment of the option of an OEL or a combination of an OEL + BLV: summarising the key aspects of the above evaluation.

When reviewing the effectiveness of only an airborne occupational exposure limit (OEL) versus a combination of an airborne occupational exposure limit and a BLV in protecting the health of workers (as requested by the European Commission), it should be noted that:

- Variations in air levels, including peaks, are difficult to capture (especially with air measurements typically made once or twice a year as indicated in the Public Consultation by ICdA) and a STEL limit value will not solve this challenge, , nor is a STEL warrented at current exposure levels. Such variations will inevitably increase the accumulation of cadmium which will only be noticed using biomonitoring, and can only be prevented by a BLV.

- Emissions of cadmium to the air will eventually result in contamination of surfaces in the workplace (and be increased by peaks), such that additional exposure from contaminated hands (hand to mouth behaviour) will increase exposure and the risk for long-term effects. Ingestion from contaminated hands has been shown to be important for metals, and again, only biomonitoring will pick up accumulation through this route, and consequently, only a BLV can prevent it.

- The internal exposure is also dependent on the degree of absorption in the workers, e.g., women with low iron stores show an increased absorption of cadmium). Only biomonitoring and not the air levels will correlate with the risk for long-term effects. A BLV will consider individual differences in absorption, and thus provide protection on an individual level.

An air limit value in isolation will protect against local effects in the respiratory system, carcinogenicity in the respiratory system and to some extent other systemic effects caused by long-term inhalation exposure. However, the air limit value alone will not sufficiently protect from long-term effects on an individual level caused by accumulation of cadmium, i.e. from peaks or contaminated surfaces.

A BLV in isolation will protect against accumulation of cadmium, but will not provide information on the exposure source and thus on what risk management measures that are needed.

A combination of BLV and air limit value is clearly more protective than only an air limit value. If combined, the 8h-TWA will limit exposure and reduce air emissions from current working practises, protect workers against local effects in the respiratory system and indicate the role of air levels for the total body burden and contamination of the workplace surfaces, while a BLV will more accurately prevent the long-term exposure to cadmium from all exposure routes and accumulation resulting in toxicological effects late in life. Moreover, since most epidemiological studies correlate toxicological effects of cadmium to the concentration of cadmium in urine, the BLV is a toxicologically more robust value than the 8h-TWA.

While the BLV is very important, this cannot at present be quantified in general terms as the circumstances are site specific. Although an 8h-TWA could suffice in a perfect occupational setting, as soon as there are fluctuating air levels and other exposure routes start to have an important role in the overall exposure (ingestion due to hand-to-mouth contact), then the BLV becomes more and more important to prevent long-term effects caused by the accumulated burden of cadmium.

Thus, implementation of both 8h-TWA and BLV are of critical importance to protect the health of workers in occupational settings, and **RAC proposes a BLV of 1 µg cadmium/g creatinine and an OEL (8h-TWA) of 1 µg cadmium/m³ (inhalable fraction)**.

Biological Monitoring (see section 6 of the Annex for full discussion)

Biological monitoring of cadmium exposure is currently performed on a routine basis, mainly in the form of measuring cadmium in urine and normalising the concentration in relation to the concentration of creatinine (µg cadmium/g creatinine in urine) or alternatively to the specific gravity (µg/L). If the specific gravity correction is used, a BLV of 1 µg cadmium/g creatinine corresponds to a value of 1.1 µg cadmium/L urine (using an average creatinine concentration of 10 mmol/L urine). Most epidemiological studies express exposure as µg cadmium/g creatinine to assess the long-term exposure to cadmium in their comparison with health effects. RAC proposes a BLV of 1 µg cadmium/g creatinine, which should be easy to measure. RAC acknowledges that the background level of cadmium in some regions may be close to the proposed BLV of 1 µg cadmium/g creatinine, and in some cases even exceed the BLV. However, the BLV is proposed based on scientific evidence showing that occupational exposure to cadmium should be avoided as background concentrations of cadmium in some cases already are too high.

Notations

No notations are needed for cadmium.

ATTACHMENTS:

Annex 1 gives the scientific background for the opinion. The list of references is included in this document.

Annex 2 Comments received on the scientific report, responses to comments provided by ECHA and RAC (excluding confidential information).