Comments on ECHA's Scientific report

for evaluation of limit values for cadmium and its inorganic compounds at the workplace

Comments of the International Cadmium Association (ICdA)

October 22nd, 2020

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1. Executive Summary

The scientific report for evaluation of limit values for cadmium and its inorganic compounds at the workplace has been issued by ECHA on September 14th, 2020.

It recommends:

"to apply the current OEL 0.001 mg Cd/m³ (1µg Cd/m³) (inhalable fraction) together with a BLV of 0.002 mg Cd/g creatinine (2 µg Cd/g creatinine) for cadmium in urine".

The International Cadmium Association (ICdA) welcomes the opportunity to provide comments on the ECHA scientific report for evaluation of limit values for cadmium and its inorganic compounds at the workplace.

ICdA brings together companies involved in the responsible management of cadmium and compounds, from by-product separation during mining, smelting and refining operations as well as their transformation, use and recycling. A key objective of ICdA is to assist members in ensuring a high level of worker protection against the adverse effects of cadmium and its compounds. The proposal on limit values (OEL, BLV) for cadmium and its compounds is therefore of extremely high relevance for the cadmium industry.

In **section 2** below, ICdA provides comments to the ECHA Scientific Report. These essentially focus on:

- the extremely severe consequences of giving strong preference to animal data over human epidemiological data,
- the limited consideration given to the practical threshold nature of cadmium in lung cancer for which ICdA recommends considering a sublinear dose-response relationship,
- the change of workplace air fraction (from respirable fraction to inhalable fraction) to be considered to control adverse lung effects, proposed with limited justification.

ICdA also wishes to highlight that the main scope of this report which:

"was to make 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"

has not been fully conducted.

In **section 3**, ICdA presents a thorough analysis in support of the SCOEL 2010 Recommendation, further confirmed in 2017 SCOEL Opinion, which combines an OEL of 4 µg/m3 (respirable fraction) with a BLV set at 2 µg Cd/g creatinine. This is presented by ICdA as an effective alternative to the OEL currently set in the directive.

In **section 4**, ICdA provides for ECHA's consideration several editorial comments which help clarify the ECHA text further.

2. Main comments

2.1. ICdA disagrees with some key hypothesis retained to derive the proposed OEL of 1 µg Cd/m³

Section 9.2.2.2. Proposal for OEL, page 57, 5th paragraph:

"If an OEL of 0.004 mg Cd/ m³ (4 µg Cd/m³) (respirable fraction) was applied together with the BLV, as proposed by SCOEL (2017) that value is considered protective against local respiratory effects like changes in residual volume of the lung. However, lung carcinogenicity is an important "local" effect linked to cadmium exposure. According the estimates of BAuA (2014), exposure at 1.6 µg Cd/m³ (respirable fraction) is linked to an increased cancer risk of 4:1 000. To protect against carcinogenicity, a value of 4 µg Cd/m³ (respirable fraction) is therefore considered too high, and it is recommended to apply the current OEL 0.001 mg µg Cd/m³ (1 µg Cd/m³) (inhalable fraction) together with the BLV."

The derived and recommend OEL value of 1 µg Cd/m³ (inhalable fraction) as stated in the ECHA report, is to be challenged for several reasons:

2.1.1. The rejection of the epidemiological study from Park et al. (2012) and Haney (2016) leads to a severe overestimation of the excess lung cancer risk to humans

In chapter 9 "Evaluation and Recommendations" (section 9.2.2.1, *Carcinogenicity*) of the ECHA report it is stated that *"The current epidemiological data cannot be used to identify a threshold for the carcinogenic effects of cadmium"* with no supporting evidence.

This rejection is unfortunate as these studies (on the same Globe smelter cohort) are key is assessing the severity of the lung cancer risk.

2.1.1.1. *The cohort study initially assessed by Thun and further by Park and Haney is fully recognized by well-established scientific and regulatory bodies*

For OELs, which are based on carcinogenicity and human data, the study by Thun et al. (1985) is the most frequently cited key study. Thun et al. performed a cohort study in a cadmium production facility, where 601 workers were exposed, from which 16 died from lung cancer. The Globe cadmium smelter was in operation from 1926 to 1993.

The Thun et al. study was used for the unit risk quantification by the US environmental protection agency within IRIS (EPA, 1999). This IRIS assessment is the background of many national OELs for cadmium based on cancer risk. However, there was criticism that it is not cadmium but rather the co-exposure to arsenic might have caused the excess lung cancer.

2.1.1.2. *Park and Haney have isolated the confounding influence of As and derived a Cd dose response relationship*

The Thun et al. study was updated by Park et al. (2012) with a closer analysis of the influence of arsenic co-exposures. By extracting data from the personal registries, the exact workplace monitoring data could relate to weekly activity of each worker. Additionally, biomonitoring data was available for both As and Cd and integrated in the assessment of the exposure. The cancer risk from the exposure to As for Cd workers was independently calculated from As cancer models. Based on reconstructed As exposure profiles of all individual workers, only one cancer case (out of 34) could be attributed to the exposure to As.

These additional exposure details enabled Park et al. to refine the initial study from Thun et al. The shortcoming of the initial study by Thun is that he could not clearly split between cancer risk related to arsenic or to cadmium. With the new much more detailed exposure analysis, Park et al. could not only convincingly demonstrate that there was an excess cancer risk related to cadmium but also clearly quantify the excess lung cancer risk related to cadmium exposure (Haney,2016, p182-183).

For mean cumulated exposures from 230, 1 470, 4 460, 11 130, 19 960 and 33 080 µg Cd/m³-years the authors describe an increase in cancer risk (SMR) of 0.77, 0.9, 0.90, 2.24, 2.98, 8.93, respectively, after adjustment for ethnicity and exposure to arsenic. These data were used by Haney (2016) to derive a unit risk for the general population, using background risk data from Texas or from the US general population and taking into account a 5-year lagged cumulative exposure. From this URF (Unit Risk Factor for the general population), the authors calculated a lifetime air concentration of 0.02 µg Cd/m³ corresponding to an excess risk of 10E-5 (general population).

These Park and Haney studies were therefore able to quantify the excess lung cancer risk associated with cadmium exposure in humans.

2.1.1.3. *Excluding the Park et al. (2012) study and upholding the Takenaka et al. (1983) study lacks coherence*

In the ECHA report (section 7.7.1 page 44, first paragraph), the conclusion from Park et al. that there is excess lung cancer which can be attributed to cadmium exposure was rejected because the lung cancer effect could not be confirmed in other epidemiological studies .

Strangely, the same conclusion is not extended to the Takenaka rat study, although other animal studies have shown no effect on other animals[1].

The criteria leading to the exclusion of the Park study should have led to the exclusion of the Takenaka study.

2.1.1.4. *The lung cancer risk derived from the Takenaka et al. (1983) rat study greatly overestimates the risk level derived from human data*

To compare the derived excess risk levels when starting from animal data (Takenaka et al., 1983) versus starting from human epidemiological data (Haney, 2016), a conversion (dosimetric adjustments) has to be taken into account to translate general population exposure back into occupational exposure (general population inhales 20 m³/day, 7 days/week; workers inhale 10 m³/day during 8 hours at the workplace, 5 days/week (formula see reference Haney, 2016, page 179). The calculated conversion factor = 2.8. **This conversion factor does not introduce any errors or uncertainties because it is the very same factor that Haney used to convert the original occupational risk into a general population risk.**

Based on the general population URF (= 0.000 487 per µg/m³) as reported by Haney, 2016, the incidence for occupational cancer is 1: 100 000 at a concentration of 0.02 µg Cd/m³ x 2.8 = 0.056 µg Cd/m³.

[1] Mice and hamster study (Heinrich et al., 1989) have shown no increase in the incidence of lung tumours in mice and hamsters.

Using the same linear extrapolations (similar to the BauA 2014 assessment starting from Takenaka et al. rat data) on the epidemiological data translate into an occupational cancer risk of 4:1 000 at a concentration of 22.4 µg/m³.

With this, one further step is needed to derive the risk for a respirable fraction. Considering that the target organ are the lung alveoli, only the respirable fraction, which is the fraction than can penetrate in the alveoli is of relevance. Workplace air sampling in the Thun-Park-Haney study was not as advanced as today. Development of special sampling heads to collect the inhalable fraction started only in 1986 by Mark and Vincent at the Institute of Occupational Medicine in Scotland. When the inhalable IOM samplers became popular, comparative studies were done to assess the ratio between the "old total" and the inhalable fraction from the IOM sampler. Opposite to what one might expect, the sampled "total" fraction is smaller than the inhalable fraction. The old 37-mm Filter cassettes for "total" sampling were never designed to represent a "physiologically relevant exposure" to the respiratory system, the aspiration efficiency is not very similar to the nose and mouth, they are not 100% efficient in collecting all sizes of dust particles and have a upper size limit (approx. 30 µm) where efficiency falls to zero (Anderson, AIHCE 2011). The ratio for total/inhalable was reported to be in the range 1:1.29 and 1:2.12 for cadmium in a lead smelter (Spear 1997), a setting which is comparable to the Globe smelter.

The correlations between inhalable and respirable fractions were recently reported in a study where large data sets were collected from occupational settings in which both fractions were sampled (Wippich et al., 2020). When splitting the results by type of exposure, reasonably strong correlations were obtained. For an exposure type (soldering, casting) that compares well with the exposure at the Globe plant, a respirable/inhalable ratio of 1:2 was found (Wippich et al., 2020, p.441).

With the above information on conversion factors, the measured cadmium concentrations at the Globe plant can be converted to the relevant respirable fraction that causes lung cancer.

- With: AIR(I) = 1.29 x AIR(T) and AIR(I) = 2 x AIR(R),
- The correlation can be calculated as: AIR(R) = 1.29/2 x AIR(T) = 0.65 AIR(T)

Assuming a linear non-threshold effect, the excess cancer risk stemming from the Haney (2016) study can therefore be recalculated as 4:1 000 at a concentration of 0.65 x 22.4µg Cd/m³ = 14.5µg Cd/m³ (respirable) (which, on the basis of a linear relationship, can also be expressed as a risk of 1.1:1 000 with a 4 µg Cd/m³ respirable fraction exposure level).

Comparing this **4:1 000 risk level value of 14.5 µg/m³ (respirable)** with the corresponding Takenaka et al. (1983) 1.6 µg Cd/m³ (respirable) (developed by means of a linear risk extrapolations by BauA (2014) and taken over in this ECHA report), we can conclude **there is a factor 9 difference** between the two cancer estimates based on linear extrapolation from rat studies versus epidemiological data.

This means there is a large overestimation of increased cancer risk when starting from rat studies used in the BAuA 2014 assessment and ECHA report, relative to human studies.

In the ECHA report however, the more conservative estimate from animal studies was used to establish an exposure risk relationship and forms the basis for the ECHA proposed OEL of 1µg Cd/m³ inhalable fraction.

2.1.2. The preference given to rat studies over human studies is unfortunate

The **Takenaka et al. 1983** study has been selected (section 9.2.2.2 page 57, 5th paragraph) for the derivation of the excess cancer risk in this ECHA assessment.

2.1.2.1. *The Takenaka et al. 1983 study has some severe drawbacks*

The exposure regime of this study is quite unusual for an inhalation carcinogenicity bioassay. Indeed, an exposure of 23 hours/day and 7 days/week for 18 months exposure is far from being conforming to standard OECD protocols (6 hours/day and 5 days/week for 24 months for rats). In addition, the post-exposure time of 13 month might increase the observed cancer cases due to spontaneously occurring tumours.

There is uncertainty in translating sensitivity of rats towards humans. The overpredicted risk when using rat data was already cited by Thun et al (1991) when comparing the lifetime risk of excess lung cancer as predicted from OHSA modelling of the Takenaka et al bioassay (1983) and from the Thun et al. (1985) epidemiological data.

Thun et al (1991) demonstrates that *"the risk as estimated from the Takenaka bioassay is substantially higher than that estimated from the human data, […] the risk is approximately one-tenth that of comparably exposed rats. The rat data overpredict risk when compared to the observed increase in lung cancer mortality in epidemiologic studies of cadmium workers."*

2.1.2.2. *Building a linear dose response relationship contradicts the practical threshold conclusion of SCOEL (2017)*

ECHA states that this study does not contradict the conclusions of SCOEL (2017) identifying cadmium as a substance with a practical threshold for carcinogenicity and therefore concludes that there is no need for the derivation of dose-response relationships (section 9.1.2, page 50). Therefore, it seems illogical that ECHA would heavily rely (section 9.2.2.2 page 57, 5th paragraph) on (linear model) dose-response relationship calculations from BAuA (2014) to draw its conclusions (Note that the BauA 2014 document is in the process of being revised, as detailed further down in this document).

2.1.3. Is the use of the linear exposure risk relationship in this assessment fully in line with the science behind cadmium?

The OEL assessment in the ECHA report is based on the BAuA/AGS (2014) assessment which uses a linear risk extrapolation from the experimental rat study by Takenaka et al. (1983).

2.1.3.1. *Performing a linear risk extrapolation is not in agreement with cadmium being a substance with a practical threshold for carcinogenicity*

This is stated in the ECHA report itself on page 50, section 9.1.2. Cancer risk assessment *"The data retrieved for this report does not contradict the conclusions of SCOEL (2017), identifying cadmium as a substance with a practical threshold for carcinogenicity. Therefore, there is no need for derivation of dose-response relationships."*

The last sentence of the quote contrasts with a crucial decision made by ECHA when proposing an OEL value. ECHA decided that the risk of 4:1 000 at 1.6µg Cd/m³ was too high and therefore lowered the proposed value for an OEL. This 4:1 000 risk could only be calculated precisely because BAuA derived a (linear) dose-response relationship.

2.1.3.2. *The strong evidence supplied by ICdA on the threshold nature of Cd should be considered*

On page 48, section 8.1.2 of the ECHA report it is stated that *'..different and a priori non-mutually exclusive mechanisms for the carcinogenicity of cadmium 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. Cadmium can therefore be considered as a genotoxic carcinogen for which a practical threshold can be identified (Bolt and Huici-Montagud, 2008).”***

A recent literature review of the available genotoxicity data on cadmium and cadmium compounds (and which also included studies published after the 2017 SCOEL evaluation) reinforces the evidence of a threshold for carcinogenic effects. Several lines of evidence are pointing to non-stochastic mechanisms and the available data indicate that that there is sufficient evidence to conclude that the dose-response relationships in vitro are compatible with a threshold. In vivo genotoxicity data (animals) and human workers data further support this conclusion. More details can be found in the document ‘PART 2: Mechanisms of action for the genotoxic activity of cadmium and its inorganic compounds’ submitted to ECHA during the call for evidence and available as well on the ICdA website.

2.1.3.3. *The BAuA/AGS (2014) linear approach is in the final steps of being amended in favour of a sublinear model*

The OEL assessment in the ECHA report is based on the BAuA/AGS (2014) assessment performing linear risk extrapolations from the experimental rat study by Takenaka et al. (1983).

It is **important for ECHA to note** that at this very precious moment the formal validation of an updated BAuA document is pending.

The updated document will be brought forward to the AGS committee of mid-November 2020 for final validation and publication (document unpublished, please refer to AGS or BAuA for a copy. ICdA will ask AGS/BAuA to submit this information during the ongoing public commenting period to the ECHA scientific report).

During future discussions within RAC, the rationale of the sublinear approach of the German AGS (2020) should be considered.

Once it is agreed upon in AGS, this reassessment will be published in the official gazette and will replace the existing (lower) ERB within the TRGS 910 and the TRGS 561 (ref.: BAuA (2020), private communications with scientific experts in the AGS/AKMetalle, Dr.F.Kalberlah and Dr. M.Wieske, Final document submitted for approval at AGS meeting in November 2020).

2.1.4. Although acknowledged by ECHA, the practical-threshold nature of the cadmium lung cancer effect was not integrated in the reasoning when assessing the excess risk level

2.1.4.1. *A sub-linear exposure risk relationship for the cancerogenic effects properly integrates the practical threshold*

Regarding the exposure risk relationship for the carcinogenic effect, the updated BAuA document is no longer reporting a linear approach but a sublinear (hockey stick like) approach is applied, starting from the experimental rat study by Takenaka et al. (1983).

This approach is in line with the mode of action for cadmium for which a practical threshold can be identified (ref.: BAuA (2020)).

BAuA translated the non-quantified threshold for cancer effects in a hockey stick shaped dose response relationship. The starting point of the hockey stick shape was the BDM10 (exposure at which excess cancer risk is 10%). The kink in the hockey stick shape was positioned at the NOAEL for non-

cancer inhalation risk. The lung cancer excess rate at this kink was divided by 10 (see graph below in cited extract of BAuA (2020)).

This updated BAuA assessment results in the exposure value at the tolerance risk level of 4:1 000 at 2.6 µg/m³ (respirable fraction), compared to a risk level of 4: 1 000 at 1.6 µg Cd/m³ (respirable fraction) linear approach in BAuA 2014. This makes a remarkable difference with the 1.6 µg Cd/m³ which was used in rounding down to the proposed OEL of 1 µg Cd/m³ (respirable, taken as inhalable) in the ECHA report.

It should however be noted that the updated BAuA assessment (2020) used animal data: the sub-chronic inhalation rat study exposed to Cadmium oxide (NTP, 1995) (for details on the study, see ECHA report page 39). The NOAEC in the lungs was 0.025 mg CdO/m³ (= 22 µg Cd/m³) for rats. Recalculating the rat exposure towards an occupational setting resulted in a NOAEL of 1.83 µg Cd/m³ respirable. This study was key in the determination of the kink in the sublinear approach applied in the updated BAuA assessment. The NOAEC of 22 µg Cd/m³ was used as the basis for the kink by extrapolating to the workplace scenario. After applying some extrapolations on the NOAEC and rounding, BAuA set the kink of the hockey stick at 2 µg Cd/m³.

Extract from updated BAuA assessment (2020):

> ***Ermittlung einer Knickstelle***
>
> *In Abschnitt 9.1.1. wurde auf Basis von Daten in Abschnitt 5.1.2 eine NOAEC für respirationstoxische Effekte in Höhe von 22 µg/m³ in einer subchronischen Studie (13 Wochen Exposition) über 6h/Tag an der Ratte ermittelt.*
>
> *Dieser NOAEC kann als Basis für die Knickstelle herangezogen werden, indem auf das Arbeitsplatzszenario (Humanexposition, keine formale HEC-Berechnung) nach Leitfaden (AGS, 2010) extrapoliert wird:*
>
> – *Expositionsdauer: Faktor 2 (subchronisch-chronisch)*
> – *Aktivität und längere tägliche Exposition (statt 6h/d hier 8h/d): Faktor 2*
> – *Variabilität (Inter- und Intraspeziesvariabilität): reduzierter Faktor 3*

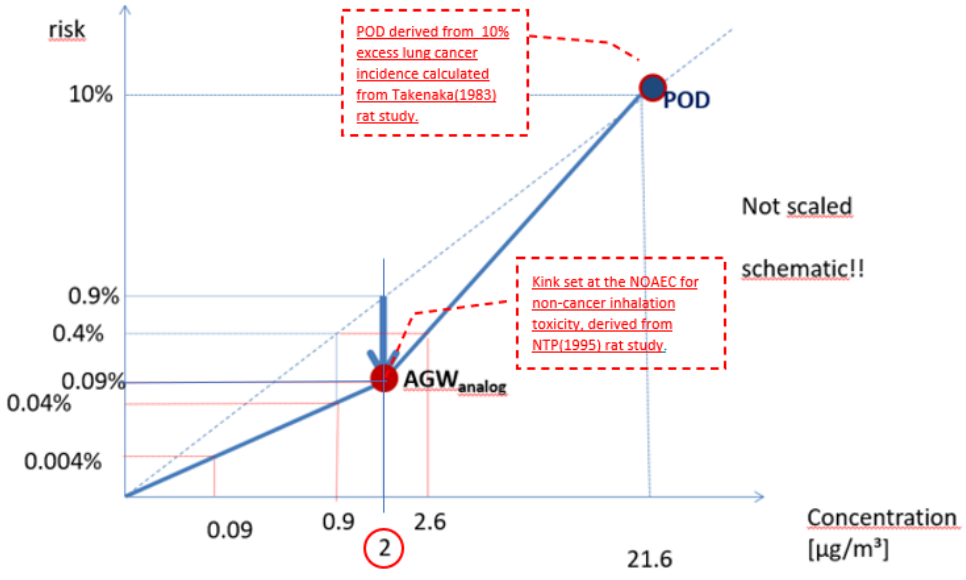


Abbildung 4: Knickfunktion für ERB (Lungenkrebs, Cadmium), A-Staub (schematische Darstellung)

Da die Ratte als besonders empfindliche Spezies in Bezug auf die hier beschriebenen Effekte angesehen wird, kann ein reduzierter Speziesfaktor angewandt werden.

Es ergibt sich: 22/(2x2x3=12) =1,83

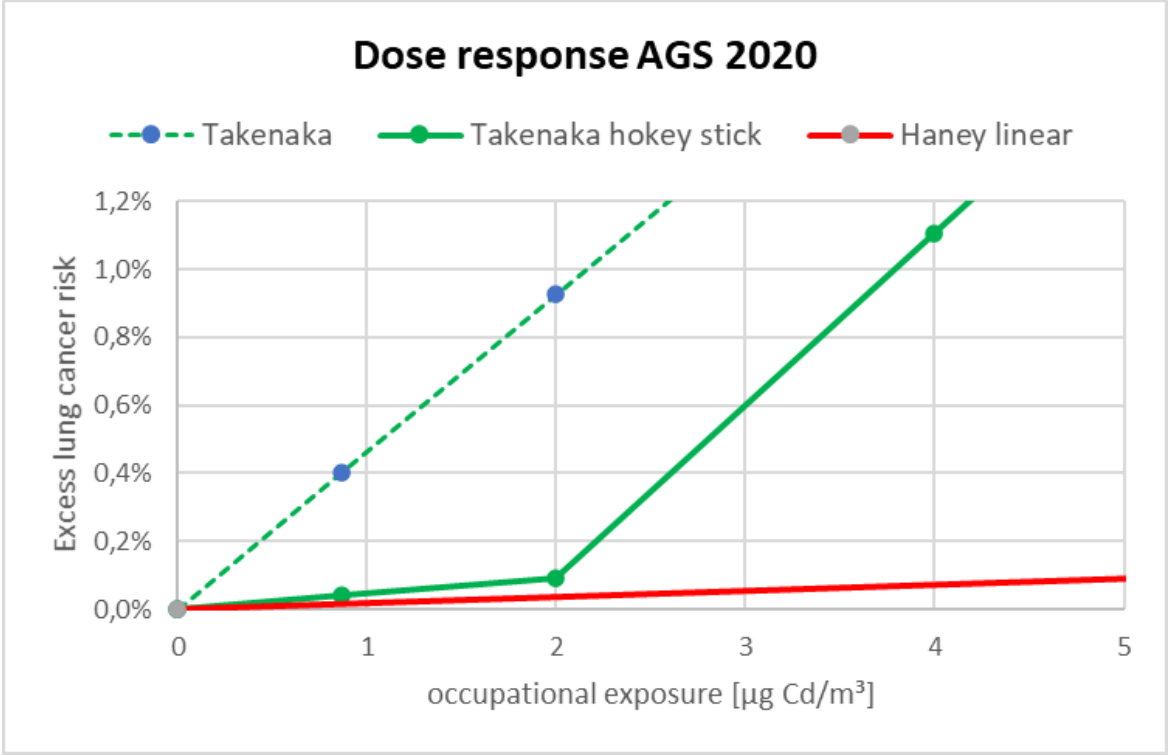
Angesichts dieses sehr ähnlichen Werts in Höhe von 1,83 µg/m³ zu dem in Abschnitt 9.1.2. abgeleiteten AGW_{analog} (Basis: Nephrotoxizität) in Höhe von 2 µg/m³ wird mit einer Rundung der Konzentration bei der angenommenen Knickstelle auf 2 µg/m³ pragmatisch eine Gleichsetzung vorgenommen: es wird somit auch angenommen, dass eine AGW_{analog} von 2 µg/m³ gleichermaßen vor respirationstoxischen (nichtkanzerogenen) und nephrotoxischen Effekten schützt und zugleich die Knickstelle für die Approximation der Sublinearität (lungenkanzerogene Wirkung) darstellt.

► ***Die Knickstelle liegt bei 1,83 µg/m³ und wird auf 2 µg/m³ aufgerundet.***

Calculating the excess lung cancer risk according to this hockey stick relationship results in a risk level of 4:1 000 at 2.6µg Cd/m³ (respirable). However, this value is still derived from animal data.

2.1.4.2. *The Park and Haney epidemiological data*

The dose response relationship of the BAuA 2020 sublinear approach ("Takenaka hockey stick") is compared below to the linear dose response derived from the epidemiological study from Park et al. 2012, and Haney, 2016 in the graph below.



Considering the remarks formulated in sections 2.1.1. to 2.1.3., the human data (Haney, 2016) should be reconsidered to derive a sublinear dose-response relationship to conclude on an acceptable excess lung cancer risk. When following the same protocol as set-up by AGS/BAuA, the BDM10 value for lung cancer is needed for setting the point of departure (POD), as well as the NOAEL for non-cancer respiratory effects to set the kink of the hockey stick shaped dose-response curve.

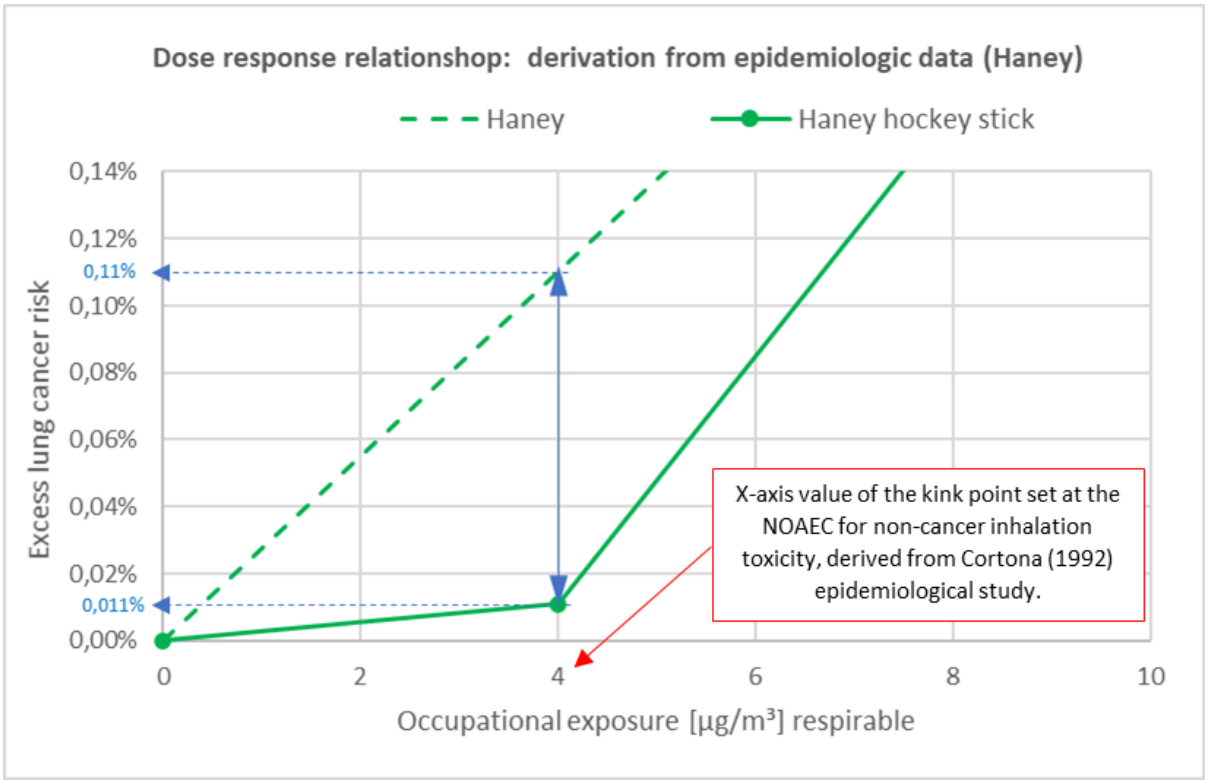
For the derivation of a NOAEC (no-observed-adverse-effect concentration) for *non-cancer lung* effects, the ECHA report refers to the human data of Cortona et al. (1992) (page 56, Respiratory effects). This is a well performed study in a factory producing silver-cadmium-copper alloys for brazing with a total of 69 male workers exposed to cadmium fumes. A LOAEC of 500 µg/m³ x years for changes in residual volume is reported. The NOAEC derived from this study resulted in a value of 4 µg Cd/m³ (respirable fraction). The recent risk assessment by Nordberg et al. (2018) agreed on the 500 µg/m³ x years as the LOAEC for respiratory effects. Nordberg et al. (2018) stated that *"None of the more recent studies has documented effects of cadmium at lower exposures that can be considered caused by cadmium and not by smoking".*

The use of these available human data is more reliable over the animal data to address the non-cancer lung effects. **Indeed, no extrapolation factors to the workplace scenario and no interspecies extrapolation factors are needed.**

2.1.4.3. *Applying the sublinear model to human epidemiological data*

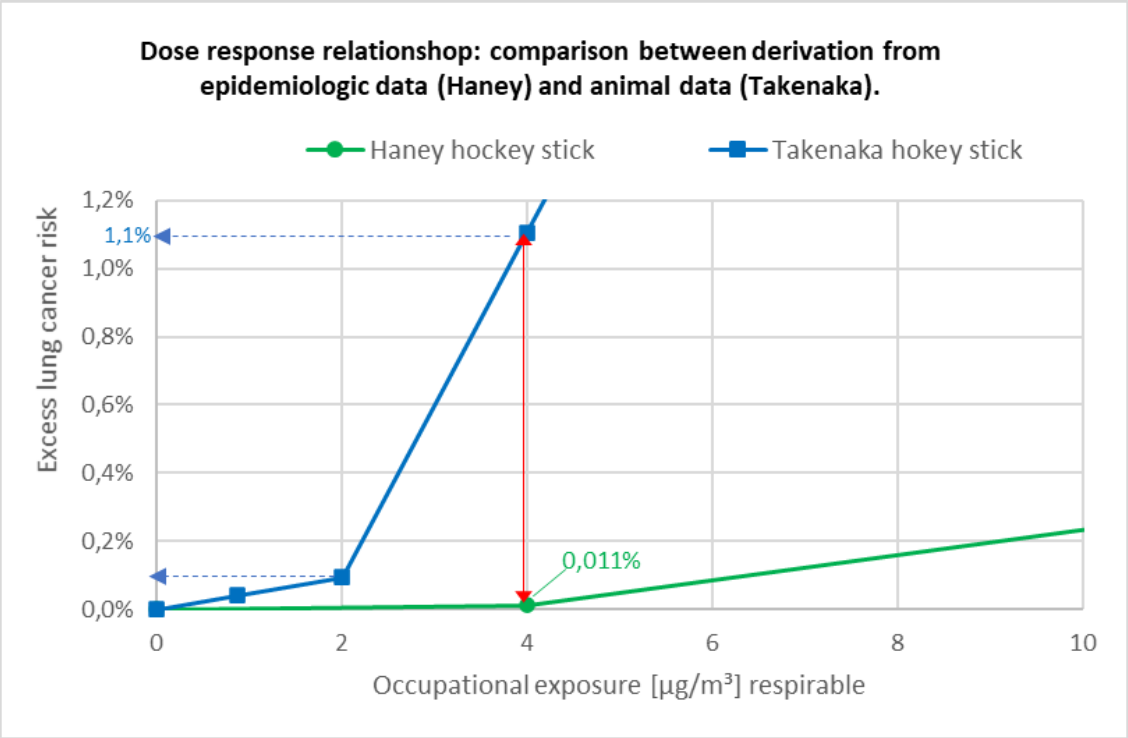
This sublinear exposure risk relationship, when starting from the human epidemiological data Cortona et al (1992) and Haney (2016) with the kink at 4 µg/m³, significantly change the excess risk.

The excess lung cancer risk at 4 µg Cd/m³ (respirable) is reduced from 1.1:1 000 to 1.1:10 000 (a factor of 10 reduction) as schematically represented in the next graph.



The excess lung cancer risk at 4µg Cd/m³ respirable from animal studies (Takenaka et al., 1983) when calculated by the sublinear approach of BAuA is 11:1 000 (blue line in the graph below).

However, when calculated on the basis of epidemiological human data from an occupational setting with the same sublinear approach, as schematically represented in the next graph (green line in the graph below), the risk is 0.11:1000.



2.1.4.4. *Conclusion on the OEL derivation*

Overall, based on the reasons listed above challenging the derived and recommended OEL value of 1 µg Cd/m³ (inhalable fraction) as stated in the ECHA report, the statement below made on Page 57, section 9.2.2.2. Proposal for OEL, 5th paragraph, is scientifically not correct in our view, and should therefore be adapted.

"To protect against carcinogenicity, a value of 4 µg Cd/m³ (respirable fraction) is therefore considered too high, and it is recommended to apply the current OEL 0.001 mg µg Cd/m³ (1 µg Cd/m³) (inhalable fraction) together with the BLV."

According to the calculated dose response relationship derived from epidemiological studies, an exposure at levels of 4 Cd/m³ (respirable) is linked to an increased cancer risk of 1.1:10 000 which can be rounded to 1:10 000.

Therefore:

- The NOAEC for non-cancer respiratory effect is 4 µg Cd/m³ (respirable)
- At 4µg/m³ (respirable) the excess lung cancer risk is 1:10 000

It should therefore be recommended to select an OEL of 4µg Cd/m³ (respirable) to protect workers against respiratory adverse health effect. Combined with a BLV value of 2µg Cd/g creatinine this will also protect against systemic effects.

The effectiveness of this combination is further discussed in section 2.2.

2.1.5. The rejection of the very conservative rat-based, linear relationship modelled value of 1.6 µg Cd/m³ (respirable) in favor of a further reduced 1 µg Cd/m³ (inhalable) is not justified

The reduction from 1.6 µg/ m³ respirable to 1 µg/m³ inhalable is not justified on three counts: why the change of fraction? What is the magnitude of the risk reduction linked to this proposed change? and lastly, why the value of 1 µg/m³ (inhalable fraction)?

2.1.5.1. *Why the change of fraction?*

Regardless of the choice of the data taken as starting point for the derivation of the OEL, it is scientifically not correct to reduce the value of 1.6 µg Cd/m³ (respirable fraction) - linked to an increased cancer risk of 4:1000 based on the very conservative assumptions discussed above – down to the limit value of 1 µg Cd/m³ (inhalable fraction) without providing the underlying justification.

The respirable fraction is the only fraction that has a causal link with lung cancer. The switch from respirable fraction to inhalable fraction without any consideration for a conversion factor is not explained.

Workplace air monitoring data collected by EU industry shows that the ratio respirable/inhalable varies significantly between the various subsectors. While in Ni-Cd battery manufacturing the average ratio is 1:4.4, it is 1:6 in pigments manufacturing and 1:36 in zinc refining plants where the dust is far coarser. (ref.: ICdA annual workplace air monitoring program OCdAir)

2.1.5.2. *What is the magnitude of the risk reduction which is introduced by this change?*

Should the excess cancer risk linked to a 1.6 µg Cd/m³ exposure (respirable) be considered too high, this value should then be lowered to another value also expressed as a respirable fraction.

The proposed reduction should be built on the basis of a lung cancer DRR. However, no revised risk estimation is supplied for excess lung cancer for this proposed OEL of 1 µg Cd/m³ (inhalable fraction).

2.1.5.3. *Why the value of 1 µg/m³ (inhalable fraction)?*

The value of 1 µg Cd/m³ proposed by ECHA is a value that was initially derived in an earlier assessment conducted by BAuA (TRGS-910 2014) for the purpose of addressing kidney toxicity, it was not derived to address lung cancer. This value was taken over and proposed in the 2017 SCOEL Opinion (4th paragraph, p10) to address systemic effects in absence of a BLV, but not lung carcinogenicity, as shown below.

> However, an isolated OEL (8-h TWA) of 4 µg/m³ (not linked with a BLV) would not appear being equally protective against the systemic nephrotoxixity of Cd. Evaluations by both WHO (2000) and the German AGS (*Ausschuß für Gefahrstoffe*; BAuA 2014) of published data (primarily by Thun et al 1991) have pointed, for nephrotoxicity, to a cumulative (life-time) lowest-effect exposure of 100-400 µg/m³ x years. For working-life exposure of 40 years, this equals an LOAEC range of 2.5 – 10 µg/m³. AGS (BAuA 2014) has deduced that nephrotoxic effects could arise in about 1% of the workforce after 40 years of airborne exposure to 4 µg Cd/m³. Accordingly, an OEL (8h-TWA, not connected with biological monitoring) for Cd and its inorganic compounds should be 1 µg/m³.

2.1.5.4. *Feasibility concerns*

Occupational exposure limits should be based first on the risk to health, not necessarily on the analytical capability of the method. However, the sampling and analytical sensitivity and accuracy at

the proposed OELVs need to be considered. Technical feasibility challenges could arise from compliance approaches and exposure measurement methodology (e.g., type of aerosol size selective sampler, pump volume, sampling time needed, personal vs. static sampling, limits of quantification [LOQs], etc.).

In personal sampling, the pump aspiration flow is 2 L/minute. A 7h full shift monitoring aspires 7x60x2L=840 L air. At a concentration of 1.6 µg Cd/m³, the filter collects 1.35 µg Cd. To demonstrate compliance, a quantity of 10% of the OEL should be measurable, which is 0.13 µg Cd. This value is close to what can be analytically quantified in a lab. (Many plants report a detection limit of 0.1µg Cd/m³ in the annual workplace air monitoring observatory OCdAir). Additionally, at such low quantities, the importance of errors due to contamination of the sample is rising.

2.2. ICdA supports the ECHA proposed biological limit value CdU = 2µg Cd/g creatinine

Page 58, 3rd paragraph, *"the following issues are relevant when considering the basis for a BLV for cadmium … […]:"*

As stated, there is indeed 'an abundant data base on the health effects of cadmium and its compounds, including human studies.'

ICdA agrees with the 3 indicated health effects: kidney, bone and respiratory effects as important and driving the proposed **BLV of 2µg Cd/g creatinine**.

However, we want to emphasize that caution needs to be paid regarding the following statement:

> *"Some data indicates effects in the general population at concentrations < 2 µg/g creatinine (even as low as 0.5 µg/g creatinine). Diuresis is however likely to cause major confounding effects at such low levels of exposure."*

The causality of the associations between urinary cadmium and biomarkers of kidney effects in populations with low levels of exposure (general population) has been seriously challenged (Bernard et al., 2016). At low environmental exposures, urinary cadmium is more a reflection of functional integrity of the nephron than of the cadmium exposure or of the cadmium body burden (Chaumont et al. 2012). These reverse causality mechanisms have important implications in the risk assessment of cadmium for the general population, which currently largely relies on the use of urinary cadmium as exposure indicator (Chaumont et al. 2012). For more detailed info, see in section 4/ comment on page 35 of the ECHA report.

> *"At lower levels, bone effects in the general population have been observed at urinary concentrations 0.5-5 µg/g creatinine, but there are also studies with no effects."*

There is evidence suggesting that low-level urinary Cd in the general population is more a reflection of the recent intake and of the physiological variations in the urinary excretion of creatinine. This is relevant for all studies using urinary Cd as cumulative exposure indicator.

Therefore, considering these new elements, a cautious interpretation of Cd-U data is needed because it is noted that the link between proteinuria and albuminuria at low Cd-U is physiological rather than causal (Cd-MT and LMW proteins share the same binding sites in the tubuli) (Akerstrom et al 2013). Moreover, since proteinuria and albuminuria are well known predictors of bone diseases (Barzilay et al., 2013), a causal relationship between CdU (at low levels) and bone effects is questionable.

For more detailed info, see in section 4/comments on page 37, 48, 56 of the ECHA report.

2.3. The comparison of the effectiveness of an OEL-only approach with a combined BLV and OEL approach is missing

Page 58, section 9.2.4.1.

This paragraph is discussing the effectiveness of on the one hand the OEL on its own, and on the other hand the BLV on its own. It concludes *"the values used individually may not provide equal protection of workers. The recommendation is to use a combination of both values"*.

This section is very short and not coming back to the main scope of the report stated on page 57 section 9.2.4 Biological limit value, 2nd paragraph: *'The main scope of this report was to make 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.'*

The main scope was therefore to make a comparison between:

1) the combination of an OEL value of **4µg Cd/m³ respirable fraction** combined with a BLV value of CdU = **2µg Cd/g creatinine** as proposed in the SCOEL Opinion 336 (2017) being the **OEL the BLV value**
2) with the OEL adopted in Directive 2019/983/EU of **1 µg Cd/m³ inhalable fraction**

However, the above stated main scope (page 57) has not been assessed or at least not reported in the ECHA scientific report.

Currently in the Carcinogens and Mutagens Directive (Directive (EU) 2019/983) it is specified that during a transition period, until 11 July 2027, in Member States with an implemented biomonitoring system with a biological (urine) limit value ≤0.002 mg Cd/g creatinine, the air limit value is 0.004 mg/m³ for the respirable fraction.

The report only concludes on page 58 section 9.2.4.1. that *"the values used individually may not provide equal protection of workers. The recommendation is to use a combination of both values".*

3. Documented summary of selecting an OEL and a BLV

3.1. An OEL only, a BLV only of a combination of an OEL and a BLV?

Answering this question was one of the key tasks given by the Commission. We believe the answer needs a better documentation to validate the final choice in chapter 9 “Evaluation and Recommendations” of the ECHA report (9.2.4.1. p.58).

3.1.1. BLV only

A BLV provides good protection against all systemic effects. Cadmium in urine, corrected for creatinine, has been considered for many years as an excellent indicator of cumulative exposure. It should be clearly noted that urinary cadmium is an exposure indicator and not an effect indicator. This exposure indicator allows to detect cumulative exposure levels before adverse health effects occur.

Addressing inhalation health effect through biomonitoring requires assumptions between bioaccumulated cadmium and respired cadmium. Although modelling has been done to address this, the uncertainty about the required assumptions cannot be removed. Biomonitoring is therefore not recommended as a first choice for addressing toxicity related to lungs and the respiratory tract. It can only be a safety net to capture unnoticed elevated Cd in air exposure.

Since a biologic limit value cannot be sufficiently protective against adverse health effect to lungs and the respiratory tract caused by inhalation, a BLV needs to be set along with an OEL.

3.1.2. OEL only

An OEL works well for preventing adverse health effect related to inhalation. To address these effects, the respirable fraction is most relevant. However, it should be noted that in practice, air monitoring is not done permanently but by periodic sampling. Exceedance of Cd in air can occur unnoticed in between samplings. Samplings typically conducted once or twice a year as prescribed in monitoring standard EN689. They are often carried out by external service providers.

Inhalation monitoring and an OEL capture only the cadmium uptake by inhalation at a point in time, and do not give any indication of an individual’s cumulated exposure (possibly arising from prior exposure in a different industrial setting), which is a key drawback for a cumulative toxicant.

Moreover, cadmium accumulates from both inhalation and ingestion (see recent regulatory activity to limit cadmium content in food).

Therefore, to include protection against systemic health effects, requires assumptions on the cadmium uptake via ingestion. Efforts have been reported (Thun et al., 1989, Järup et al., 1988 and Kjellström et al., 1977), to statistically link inhalation with kidney cadmium, but these are methodologically weak as the ingestion contribution can only be assumed.

These studies rely on statistical observed correlations, but in daily practice plant industrial hygienists experience elevated urinary levels for people with a very low Cd in air exposure. Such effects are in the end always related to not fully implemented or neglected hygiene measure, resulting in an elevated oral uptake of cadmium. Indeed, small quantities of ingested cadmium due to lack of strict hygiene can lead elevated exposure unnoticed by air monitoring. Even by setting the air limit value at zero, excessive cadmium exposure through ingestion will continue to occur unnoticed if no biomonitoring is in place.

Since an OEL cannot be sufficiently protective against cadmium related systemic health effect caused by ingestion, an OEL needs to be set along with a BLV.

3.1.3. A combination of an OEL and a BLV

From the discussion in the previous two sections (3.1.1 and 3.1.2.), it is clear that appropriate protection of workers against the adverse health effect of cadmium is only possible by having both air monitoring and biomonitoring in place together, hence the need for an OEL and a BLV.

This conclusion supports the earlier recommendations from the SCOEL in 2010 which was confirmed in 2017 as well as the 2019 conclusion from the Dutch Health Council (DECOS).

Similarly, the ECHA Scientific Report concludes in section 9.2.4.1.:

- *The OEL on its own would protect against systemic and local effects upon current inhalation exposure but not against cumulative effects due to previous exposure and not against indirect (oral) exposure.*
- *The BLV on its own would protect against systemic effects, cumulative effects and effects due to indirect exposure but perhaps not against local respiratory and carcinogenicity effects.*
- *Thus the values used individually may not provide equal protection of workers. The recommendation is to use a combination of both values.*

Although many EU member states have only an OEL in place, all plants where exposure to cadmium occur have implemented since many years biomonitoring, as recommended by ICdA.

3.2. Proposal for concluding on a BLV

Biological monitoring of Cd in urine is the best indicator for cumulative exposure. The literature presented in section 7.3 of the ECHA scientific report suggest a NOAEC of 2 µg Cd/g creatinine to cover specific target organ toxicity and repeated dose toxicity (kidney and bone effects). More detailed comments are given in section 2.2. of this submission.

3.3. Proposal for concluding on an OEL value

As indicated in section 3.1.2, an OEL can only assure protection against adverse health effect to lungs and the respiratory tract caused by inhalation. The focus should therefore be on these two identified respiratory effects:

- non-lung cancer adverse respiratory health effects.
- lung cancer.

3.3.1. Non-lung cancer adverse respiratory health effects

ECHA did not document in much detail its choice for the most relevant scientific report to conclude on a NOAEL for non-lung cancer adverse respiratory health effects. (p.56, 9.2.2.1. *Respiratory effects*) Therefore, we want to summit additional comments to validate the choice.

Two key studies have been identified to derive a NOAEL for non-lung cancer adverse respiratory health effects:

3.3.1.1. *Animal study*

The most relevant animal study was conducted in the National Test Program NTP 1995 (ECHA report p. 39, section 7.3.2.1.), (our comments reported in the section 4. "Clarification and editorial comments").

AGS (2020) derived an equivalent occupational exposure of 1.83µg/m which can be rounded to 2µg/m³(respirable) which can be considered for a NOAEL.

3.3.1.2. *Human data from epidemiological studies*

For the derivation of a NOAEC (no-observed-adverse-effect concentration) for non-cancer lung effects, the ECHA scientific report refers to the human data of Cortona et al. (1992) (section 9.2.2.1. page 56, Respiratory effects). This is a well performed study in a factory producing silver-cadmium-copper alloys for brazing with a total of 69 male workers exposed to cadmium fumes. A LOAEC of 500 µg/m³ x years for changes in residual volume is reported, corresponding to 40 years exposure at a level of 12.5 µg Cd/m³ (Cortona et al. 1992). Applying an extrapolation factor of 3 (LOAEL to NOAEL) would result in a NOAEL value of 4 µg Cd/m³ (respirable fraction).

The recent risk assessment by Nordberg et al. (2018) agreed on the 500 µg/m³ x years as the LOAEC for respiratory effects. Nordberg et al. (2018) stated that *"None of the more recent studies has documented effects of cadmium at lower exposures that can be considered caused by cadmium and not by smoking"*.

3.3.1.3. *Conclusion on the strength of animal versus human data*

The NTP animal study was limited in size and does not bring higher quality or better quantified data than the information from Cortona et al., 1992. Additionally, it included uncertainty on quantitatively transposing observations on animal to humans.

The use of the available human data is more reliable over the animal data to address the non-cancer respiratory effects. No extrapolation factors to the workplace scenario and no species extrapolation is needed. The number of test specimens in the rat study was small and smaller than the number of workers in the epidemiological study.

When human data is present that allow not only qualitatively but also quantitatively to identify the risk, preference is given to human data over animal data.

Note: In the updated draft AGS/BAuA assessment (2020) the sub-chronic inhalation animal study (NTP, 1995) was considered as most relevant. This choice was probably made due to preference for using animal data to establish the lung cancer dose response relationship (ERB) (ref.: BAuA 2020).

3.3.1.4. *Conclusion on non-lung cancer adverse respiratory health effects*

A NOAEL value of 4 µg Cd/m³ (respirable fraction) based on human data is a well-documented valid choice.

3.3.2. Lung cancer

We believe that the decision for not considering the most relevant epidemiological studies on lung cancer was not sufficiently documented in the ECHA report (p.43, section 7.7.1) and as a result, erroneous conclusions were drawn (9.2.2.1. *Carcinogenicity*). This is explained at length in section 2.1. of this document.

Two key studies have been identified to derive the excess occupational cancer risk.

- Animal study with rats reported by Takenaka et al., 1983.
- Epidemiological study of cadmium smelter workers, multiple times refined by Thun et al., 1985, Stayner et al., 1992, Sorahan et al., 2004, Park et al., 2012, Haney, 2016

A proper assessment of the details in both studies is missing for robust conclusion. Especially the evolution of the amount of additional detailed information on exposure that was entered in the assessment by the different researchers, was not acknowledge in the ECHA report. Therefore, we discuss here the details of both studies.

3.3.2.1. *Animal study*

The most relevant animal study was conducted by Takenaka et al., 1983 (ECHA scientific report page 48, section 7.7.2.).

A total of 120 male rats were exposed to CdCl2 cadmium aerosol exposure: 40 rats at each of the 3 tested concentrations. The exposure was: 23 hours/day and 7 days/week for 18 months and a post-exposure time of 13 month for observing cancer cases.

The calculated excess cancer risk was 4:1000 at 1.6 µg Cd/m³ (respirable) according to the linear risk extrapolations by AGS/BauA (2014) and taken over in the chapter 9 "Evaluation and Recommendations" of the ECHA report (page 57, section 9.2.2.2).

3.3.2.2. *Human data from Epidemiological study:*

Calculating the excess risk related to cadmium and isolating it from As (arsenic) cancer effect.

In section 2.1.1. of our main comments, we extensively document that the studies from Park et al., 2012 and Haney, 2016 are of good quality and have quantified the risk. They are the preferred choice to derive an OEL.

A risk of 4:1000 at a concentration of 22.4µg Cd/m³ (total) was derived.

In section 2.1.1.4., the conversion of the total concentration to a relevant respirable concentration was documented, leading to an excess lung cancer risk of 4:1 000 at a concentration of 14.5µg Cd/m³ (respirable).

This is about a factor 9 lower as what was calculated from the Takenaka rat study.

3.3.2.3. *Conclusion on the strength of animal versus human data*

3.3.2.3.1. Animal data:

In section 2.1.2 of our Main comments, the quality of the Takenaka study was addressed. The exposure regime in the study of Takenaka is quite unusual for an inhalation carcinogenicity bioassay and deviates much from OECD standards. Further, there is uncertainty in translating sensitivity of rats towards humans.

Comparing the epidemiological with animal data, we can conclude the excess cancer estimate based on linear extrapolation from rat studies is a factor 9 higher than the risk derived from epidemiological data.

3.3.2.3.2. Human data:

For OELs, which are based on carcinogenicity and human data, the study by Thun et al. (1985) is the most frequently cited key study. Furthermore, the data are from an occupational setting. Thun et al. performed a cohort study in a cadmium production facility, where 601 workers were exposed, from which 16 died from lung cancer (out of a total of 444 death at the end of the follow up in 2002). This cohort has extensive follow-up through 2002.

Considering the level of detail both on exposure (As, Cd, smoking, ethnicity) and cancer incidence that was available and used in this study, it is considered of high quality. Both qualitative and quantitative well documented conclusions could be drawn.

However, the ECHA scientific report (section 7.7.1.) suggest that the epidemiological study by Park cannot be used: *"In particular, the dose-response relationship between cadmium 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."* This incorrect argument was already refuted in the Main comment above (2.1.1). An extensive documentation of the validity of the Park et al., 2012 dose-response relationship between cadmium exposure and lung cancer mortality rates is reported by Haney, 2016 (page 182-183).

ECHA report (section 7.7.1.) further suggests that the excess cancer risk cannot be demonstrated with certainty from the Thun-Stayner-Park study because the cancer effect could not be confirmed in other epidemiological studies. This is a fault argument, as it would imply that there is no excess cancer risk related to cadmium. Following such logic, the Takenaka study should be rejected as well because the cancer effects in rats could not be confirmed in humans and the extrapolation from rat to humans is not valid.

Further it should be noted that even if the excess cancer risk caused by co-exposure to As was not fully carved out from the cadmium excess cancer, the calculated risk by Park et al., 2012 and Haney, 2016 can only be a conservative estimate of the real excess cancer risk of cadmium. But when comparing with the excess risk calculated by Haney (2016), this conservatively calculated risk is 10 times lower as the calculated value from a rat study by Takenaka et al., 1983.

The use of human data from an occupational setting is more reliable over the animal data to address the non-cancer lung effects. No extrapolation factors to the workplace scenario and no species extrapolation is needed. The number of test specimens in the rat study was small (3x40) and smaller than the number of workers in the epidemiological study (601).

When human data is present that allow not only qualitatively but also quantitatively identify the risk, preference is given to human data over animal data.

3.3.2.4. *Integration of the practical threshold for carcinogenic effect*

Recent literature added more convincing evidence of a threshold for carcinogenic effects. (See for more detail: document 'PART 2: Mechanisms of action for the genotoxic activity of cadmium and its inorganic compounds' on the ICdA website). Performing linear risk extrapolations is not in agreement with Cadmium being a substance with a practical threshold for carcinogenicity. This is stated in the ECHA scientific report itself on page 50, section 9.1.2. Cancer risk assessment *"The data retrieved for this report does not contradict the conclusions of SCOEL (2017), identifying cadmium as a substance with a practical threshold for carcinogenicity".*

In section 2.1.4. of our main comments, we report of the approach proposed by AGS/BAuA to integrate a practical threshold in the dose response relationship by making the linear relationship sub-linear. This results in an excess cancer risk of 1:10 000 at 4µg/m³ (respirable).

3.3.2.5. *Conclusion on lung cancer*

Based on human data from an occupational exposure setting, and after integrating a concept of a practical threshold for cancer effect, the excess cancer risk is 1,1:10 000 at 4µg/m³ (respirable).

3.3.3. Proposal for an OEL

We believe that a not correctly validated choice of the key studies in the ECHA scientific report have led to unrealistic conclusions (p.56, section 9.9.2). The consideration of the comments included in this file would lead to different conclusions.

Based on human data from occupational exposure settings, and after integrating a practical threshold, the following is concluded:

An OEL at 4µg/m³ (respirable) is protective against non-cancer respiratory adverse health effect (NOAEC= 4µg/m³ respirable).

At 4µg/m³ (respirable) the excess cancer risk is rounded to 1:10 000.

An OEL set at 4µg/m³ (respirable) provides very good protection of workers against adverse health effects of cadmium by inhalation.

This conclusion supports the earlier recommendations from the SCOEL in 2010 and 2017.

4. Clarification and editorial comments

Page 19, section 5.2:

"More recent data from industrial monitoring indicates that the majority of workers (76%) are exposed to < 4 µg/m³ and 99% or workers are exposed to < 10 µg/m³."

A spelling typo is noted, and the number of workers cited are according to the 90 PERCENTILE calculations.

Therefore, it is suggested to correct the sentence to:

"More recent data from industrial monitoring indicates that the majority of workers (76%) are exposed to < 4 µg/m³ and 99% of workers are exposed to < 10 µg/m³ (assessment done according to 90th Percentile criterion)."

See for more detail the 2020 monitoring document on the ICdA website:
It has to be noted that ICdA/REACH Cadmium consortium are currently in the process of working on updated exposure scenario's for the REACH dossiers Cd, Cd(OH)2 and CdO conform the latest REACH requirements including the latest Cd monitoring data. The updated REACH dossiers will be uploaded on the REACH-IT platform not later than November 30th. Should it become available sooner, we will communicate.

Page 20, section 5.3:

Table of cadmium smelters: Plant in Nordenham, Lower Saxony, Germany is missing.

Page 21- 24: Applications.

Much of the information is outdated. A recent update is available at the ICdA website:
https://www.cadmium.org/introduction
https://www.cadmium.org/cadmium-applications

Please note that silver-cadmium batteries have been used by NASA in the course of the space program of the 1960's and 1970's. This technology is no longer placed on the market today.

Page 33: section 7.2.3 Summary:

The last sentence should be corrected into:

'Soluble cadmium compounds are more toxic than **less** soluble ones, as seen in animal studies.

Page 35, section 'kidneys' last paragraph, line 2

"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 Cd-U below 5 µg Cd/g creatinine and even from 2 µg Cd/g creatinine or below."

This statement and reference to those general population studies indicating kidney effects at CdU concentrations ≤ 2µg/g creatinine is made several times throughout the ECHA scientific report (see also page 47 section 8.1.1, 3rd paragraph; page 58 second bullet point).

Although indicated on page 36 and page 47 about 'the continuing scientific debate about the health significance of these early changes' a clear overview on the recent evidence questioning the causality of these associations between U-Cd and biomarkers of kidney effects (urinary proteins) in populations with low levels of exposure is lacking. This is important to emphasize as it is strongly recommended to consider the anticipated effects on kidney at low Cd exposure with caution. It is emphasized that at higher exposures, the causal relationship is not questioned (Chaumont et al 2011). The use of biological indicators in e.g. worker environment is thus justified.

Recent evidence questions the causality of the associations between urinary cadmium and biomarkers of kidney effects (urinary proteins) in populations with low levels of exposure. There are physiological mechanisms that could potentially result in an association between excretion of cadmium and LMW (low molecular weight) protein excretion, without cadmium toxicity being the cause. The review of Nordberg et al. (2018) provides a comprehensive discussion:

After filtration through the glomeruli, LMW (low molecular weight) proteins, albumin (in small amounts), and cadmium-MT (metallothionein) compete for reabsorption in the proximal tubules. LMW proteins and cadmium-MT seem to have similar affinity for tubular binding sites (Bernard et al. 2008, Haddam et al. 2011, Chaumont et al. 2011, Chaumont et al. 2012) and normal physiological changes in renal tubular reabsorption function can therefore cause a co-excretion of cadmium and LMW proteins. It should be noted that, compared to the LMW proteins used for screening cadmium nephrotoxicity, MT occurs in tubular fluid in much lower concentrations and its tubular reabsorption can be competitively inhibited by these LMW proteins, as well as by albumin. Variation in diuresis (urinary flow rate) is an example of such normal renal physiological variability and can result in altered tubular reabsorption of solutes and water (Järup et al. 1983). Moreover, urine flow rate had a clear positive impact on the excretion of cadmium within individuals. Thus, it is possible that normal physiological variability in renal reabsorption of LMW proteins causes an increase in urinary cadmium by inhibiting tubular uptake of MT-bound cadmium; in other words, this is a possible case of reverse causality (Chaumont et al. 2012).

These recent findings suggest that at low environmental exposures, urinary cadmium would be more a reflection of the functional integrity of the nephron than of the cadmium exposure or of the cadmium body burden (Chaumont 2012). These reverse causality mechanisms might have important implications in the risk assessment of cadmium for the general population, which currently largely relies on the use of urinary cadmium as exposure indicator (Chaumont et al 2012).

Page 37, 4rd paragraph:

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

It is emphasized (see also **Page 35, section 'kidneys' last paragraph, line 2)** that the significance of Cd-U as an exposure marker in situations of very low exposure to Cd, has recently been questioned (Chaumont 2012, Akerstrom 2013). Consequently, this association between urinary Cd and bone effects must be questioned too.

Therefore, considering these recent elements of scientific knowledge, the suggested threshold for bone effects of Cd at a level around 0.5 µg/g creatinine for the general population exposed by the oral route, is considered highly questionable.

There is evidence suggesting that low-level urinary Cd in the general population is more a reflection of the recent intake and of the physiological variations in the urinary excretion of creatinine. This is relevant for all studies using urinary Cd as cumulative exposure indicator.

Therefore, considering these new elements, a cautious interpretation of Cd-U data is needed because it is noted that the link between proteinuria and albuminuria at low Cd-U is physiological rather than causal (Cd-MT and LMW proteins share the same binding sites in the tubuli) (Akerstrom et al 2013). Moreover, since proteinuria and albuminuria are well known predictors of bone diseases (Barzilay et al., 2013), a causal relationship between CdU (at low levels) and bone effects is questionable.

Page 38: section Cardiovascular

Typo: in 2nd paragraph the reference Sjögren et al. 2020 is mentioned two times wrongly as Sjögren et al 20**02**. This should be corrected.

"Associations have been demonstrated also in never-smokers and suggest increased cardiovascular risk already at cadmium concentrations around 1µg/g creatinine in urine or 1 µg/L in blood"

Referring to the above comments challenging the significance of U-Cd as biomarker of cumulative exposure at low levels of exposure, this is also relevant for these studies using Cd as cumulative exposure indicators, showing cardiovascular effects at low CdU.

Furthermore, some of the studies do not take into account potential confounding by other heavy metals, trace elements or organic pollutants (Larsson and Wolk, 2016). Finally, the study by Tinkov et al (2018) does not demonstrate an association between cadmium in blood or urine and atherosclerosis as cited in the 1st paragraph:

"Dozens of studies in the 2000s have demonstrated associations between cadmium in blood or urine and atherosclerosis and cardiovascular disease as presented in reviews and meta-analyses by for example Tellez-Plaza et al. (2013), Chowdhury et al. (2018), and Tinkov et al. (2018)."

In fact, they conclude that *"no significant association between Cd intake and atherosclerosis was demonstrated in humans"*.

Therefore, the relationship between cadmium exposure and cardiovascular disease observed in the general population studies has to be interpreted cautiously. More evidence is needed in order to establish causality and dose-response relationships (Nordberg et al. 2018). Moreover, it has to be noted that positive findings have not been reported in occupational studies with higher CdU levels.

Page 39: Section 7.3.2.1. Inhalation

Additional information:

AGS (2020) analysed the results from the NTP study:

The NOAEC of 25µg/m³ CdO (=22µg/m³ Cd) can be extrapolated to the workplace scenario (human exposure, no formal HEC calculation according to the guidelines (AGS, 2010) :

- Duration of exposure: factor 2 (subchronic-chronic)
- Activity and longer daily exposure (instead of 6h/day here 8h/day): 10/6.7 x8/6 = 1.99 (factor 2)
- Variability (inter- and intra-species variability): reduced factor 3

Since the rat is considered to be a particularly sensitive species with regard to the effects described here, a reduced species factor can be used.

The result is: 22 / (2x2x3 = 12) = 1.83µg/m³ in an occupational exposure which can be rounded to 2µg/m³(respirable). AGS calculated this an equivalent occupational exposure of 1.83µg/m which can be rounded to 2µg/m³(respirable).

The most relevant animal study was conducted in the National Test Program NTP 1995 (ECHA report p. 39, section 7.3.2.1.) In this animal study with a 6h/d, 5d/week, 13 weeks CdO aerosol exposure, male rats were selected which are more sensitive to such exposure than female rats. At each of the 3 tested concentration, 10 rats were exposed.

- NOAEC for lung effect in rats at 25µg/m³ CdO (=22µg/m³ Cd)
- NOAEL for nasal cavity effect in rats at 50µg/m³ CdO (=44µg/m³ Cd)

AGS (2020) analysed these results. This NOAEC can be extrapolated to the workplace scenario (human exposure, no formal HEC calculation) according to the guidelines (AGS, 2010) :

- Duration of exposure: factor 2 (subchronic-chronic)
- Activity and longer daily exposure (instead of 6h / day here 8h / day): 10/6.7 x8/6 = 1.99 (factor 2)
- Variability (inter- and intra-species variability): reduced factor 3

Since the rat is considered to be a particularly sensitive species with regard to the effects described here, a reduced species factor can be used.

The result is: 22 / (2x2x3 = 12) = 1.83µg/m³ in an occupational exposure which can be rounded to 2µg/m³(respirable).

Page 41: 7.5.1 Human data:

*"… an involvement of irritation is uncertain (see **8.4.1**)"*

The numbering '8.4.1' should be corrected into 7.4.1

The numbering '7.5.1'. In vitro data should be corrected into 7.5.3.

Page 43: 1st paragraph

"Increases of erythrocyte micronuclei have been reported in several studies (e.g…)"

The study of Kasuba et al 2002 is not in erythrocytes but in peripheral lymphocytes

Page 43: section 7.6.3. in vitro data, 2nd paragraph

There is more data available for increased DNA damage, chromosomal aberrations and micronuclei. We refer to the submission of document 'PART 2: Mechanisms of action for the genotoxic activity of cadmium and its inorganic compounds' in the ECHA call for evidence, by the International Cadmium Association.

Why is only this selection of references reported? Otherwise we advise to put "e.g." before the listed references.

Page 43: section 7.6.4 Summary

"Cadmium and several cadmium compounds have a harmonized classification under the CLP regulation"

No clear explanation could be found (e.g. related to mechanism of action) to explain the difference in mutagenicity classifications in Annex VI between the different cadmium compounds (e.g Cadmium chloride = Muta 1B vs Cadmium oxide and Cadmium = Muta 2)

Page 44 section 7.7.1.

The ECHA report suggests that the epidemiological study by Park cannot be used: *"In particular, the dose-response relationship between cadmium 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."* This statement is correct for the original Thun study but less for the study by Stayner and completely wrong for the study from Park.

The Thun et al., 1985 study was further updated by Park et al. (2012) with a closer analysis of the influence of arsenic co-exposures. By extracting data from the personal registries, the exact workplace monitoring data on both As and Cd could be connected with weekly activity of each worker. Additionally, biomonitoring data was available for both As and Cd and integrated in the assessment of the exposure. The cancer risk from the exposure to As was independently calculated by using dedicated As excess cancer models developed by others. Based on reconstructed As exposure profiles of all individual workers, only one cancer case (out of 34) could be attributed to the exposure to As. All this additional exposure details enabled Park et al., 2012 to refine the initial study from Thun et al., 1985.

The shortcoming of the initial study by Thun et al., 1985 is that he could not clearly split between cancer risk related to arsenic or to cadmium. With the new much more detailed exposure analysis, ethnicity and smoking habit, Park et al., 2012 could not only convincingly demonstrate that there was an excess cancer risk related to cadmium but also clearly quantify the excess lung cancer risk related to cadmium exposure (Haney, 2016, p182-183). These data were used by Haney (2016) to derive a unit risk for the general population, using background risk data from Texas or from the US general population and considering a 5-year lagged cumulative exposure. From this URF (Unit Risk Factor for the general population), the authors calculated a lifetime air concentration of 0.02 µg Cd/m³ corresponding to an excess risk of 10E-5 (general population).

Based on epidemiological data [Park et al. (2012) update of the Thun et al. (1985) cohort], Haney (2016) estimated an excess risk level of 1:100 000 for a lifetime air concentration of 0.02 µg Cd/m³ (continuous environmental exposure, corresponding to 1:1 000 at 2 µg Cd/m³) for the general population in the State of Texas. (ECHA scientific report page 44, section 9.1.1.)

When doing the reverse calculation from Haney (2016) to go back from general population to occupational setting, the calculated excess cancer risk of 1:1 000 is at 2µg/m³ x 20/10 x 7/5 = 5.6µg Cd/m³ (dosimetric adjustments has to be taken into account to translate general population exposure into occupational exposure: general population inhales 20m³/day, 7 days/week; workers inhale 10m³/day at the workplace, 5 days/week (See calculation: Haney 2016, p179). This corresponds to a risk of 4:1 000 at a concentration of 22.4µg Cd/m³(total)

Section 7.7.1. further suggests that the excess cancer risk cannot be demonstrated with certainty from the Thun-Stayner-Park study <u>because</u> the cancer effect could not be confirmed in other epidemiological studies. This is an erroneous argument, as it would imply that there is no excess cancer risk related to cadmium. Following such logic, the Takenaka rat study should be rejected as well because the cancer effects in rats could not be confirmed in humans and the extrapolation from rat to humans is not valid.

Further it should be noted that even if the excess cancer risk caused by co-exposure to As was not fully carved out from the cadmium excess cancers - only one cancer was attributed to As exposure -, the calculated risk by Park and Haney can only be a conservative estimate of the real excess cancer risk of cadmium. But when comparing with the excess risk calculated by Haney, the conservatively calculated risk is 10 times lower as the calculated value from a rat study by Takenaka et al., 1983. This observation rather supports the position that rat studies overestimate the lung cancer risk related to cadmium.

<u>Page 45-46: section 7.8.1 Reproductive toxicity -Human data</u>

This section 7.8.1 on Human data, describes 9 recent papers and cites them on page 45 as '*studies presenting an association between non-occupational maternal cadmium exposure and developmental toxicity*'.

The reasons below demonstrate this statement and the statement on '*developmental toxicity in the section 9.2.2.1 'Identification of critical effects and doses'*, should be taken with caution and have to be challenged.

1. <u>Claim of 'increased' environmental exposure</u>

On page56, regarding developmental toxicity, the ECHA report concludes that *"In studies focusing on pregnant women with an <u>increased</u> environmental cadmium exposure, an association with developmental effects on the (unborn) child have been reported. The available data can however not be used to derive an OEL."*

When considering the articles cited in section 7.8.1, this conclusion seems reasonable, however, the studies do not relate an 'increased' exposure, as stated.

For one, only two of the studies referenced report any environmental measures. The first is a study by Bao et al. (2009) (referenced in the meta-analysis by Rodriguez-Barranco et al., 2013) that measured Cd values in water (mean: 7.09 µg/L) and soil (mean: 0.528 µg/g). The second is a study by

Tian et al., 2009 which reported Cd values in water used for irrigation in the area (0.26 mg/L) and in soil (1.41–9.01 mg/kg).

Therefore, it is to be supposed that the ECHA statement is based on biological values of Cd-U, since it is the biological sample of choice in 8 of the 9 articles cited. Yet, of these 8 articles, only one has Cd-U values adjusted for diuresis, for which values range from <0,29 to 1 µg/g creatinine (Huang et al., 2019). This is significantly **lower** than the biological limit values for occupational workers which is of 2µg/g creatinine, and not *increased* as stated on page 56. This Cd-U range (<0,29 to 1 µg/g creatinine) is in line with current background Cd exposure levels (i.e., Cd-U < 1µg/g creatinine).

On page45: human data for reproductive toxicity, the ECHA report present the articles as *"studies presenting an association between non-occupational maternal cadmium exposure and developmental toxicity."* Therefore, when compared to occupational exposure, these non-occupational exposure levels are lower and not increased, as cited on page 56

This is an important detail, since recent literature (Bernard, 2016 ; Chaumont et al, 2012 ; Chaumont et al, 2013) has demonstrated a <u>risk of secondary associations</u> between biomarkers of Cd exposure and outcomes involving renal function at low exposure levels of Cd.

2. <u>Choice of biological sample in the studies</u>

As mentioned, 8 of the 9 articles cited in section 7.8.1 use Cd-U as their biological sample of choice. 3 of which use it as their only sample.

According to literature (Bernard, 2016 ; Chaumont et al, 2012; Chaumont et al, 2013), the use of Cd-U as a reliable marker of chronic exposure has recently been put into question, for **low** exposure levels of cadmium.

The reported Cd-U samples cannot be taken as reliable samples especially considering the low exposure since *"U-Cd varies greatly within and between individuals, depending mainly on recent exposure, <u>essential element needs</u>, and renal parameters such as <u>diuresis</u>, proteinuria, and glomerular filtration rate. The key issue to keep in mind when studying the effects of low exposures to Cd is that this heavy metal uses the same transport pathways as plasma proteins for its urinary excretion and the same transport pathways as essential elements for its intestinal absorption. Variations in these transport mechanisms […], may generate <u>secondary associations</u> between biomarkers of Cd exposure and outcomes involving renal function or the requirement of essential elements."* (Bernard, 2016)

The choice of Cd-U as a biological sample at low exposure levels of cadmium is put into question here.

This further casts doubt on the weak associations cited in some of these articles, since 8 of the 9 articles cited, all use Cd-U as a biological sample, and 3 of them use it as their only sample (Kippler et al, 2012 ; Gustin et al, 2018 ; Chatzi et al, 2019). Furthermore, these 3 articles do not adjust for diuresis and only have a single sample (spot urine sample). Therefore, the weak associations that are claimed in these articles are questionable when considering these elements.

3. <u>Corrections/adjustments for confounding factors</u>

Seven of the nine articles report co-exposure to other metals (arsenic, lead, mercury and manganese) or environmental pollutants. Two of the articles did not explore/take into account confounding by co-exposure to other elements.

Another major potential factor affecting Cd uptake and by extension, Cd measurements is essential elements needs. As previously cited by Bernard et al (2016), Cd follows the same transport pathways as essential elements for its intestinal absorption, so variations in this could generate secondary associations between biomarkers of Cd exposure and outcomes involving renal function or the requirement of essential elements. One such vital element is iron, which may affect both the gastrointestinal uptake of Cd (Akesson et al., 2002; Meltzer et al., 2010) and fetal growth (Scholl, 2011).

Yet none of the studies related iron measures in pregnant mothers. This is especially important since studies have reported an increased risk for low birth weight and preterm birth, mainly related to overt iron deficiency anemia in early gestation (Scholl, 2011).

This is further echoed in one of the articles cited in the ECHA report: *"Moreover, zinc can be effective in pregnancy outcome, so the deficiency of this element during pregnancy has been associated with the delivery of low birth weight infants"* (Khoshhali et al., 2019)

4. Further confounding elements in each cited article

- Kippler et al (2012) concludes that they found a "*significant inverse associations between maternal Cd exposure and birth anthropometry in girls, especially head circumference and birth weight.*"
  However, their only biological sample is a spot concentration measure of maternal Cd-U which was not adjusted for diuresis (values in µg/L).
  Furthermore, in their bivariate analyses, maternal urinary Cd was not significantly correlated with birth weight, length, and head or chest circumference but was positively correlated with maternal age and urinary As concentrations.

  Additionally, co-exposure with high levels of arsenic through drinking water was reported as well as a BMI of < 18.5 kg/m^2 for one-third of the participants in the study, both of which could affect birth anthropometry.

- Gustin et al., 2018 concludes that *"Childhood cadmium exposure was associated with lower intelligence in boys, and indications of altered behavior in girls for both prenatal and childhood exposures."*
  This conclusion faces the same critique regarding choice of biological sample: their only biological sample is a spot concentration measure of maternal Cd-U, non-adjusted for diuresis (values in µg/L).
  Furthermore, 42% of the children were underweight which is a big potential confounding element, considering that mal/undernourishment can have a significant impact on growth and development.
- Chatzi et al., 2019 concludes that *"elevated maternal cadmium exposure during pregnancy was associated with delayed growth in early childhood."*
  This conclusion can be met with the same critique regarding choice of biological sample: their only biological sample is a spot concentration measure of maternal Cd-U, non-adjusted for diuresis (values in µg/L).

Furthermore, this study did not consider or explore eventual confounding factors such as environmental pollutants or co-exposure to other metals/pollutants.

- Gustin et al., 2020 concludes that "*The present study showed that maternal erythrocyte Cd and Hg were associated with poorer birth anthropometry, even at low levels prevalent in most populations world-wide. Studies on fetal outcomes following low-level maternal exposure to Cd, Pb, and Hg are very scarce, and thus, our findings should be confirmed in further large prospective studies.*"
  Co-exposure to both mercury and lead was reported, both of which are known to be associated with neurodevelopmental deficits.
  This study also includes maternal Cd-U unadjusted for diuresis (spot concentration) but it is supplemented by measures of Cd in erythrocytes.
  Further residual confounding cannot be excluded as possibly suggested by the positive associations with birth anthropometry observed at the lower metal concentrations.
- Igra et al., 2019 concludes that they *"found evidence that chronic cadmium exposure during early childhood might affect bone remodeling and growth at a prepubertal age".* Yet no measurements of bone mineral density were performed. Such measurements could have indicated whether the associations between cadmium exposure and bone-related biomarkers resulted in functional changes in bone health.
  Additionally, puberty was not assessed, although it could affect bone-related biomarkers. According to Jürimäe (2010), markers of bone remodeling are highly expressed during the first 3y of life, followed by a lower expression until the start of puberty, when biomarkers of bone remodeling area gain highly upregulated. Therefore, failing to investigate whether the children in the present study were pubertal or not, leaves doubt as to whether Cd is really the causal element or whether the association simply reflects the physiological changes in bone remodeling that are associated with puberty.
  Furthermore, measurements of TSH (instead of T3/4) and Ery-Cd analyses were only performed in a subsample of the children, which restricts the sample size and the power of the analysis.
- Tian et al., 2009 concludes that *"cord blood cadmium concentration was a factor that influenced fetus growth and later IQ development".*
  This study had the smallest sample size (109 pregnant women) and reported co-exposure to lead, which is known to be associated with neurodevelopmental deficits.
  Furthermore, this study is the only one of four studies evaluated in the Rodriguez-Barranco et al. (2013) paper, that showed a significant negative effect on the evaluated effects of cadmium exposure on neurodevelopment.
- Rodriguez-Barranco et al., 2013 concludes that "there is evidence that relates arsenic and manganese exposure with neurodevelopmental problems in children, but there is little information on cadmium exposure."
  Only 6/41 articles examined cadmium of which only two studies evaluated exposure to cadmium and found an association with neurodevelopmental or behavioral disorders. Of these, only one of the four studies that evaluated the effects of cadmium exposure on neurodevelopment showed a significant negative effect.
- Khoshhali et al. (2019) concludes the presence of a *"weak but significant association between maternal exposure to Cd and birth weight."*
  In this systematic review and meta-analysis, eight (45%) of the studies used maternal urine samples, and the others (55%) used maternal blood or cord blood samples to evaluate the relationship between cadmium exposure and neonatal anthropometric measures. That means that almost half of the studies have the same issue as mentioned above, regarding the choice of biological sample: maternal Cd-U

- Huang et al. (2019) concludes that *"a 50% increase of UCd was associated with a 6.15 g decrease in neonatal birth weight, and a 50% increase of BCd was associated with an 11.57 g decrease."* However, in their systematic review and meta-analysis, a majority of their articles used Cd-U as their biological sample, once again bringing into question the validity considering the low exposure levels of Cd. To their credit, five of the six articles adjusted the values for diuresis by correcting the measurements with creatinine values (expressed in µg/g cr).

  This study did not mention (or explore?) eventual confounding factors such as environmental pollutants or co-exposure to other metals/pollutants, to include essential element measures.

Page 48, 1st paragraph:

"There is consistent information on dose-response relationships between adverse effects on bones and cadmium exposure causing urinary cadmium levels ≥ 5 µg/g creatinine. At lower cadmium levels, ***bone*** *effects have been observed in several studies in the general population."*

Referring to the 'comment page 37, 4rd paragraph' already made on the cited bone studies at CdU levels < 5µg/g creatinine (as low as 0.5- 2µg/g creatinine), we would like to emphasis on a cautious interpretation of these data because also U-Cd is physiologically linked to proteinuria and albuminuria (Akerstrom et al. 2013), which are well-known predictors of bone and cardiovascular diseases (Barzilay et al. 2013; Smink et al. 2012).

Page 48, 2nd paragraph:

The above comment (page 48, 1st paragraph) applies also to the statement *" A relationship between cadmium exposure and cardiovascular disease has been observed in studies on the general population"* based on studies in the general population suggesting an increased cardiovascular risk already at cadmium concentrations around 1µg/g creatinine in urine (page 38)

Page 49, paragraph 2 and 3

These paragraphs state *"In the SCOEL (2017) recommendation, which was the basis for the current BOEL, the 8-hour value of 1 µg/m³ (0.001 mg/m³) was derived to protect for kidney effects (see Section 9.2.1). SCOEL considered evaluations by WHO (2000) and the German AGS (Ausschuß für Gefahrstoffe; BAuA 2014) of published data (primarily the publication of Thun et al. 1991), which indicated for nephrotoxicity a cumulative LOAEC of 100-400 µg/m³ x years. For 40 years of occupational exposure, this would mean an LOAEC range of 2.5 – 10 µg/m³. (0.0025-0.01 mg/m³)."*

As stated further in the ECHA report on page 55, section 9.2.2. OELs *"However it has been noted that the basis for the derivation of the OEL (see section 9.2.2.) is not very robust and the limitations of the data used in the key study (Thun et al. 1991), WHO, 2000 have been debated (DECOS 2019, BAuA 2014)", and also on page 56: "As explained in Section 8.2, some level of uncertainty is related to the data (e.g., few cases with kidney effects at exposure levels in the LOAEC range), and it is therefore not considered the best starting point for an OEL.",*

in the below, we document why we support these statements of the ECHA report on p55 and p56 and document further why the derived OEL of 1µg/m³ inhalable is not justified and scientifically correct:

Key information was omitted, essentially by the BAuA 2014, in the derivation of the SCOEL 2017 recommendation and basis for the current BOEL of 1µg/m³ inhalable fraction as in the CMD.

The error originates in improper use of data collected in a study from Järup et al., 1988, for the purpose of assessing the relationship of two exposure indicators: cumulated Cd in Blood (CumCdB) and cumulated Cd in air (CumCdAIR) with kidney tubular dysfunction (expressed as elevated Beta2M urinary excretion).

This information was carried forward in several subsequent studies, and some information was lost in the process, eventually leading to the error stated above.

The following publications/documents are below discussed, laying at the basis of the incorrect derivation of the 1µg/m³ inhalable OEL:

1. Järup et al. 1988
2. Thun et al 1991
3. WHO 2000
4. BAUA 2014
5. This error then flowed into SCOEL 2017.

<u>1/. Järup et al., 1988</u>

This summary of Järup et al, 1988 states *"Our results suggest that cumulative blood-cadmium is a more sensitive indicator of cadmium-induced renal dysfunction than cumulative air-cadmium"*

Hence, this is giving clear preference of the use of an exposure biomarker over an OEL for the prevention of systemic adverse effects.,

However, the process below (1-5) will favor an OEL over a BLV.

Interestingly, the important data of this study (which will be picked up by several studies below) is the relationship established between a "Cum Air Exposure Index" and proteinuria (measured as elevated Beta2Microglobulin(B2M) in urine).

A key important information is recorded below: the authors recognize that there is a natural distribution of B2M with a 97.5th percentile at 35 µg Cd/mmol creat. (= 310 µg Cd/g creat.).

Data on both the dose and effect variables have been collected up to 1982. Workers with β_2-microglobulin exceeding

35 µg/mmol creatinine were defined as responders, i.e. having tubular proteinuria. This level is somewhat arbitrarily chosen, but is similar to the upper limits chosen by other researchers in the field and is based on the upper 2.5 percentile for the urinary excretion of β_2-microglobulin among persons without tubular dysfunction [3, 14, 15].

This point made; the authors stratify a cohort of workers in the Saft Swedish battery plant based on the "Cum Exposure Index" and record the prevalence of elevated B2M for each exposure class.

Table 1a. Dose-response relationship using cumulative air-cadmium as the dose indicator

Dose-class	Cum CdA µg · yrs/m³	No. of cases	Total	Mean Cum CdA µg · yrs/m³	Response %
1	< 359	3	264	131	1.1
2	359–< 1710	7	76	691	9.2
3	1710–< 4578	10	43	3460	23.3
4	4578–< 9458	10	31	6581	32.3
5	9458–< 15000	5	16	12156	31.2
6	15000 +	5	10	21431	50.0

See further how this information is then used.

2/. Thun et al., 1991

Thun et al., 1991 discusses several end points, including tubular kidney damage.

Thun et al. 1991 report several studies (including the Järup et al 1988 study) in a table and plot the data on a graph.

TABLE IV. Occupational Studies Relating Kidney Dysfunction to Cumulative Exposure to Cadmium

Reference	Criteria for kidney effect[a] (mg/mol creat.)	No. exposed	Prevalence at exposures between 100–499 µg/m³-year) 100–	200–	300–	400–
CD recovery plant, U.S.						
[Ellis et al., 1985]	β-2 > 22.6	82	0/3	—	0/3	2/3
[Thun et al., 1989]	β-2 > 54.9	45	0/2	0/4	0/2	0/1
CD brazing, U.S.						
[Falck et al., 1983]	β-2 > 71.0	33	—	1/3	1/2	0/7
NI-CD battery, Sweden						
[Kjellstrom et al., 1977]	β-2 > 32.8	240		(Included in Jarup)		
[Jarup et al., 1988]	β-2 > 35.0	440	1/110	1/35	1/25	0/20
CD soldering, Sweden						
[Elinder et al., 1985c]	β-2 > 34.0	60	—	—	0/2	0/1
CD Brazing, U.K.						
[Mason et al., 1988]	RBP > 10.16	75	2/10	0/6	0/8	1/2
		Pooled data	2.4%	4.2%	4.8%	8.8%

[a]Kidney dysfunction defined by Ellis as either high β-2 or total protein (>250 mg/g creatinine) in spot urine; by Falck as high β-2, total protein, and glucose in spot and 24-hour urine samples; by other investigators as high β-2 or RBP in spot urine.

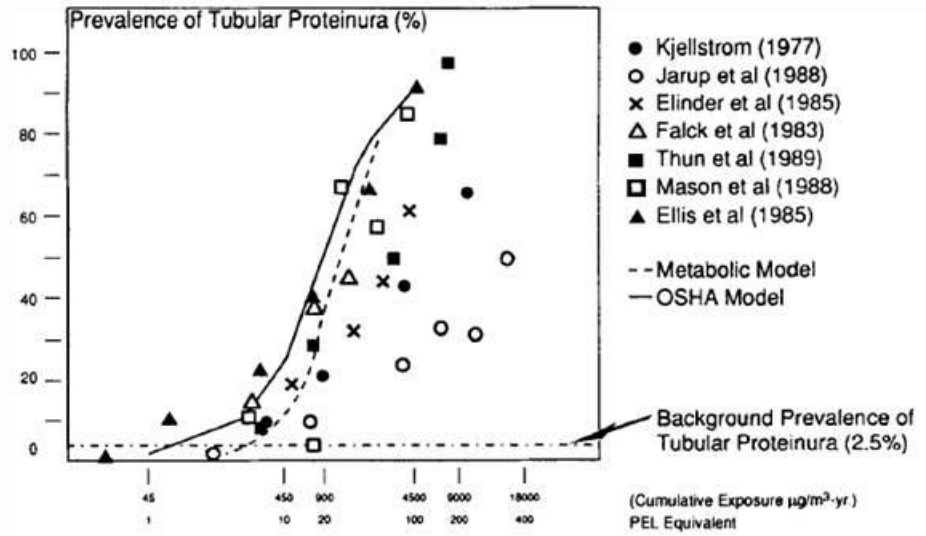


Fig. 1. Prevalence of tubular proteinuria by cumulative exposure to cadmium in seven cross-sectional studies compared to prediction by the OSHA risk assessment and by the Kjellstrom metabolic model.

The background prevalence of tubular proteinuria is properly recorded at 2.5% of the population.

Thun et al., 1991 concludes that although a gradual rise in prevalence is noted between CumCdAIR of 100 µgCd/m³*yr and 499 µgCd/m³*yr, it is not possible to determine a NOAEL with certainty.

Concept of a Renal Threshold

Figure 1 is theoretically compatible with the concept of a renal threshold, or critical concentration of cadmium above which kidney dysfunction appears. A distribution of such thresholds in the population would explain the gradual rise in the prevalence of kidney dysfunction at cumulative exposures between 100 and 499 µg/m^3-years. However, with the exception of the study by Jarup et al. [1988], there are few workers with cumulative exposures below 500 µg/m^3-years from which to estimate the prevalence of kidney dysfunction at these levels. Three studies [Falck et al. 1983; Ellis et al., 1985; Jarup et al., 1988] show a few cases of tubular proteinuria at cumulative exposures below 500 µg/m^3-years but the studies are too small to estimate prevalence at low exposures (Table IV). Pooled data suggest that prevalence may increase at cumulative exposures between 100 and 499 µg/m^3-years. However, the limited sample size, methodologic differences between the studies, and imprecision of the exposure data make it impossible to identify a no-effect level with certainty.

Thun et al, 1991 then stresses the fact that there is a natural background prevalence for unexposed persons, and that some models fail to account for this.

Mathematical models used in risk assessment appear to quantify the risk at low exposure levels, but these estimates are dependent upon the assumptions of the model and may not reflect reality. For example, the logistic regression model used by OSHA to estimate kidney dysfunction is misleading in that it predicts zero probability among unexposed persons for conditions that have a finite background prevalence. Such a model cannot predict excess risks of 1:1,000 when it ignores a background prevalence of 2.5%. Even if the model were appropriate, however, such modelling generally implies greater certainty than exists at low doses.

3/. WHO, 2000

When addressing the kidney endpoint, the document quotes the Thun et al. 1991 study and properly recalls the background level of 2.4% (derived from the 100-199 column of table IV above).

It correctly states that the proportion of workers with increased B2M rises when CumCdAIR increases from 100 to 400 µg/m³*yr (should state 499, not 400) from 2.4% to 8.8%.

It goes on by stating that the Kjellström model will predict critical concentration in the renal cortex will be reached in 1% of exposed workers after 10 years of exposure to 16 µg/m³ (CumCdAIR = 160 µg/m³*yr).

Health risk evaluation

Pooled data from seven studies which have examined the relations between the occurrence of tubular proteinuria and cumulative cadmium exposure show that the prevalence of tubular dysfunction (background level 2.4%) increases sharply at cumulative exposure of more than 500 µg/m^3-years (8% at 400 µg/m^3-years, 50% at 1000 µg/m^3-years and >80% at more than 4500 µg/m^3-years) *(29)*. Some studies suggest that a proportion of workers with cumulative exposures of 100–400 µg/m^3-years might develop tubular dysfunction (prevalences increasing from 2.4% to 8.8%, increase above background from 200 µg/m^3-years). These estimates agree well with that derived from the kinetic model of Kjellström *(30)*, which predicted that the critical concentration of 200 mg/kg in the renal cortex will be reached in 10% of exposed workers after 10 years of exposure to 50 µg/m^3 and in 1% after 10 years of exposure to 16 µg/m^3 (cumulative exposures of 500 and 160 µg/m^3-years, respectively).

4/.BAuA, 2014

When addressing the renal toxicity, the *"Begründung zu ERB Cadmium"* document makes the following statement:

*"From a WHO evaluation (2000), which is essentially based on the Thun et al 1991 paper, a LOAEL is derived for renal toxicity at an occupational exposure of 100 - 400 µg Cd/m³*yr, or at approximately 2.5 µg/m³ (assuming 40 yr exposure)".*

Nierentoxizität

Es erfolgt eine tubuläre Schädigung über Enzyminaktivierung, Calmodulinaktivierung und oxidative Effekte durch freies Cadmium nach Akkumulation in der Nierenrinde (ATSDR, 2008; Greim, 2004). Nach ATSDR (2008) lag die Urincadmiumkonzentration bei beruflichen Kollektiven in Europa, bei denen noch eine 10% Inzidenz für Proteinurie gefunden wurde, bei 7,5 µg/g Kreatinin und bei einer chinesischen Kohorte bei 4,58 µg/g Kreatinin. Bei 5 µg Cd/g Kreatinin ist demnach davon auszugehen, dass Nierenschäden noch möglich sind. Dies entspricht einer Menge von 7,5 µg Cd/L Urin (Drexler und Greim, 2008). Ein leicht darunter liegender Wert von 7 µg/L wurde deshalb als „biologischer Leitwert" (BLW) am Arbeitsplatz vorgeschlagen (Drexler und Greim, 2008). Vergleicht man diesen BLW mit dem von der Human-Biomonitoring-Kommission vorgesehenen HMB-I-Wert (Kommission "Human-Biomonitoring", 2003/2004) und weiteren Daten zur Nephrotoxizität von Cadmium (ATSDR, 2008; EFSA, 2009), so erkennt man, dass auch bei beruflicher Exposition unterhalb des BLW eine nephrotoxische Wirkung nicht ganz ausgeschlossen werden kann. Nach einer WHO-Abschätzung (WHO, 2000), die sich im wesentlichen auf die Veröffentlichung von Thun et al. 1991 bezieht läge der LOAEL für Nierentoxizität nach beruflicher Exposition bei 100-400 µg/m³ x Jahre oder (bei Bezug auf die Untergrenze dieses Intervalls) bei ca. 2,5 µg/m³ (Annahme: 40 Jahre Exposition). Wörtlich diskutiert WHO: *„Some studies suggest that a proportion workers with cumulative exposure of 100-400 ...,µg/m³-years might develop tubular dysfunction (prevalences increasing from 2.4 to 8.8 % ,increase above background from 200 µg/m³-years) ....These estimates agree well with that dirived from the kinetic modell of Kjellstoem..,which predicted that the critical concentration of 200 mg/kg in the renal cortex will be reached .....in 1% after 10 years of exposure to 16 µg/m³ (cumulative exposures of*

...160 µg/m³ - years). " Thun et al. 1991 beziehen sich bei der quantitativen Abschätzung des Risiko für Nierentoxizität auf die Arbeitsplatzstudien von Kjellström et. 1977, Jarup et al. 1988, Elinder et al. 1985, Falck et al. 1983, Thun et al. 1989, Mason et al. 1988 und Ellis et al. 1985. Diese Arbeitsplatzstudien sind in verschiedenen Cd-Gewinnungs- und Cd-Verwendungsbetrieben durchgeführt worden. Cd wurde analytisch als gesamtes atmosphärisches Cd bestimmt oder abgeschätzt. Die Arbeitnehmer in diesen Studien waren verschiedenen Cd-Verbindungen ausgesetzt. Da sich die Expostionsangaben auf das gesamte luftgetragene Cadmium beziehen, muß bei diesen Studien von einer Expositionsmessung von Cd-Gesamtstaub bzw- Cd E-Staub ausgegangen werden.

Die Umrechnung dieser Betrachtung von Kjellström auf eine Expositionsdauer von 40 Jahren würde einen Arbeitsplatzgrenzwert von 4 µg/m³ unterstützen. Allerdings wurde in zahlreichen Bewertungen eine Nierenkortexkonzentration von 200 mg/kg (Feuchtgewicht) als zu hoch eingeschätzt. Nach Amzal et al. (2009) entsprechen 50 mg/kg im Nierenkortex einer Urinausscheidung von 1,7-2,5 µg Cd/g Kreatinin. Wenn man für beruflich Beschäftigte von einer tolerablen Urinausscheidung von 2 µg Cd/g Kreatinin ausgeht (vgl. auch SCOEL 2010), sollte demnach im Bezug auf den Schutz vor nephrotoxischen Effekten ein Arbeitsplatzgrenzwert noch deutlich unter 4 µg/m³ liegen. Zudem ergibt sich aus der WHO-Bewertung, dass sich bei 1 % der Arbeiter auch bei 40 Jahren Exposition gegenüber 4 µg/m³ eine Nierenschädigung ergeben kann.

As you can see, the fact that the 2.4% prevalence (in the 100 – 199 range) is equal (or slightly lower) to the background prevalence of 2.5% is omitted. The lower end of the interval 100 - 499 is selected, generating an incorrect (because it disregards background) LOAEL of 2.5 µg Cd/m³.

The document further establishes the NOAEL with a safety factor of 3.

Analyse:

Nach der WHO-Abschätzung läge demnach der LOAEL für Nierentoxizität bei ca. 2,5 µg/m³ (Annahme: 40 Jahre Exposition). Wenn zugleich ein üblicher Faktor 3 für die Extrapolation von LOAEL auf NOAEL herangezogen wird (wobei es sich bei diesem Faktor um eine äußerst unsichere Konvention handelt), so erhalten wir einen NOAEL (Nierentoxizität) für berufliche Exposition von aufgerundet 1 µg/m³. Hierbei ist zu unterstellen, dass die Exposition über Belastungen mit E-Staub erfasst wurde.

5/.SCOEL, 2017

Unfortunately, this erroneous BAUA conclusion is taken over into the 02/2017 SCOEL opinion for which no "due process" (no consultation, no opportunity to submit dissenting opinions) was provided, and taken as the proposed OEL without any further development or analysis.

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

Page 49: second last paragraph

ATSDR Toxicokinetic models for the prediction of the relationship between inhalation exposure and cadmium concentrations in the kidney cortex and urine.

*"Nordberg et al. (2018) identified kidney effects as the critical effect and considered **2 µg/g creatinine** as a critical dose level, at which LMW proteinuria may occur in a susceptible subsection of the population. For the **derivation of a corresponding air concentration**, the authors referred to calculation of ATSDR (2012), who applied toxicokinetic models for the prediction of a relationship between inhalation exposure and cadmium concentrations in the kidney cortex and urine. A cadmium mass fraction of 120 µg Cd/g in the kidney cortex was predicted to correspond to 2 µg/g creatinine, and 84 µg Cd/g (the estimated lower confidence limit on the renal cortex concentration associated with a 10% probability of low molecular mass proteinuria (Diamond et al., 2013)) to correspond to 1.4 µg/g creatinine. The authors estimated that occupational exposure via inhalation of air containing 2.7 µg cadmium sulfide/m³ (uniform particle size 1 µm) for 40 years (8 h/day, 5 days/week) would result in a kidney cortex mass fraction of 84 µg Cd/g. For cadmium oxide, the corresponding air concentration was calculated as 5.1 µg/m³."*

A relative high degree of uncertainty is associated with this derivation of corresponding air concentration value based on the ATSDR Toxicokinetic models for the prediction of the relationship between inhalation exposure and cadmium concentrations in the kidney cortex and urine.

The ATSDR itself uses the pharmacokinetic model developed by Kjellström and Nordberg (1978) and the ICRP Human Respiratory Tract Model (1994) to predict cadmium air concentrations. Such an extrapolation is built on a number of assumptions, which require verification in order to reliably predict safe exposure levels. The ATSDR concludes that "*Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (MMAD=1 µm) and oral intakes that yield the same urinary cadmium level, exposure to an airborne cadmium concentration of 0.1 µg/m³ and a dietary intake of 0.3 µg/kg/day would result in a urinary cadmium level of 0.5 µg/g creatinine*"

A relative high degree of uncertainty is associated with this derivation of corresponding air concentration value, since:

- the methodology treats ingestion as a fixed value, whereas workplace conditions show that actual ingestion can vary widely across individuals, depending on their specific workplace and personal hygiene. Therefore, it seems the control measure should be based on an indicator controlling exposure from all possible modes of uptake.
- inhalation exposure was assumed to be towards an aerosol with an MMAD of 1µm which appears to be a simplified approximation of the workplace exposure conditions
- a point estimate for baseline non-occupational cadmium dietary intake of 0.3 µg/kg/d was assumed, which may constitute an underestimation of the true exposure
- absorption factors for oral and inhalation were not reported in the ATSDR
- the pharmacokinetic model uses a point estimate for the correlation of cortex cadmium concentration and urinary cadmium concentration (84 mg/kg corresponding to a mean 1,4 µg Cd/g), although lower and higher values are also within the confidence interval

This approach is based on the total cortex cadmium concentration as dose descriptor for kidney adversity. However, this approach does neither consider any pre-occupational cadmium exposure nor does it foresee any modification to be above described uncertainties. In order to safely protect workers against cadmium related kidney toxicity, urinary cadmium determination appears the best possible way forward, also knowing that its monitoring is already widely in use in the cadmium industry.

Page 50: section 9.1.1, 2nd paragraph

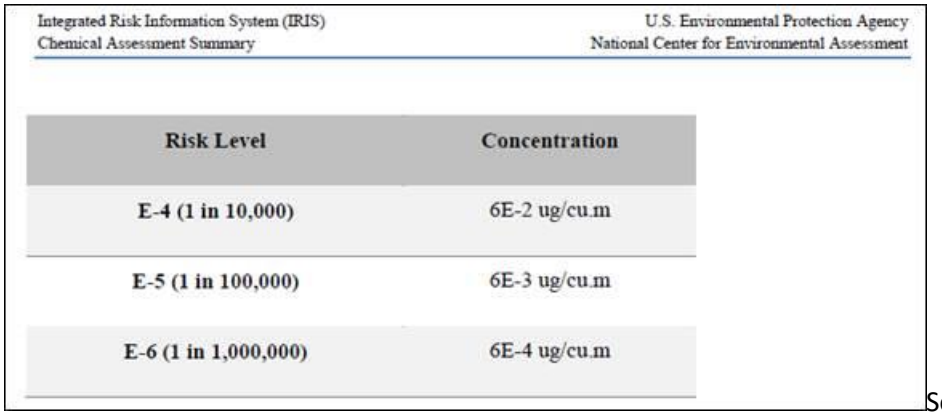
Second paragraph: *"data from the inhalation carcinogenicity bioassay with CdCl2 by Takenaka et al 1983 were considered by EPA (1994) and by the Ausschuss für Gefahrstoffe (BAuA 2014). "*

It should be noted that the correct reference is EPA (199**9**) and not EPA (1994).

It should also be noted that EPA is not considering Takenaka et al 1983 as starting point but the epidemiological study Thun et al 1985 which was less accurate in assessing the actual cumulative Cd exposure and had not yet corrected for confounding factors (arsenic, smoking, ethnicity). Later refinements by Stayner et al., 1992, Park et al., 2002 and Haney (2016) calculated a lower cancer risk. (see comments on section 7.7.1.)

Furthermore, the value EPA has derived for an additional cancer risk of 1:1 000 is at 0.6 µg and not

1µg as indicated at p50


Integrated Risk Information System (IRIS)
Chemical Assessment Summary

U.S. Environmental Protection Agency
National Center for Environmental Assessment

Risk Level	Concentration
E-4 (1 in 10,000)	6E-2 ug/cu.m
E-5 (1 in 100,000)	6E-3 ug/cu.m
E-6 (1 in 1,000,000)	6E-4 ug/cu.m

Source EPA(1999)

Page 51: table 15:

SCOEL (2017): 4µg/g creatinine is not correct. This should be corrected to: 4 µg/m³ (respirable)

Page 52: second para:

"Based on recent studies, it appears that renal effects can be detected in the general European population (mainly exposed by the oral route) for cadmium body burdens at or even below 2µg Cd/g creatinine (LOAEL)."

We refer back to comment page 35 contesting already this statement and reference to those general population studies indicating kidney effects at CdU concentrations ≤ 2µg/g creatinine. This statement is made several times throughout the ECHA scientific report (see also page 47 section 8.1.1, 3rd paragraph; page 58 second bullet point).

Page 52, 6th bullet point:

- *"The point of departure identified from human studies in occupational settings (5 µg Cd/g creatinine) is a LOAEL for renal effects (chapters 8.1.5, Table 2; 8.3.1, Table 3) "*

The indicated numbering is not correct and should be corrected to 7.1.5. Table 5; 7.3.1. Table 6

Page 53: section 9.2.1.2 AGS (BAuA 2014)

"The tolerable cadmium cancer risk (1:1 000) derived by AGS corresponds to a work life-long exposure at 1.6 µg/m³ (respirable fraction) (see also 9.1.1) (BAuA 2014)."

The tolerable cadmium cancer risk (1:1 000) is not correct and should be corrected to 4:1 000

Page 55: section 9.2.2. OELs – 8hTWA

'However, it has been noted that the basis …. Is not very robust and the limitations of the data used in the key study (Thun et al. 1991)…"

See more detailed comment on ECHA report page 49: comment on Thun et al. 1991 paper used to derive OEL of 1µg/m³ (inhalable) to protect for KIDNEY effects

This is also reported and confirmed on page 56: *"As explained in Section 8.2, some level of uncertainty is related to the data (e.g., few cases with kidney effects at exposure levels in the LOAEC range), and it is therefore not considered the best starting point for an OEL."*

Page 55, section 9.2.2.1, 2nd paragraph

See comment ECHA report page 49: on ATSDR Toxicokinetic models for the prediction of the relationship between inhalation exposure and cadmium concentrations in the kidney cortex and urine.

Page 56: Kidney effects, 1st paragraph

"As explained in Section 8.2, some level of uncertainty is related to the data (e.g., few cases with kidney effects at exposure levels in the LOAEC range), and it is therefore not considered the best starting point for an OEL."

See more detailed comment on ECHA report page 49: comment on Thun et al. 1991 paper used to derive OEL of 1µg/m³ (inhalable) to protect for KIDNEY effects

Page 56:

Bone effects

*'Other studies report effects also at lower exposure levels, but **uncertainties and confounding factors** make it difficult to identify thresholds (LOAEL/NOAEL) based on that data.'*

There is no clear explanation in the ECHA report on the uncertainties and confounding factors as cited above. The review of Nordberg et al. (2018) provides a clear summary *"When interpreting epidemiological findings on bone effects, additional information is required. This includes information about nutritional factors, as well as the toxicodynamics associated with tissue levels of cadmium that cause decalcification of bone. It is also important to have a better understanding of the toxicokinetics of cadmium in bone and the relationship between bone effects and biomarkers of exposure. Without this information, while it is possible to conclude these effects are adverse, it is not possible to be certain that there is a causal relationship between urine cadmium in the range 0.5–5 µg g−1 creatinine (0.5–5 nmol mmol−1 creatinine) and decreased Bone Mineral Density."*

Cardiovascular effects
"A clear relationship between cadmium exposure and cardiovascular disease has been observed in studies on the general population"

Referring to the above comment (page 38-cardiovascular/p48) it is not possible to state whether the effects have a true quantifiable causal relationship with Cd exposure

Page 57, section 9.2.2.2. Proposal for OEL, 5th paragraph

*If an OEL of 0.004 mg **µg** Cd/m³ (4 µg Cd/m³) (respirable fraction) was applied together […]*

The "µg" should be deleted in the *0.004 mg **µg** Cd/m³*

Page 58:

"- Kidney effects are still considered the critical effects of cadmium exposure. Several studies indicate a LOAEL of 2 µg/g creatinine in the general population. In occupational settings the LOAEL has been identified as 5 µg/g creatinine. No NOAEL was identified. Some data indicates effects in the general population at concentrations < 2 µg/g creatinine (even as low as 0.5 µg/g creatinine). Diuresis is however likely to cause major confounding effects at such low levels of exposure. "

We refer to detailed comment on ECHA report page 35, related to cautious interpretation of 'some

data indicates effects in the general population at concentrations < 2µg/g creatinine (even as low as 0.5 µg/g creatinine).

"-At lower levels, bone effects in the general population have been observed at urinary concentrations 0.5-5 µg/g creatinine, but there are also studies with no effects."

We refer to detailed comments on ECHA report page 37 and 48, related to cautious interpretation of 'bone effects in the general population have been observed at urinary concentrations 0.5-5 µg/g creatinine…'

5. References not already cited in ECHA's Scientific report (September 2020)

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