

Summary of Comments:

The Annex XV report on Cadmium sulphate highlights two areas of risks:

1. risk of increased bone and kidney effect on the general population due to exposure to Cd and its compounds from the environment,
2. risk to a large number of EU workers occupationally exposed to cadmium compounds.

These risks are taken forward as a basis to request that cadmium sulphate be submitted to the REACH authorization process.

However, no effort is made in this Annex XV to try to link “uses” of cadmium sulphate to the risks to the general population. It is to be noted that only intermediate uses were reported in EU REACH registration files, which are not supposed to be in the scope of “Authorisation procedure”

Moreover, the Annex XV fails to recognize that the vast majority (over 98%) of workers is exposed to cadmium and its compounds present as impurity in commodities.

In these comments, industry will show that:

1. The contribution of the industry deliberately using cadmium sulphate to general population Cd-exposure is insignificant as compared to the contribution of the industry manipulating goods in which cadmium is an impurity. In other words, the manufacture and formulation of cadmium sulphate has no influence on general population cadmium exposure,
2. The use of articles containing Cd and Cd compounds is already under many restrictions, prohibitions and limitations within the EU. Industry will show that exposure from the remaining articles, including their end of life, is insignificant
3. The sectors of industry that are deliberately using cadmium and its compounds only employ a small fraction of the estimated number of occupationally exposed workers (1.6%). These sectors deliberately using Cd and its compounds have a solid record of risk management and risk reduction; since 2008 they voluntarily implemented the Swedish Occupational Risk Agency management tools and implemented a DNEL based on the OEL set by SCOEL in 2010 (SUMDOC 136 2010).

In clarifying these points, it will become clear that authorization of CdSO₄ uses will not lead to any influence on general population and worker exposure, and as such will be insignificant to “ensure that the risks posed by the substance of very high concern will be properly controlled” (REACH art 55). Indeed, it will be clear that any Risks are already properly controlled.

Some claim that the candidate listing of cadmium sulphate is quasi automatic, as that substance has been classified CMR. According to the findings of the Board of Appeal, though, ECHA is expected to assess “*all the information which must be taken into account in order to assess a complex situation*”, and all the evidence, which “*is capable of substantiating the conclusions drawn from it*” (Decision of the Board of Appeal in case A-005-2011, paragraph 75, judgment of the European Court of Justice in case C-12/03 P Tetra Laval [2005] ECR I-987, paragraph 39).

We trust ECHA will take into account “*all the relevant factors and circumstances of the situation the act is intended to regulate*” (Decision of the Board of Appeal in case A-005-2011, paragraph 77), as

we feel that position is also part of ECHA's duty of sound administration – a general principle of EU law according to which, before they take any decision, institutions and bodies of the European Union with decision-making power have a duty to prepare it carefully and in particular to verify all the elements of fact which may have an impact on it (Case T-73/95, *Estabelecimentos Isidoro M. Oliveira SA v Commission of the European Communities*, paragraph 32 [1997] ECR II-381).

The analysis of the most appropriate risk management option for cadmium sulphate (submitted by Sweden, March 2014) concludes that *“Even though there is no full registration for cadmium sulphate, the substance is considered relevant for the Candidate list from a grouping point of view. At present, there are six cadmium compounds with a harmonised classification as Carc. Cat 1B; three of those are already on the Candidate list and a fourth has recently been proposed. To some extent cadmium compounds may be used as alternatives to each other and it is therefore considered important to treat all these compounds in a similar manner in order to promote substitution to other less toxic substances.”*

The six referred CMR Cadmium compounds are: Cd, CdO, CdS, CdCl₂, CdSO₄ and CdF₂.

- Cd is mainly used (industrial use) for industrial batteries, alloys and when permitted for plating. A metal is never substitutable in its uses by a metal compound
- CdO is mainly used (industrial use) for industrial batteries and for electrical contacts. This oxidic compound cannot be substituted in its uses by any other Cd CMR compound
- CdS is, besides its intermediate uses, mainly used in electrophotovoltaic applications and there is no way to be substituted by any other Cd CMR compound
- CdCl₂ is, besides its intermediate uses, reported to be used as activator in photovoltaic layers; alternatives are sought but no substitute are available today and certainly not the other Cd CMR compounds
- CdSO₄ is only reported to be used as intermediate in pigment manufacturing and photovoltaic component manufacture
- CdF₂ is not registered above 1T use and is probably limited to minor laboratory reagent uses

In summary, there is no rationale a) for suspecting any substitution and b) for claiming for grouping under an authorization procedure, for substances for which no uses are reported.

In the following, a number of comments on the Annex XV document on cadmium sulphate are given. This master-file contains also the references.

Comments

Comment 1

Page 6, section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH”, heading “equivalent level of concern”, 3rd paragraph, 4th line -

Annex XV states that “Deposition from air is an important source to the input of cadmium to soil and must therefore be reduced. In order to achieve this all uses of cadmium and cadmium compounds should wherever possible, be substituted”. This statement ignores (a) the one major source of Cd-input to soil, i.e. use of P-fertilizer (see below), and (b) makes the wrong assumption that (REACH) uses of cadmium contribute to human exposure, which is not the case (see comment 5).

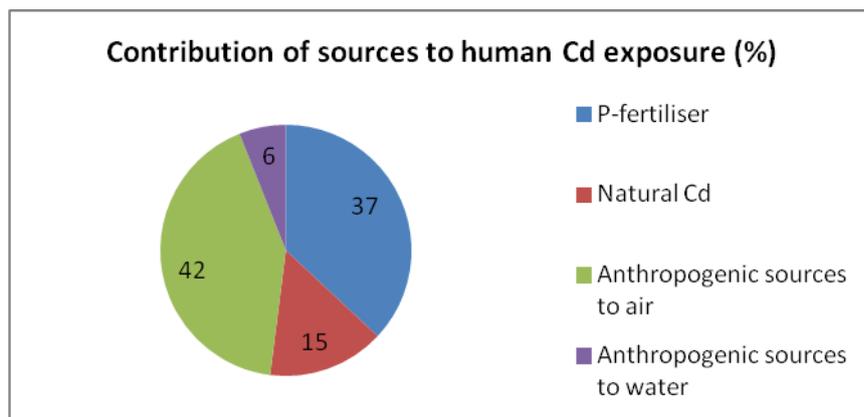
- the major single source of Cd input to agricultural soils, i.e. the use of P-fertilizer, is ignored in the Annex XV dossier. P-fertilizer which may have significant Cd-content of natural origin (3-90ppm, ICdA 2012), is directly applied on the soil and as such is the main direct source of Cd into the food chain. The contribution of P-fertilizer to human exposure is estimated to be significant, as is explained below (see figure 1.1¹) This was also recognized by Sweden where, at one time, taxes on fertilizers with high cadmium contents were imposed. (These taxes were dropped later for unknown reason.)
- Industrial emissions to atmosphere are also important. These are mainly related to the cadmium that is present as an impurity in mineral commodities that are processed/combusted by industry (see comment 5).
- Last but not least, it is emphasized that manufacturing and use of Cd-containing products (including end of life) does not lead to exposure to the general population, as is demonstrated in comment 5.

In figure 1.1 the main sources categories of Cd to the general population are presented for non-smokers (Van Assche 2011). Based on quantitative modeling of the transfer pathways of Cd from the environment into the food chain², it is estimated that the main inputs to soils (and, consequently, to the food) are P-fertilizer (37% of total human exposure), and sources of Cd-emission to the atmosphere (42% of total human exposure). In a conservative approach, natural soil Cd is contributing for about 15%, and exposure from water-related sources is rather limited (6%). These results correspond to data given for a number of member states in Annex VII of the human health risk reduction strategy (OJ 2008/C 149/03)

¹ We note that the percentages provided are averages for the EU, and that differences between countries in Cd-sources to soil can occur. Yet, the averages are quite consistent throughout EU member states (OJ 2008/C 149/03) and thus provide a good quantitative estimate of the contribution of different sources of Cd to the exposure of the general population.

² Basic quantifications of the model: total internal exposure 100%; 96% food, 4% air inhalation (non-smokers); food: 98% terrestrial origin (crop), 1% sea and river food, 1% drinking water; crop Cd: 80% soil uptake, 20% atmospheric deposition; soil Cd: 80% antropogenic, 20% natural; antropogenic input into soil: P-fertilizer 60%, atmospheric deposition: 30%, sludge 10%. For further details see Van Assche (1998).

Fig 1.1: Relative contribution of different Cd sources to human exposure – general population-non-smokers (after Van Assche 2011).



As follows from figure 1.1, atmospheric emissions are important as source to general population exposure (apart from P-fertilizers) because of the direct relationship with crop Cd-content (atmospheric deposition on edible plant parts and deposition on soil, resulting in root uptake). Given this importance of this relationship, a correct assessment of the emissions sources of cadmium to atmosphere is key for understanding sources of general population exposure. This analysis will be presented under comment 5.

In comment 5, it is estimated that, taking all EU emissions together from the production, processing, use and end-of-life incineration of all Cd products account for less than 1% of the anthropogenic Cd-emissions to the EU-atmosphere. Accordingly, it can be calculated that <0.42% of the Cd-exposure of the general population could originate from the Cd industry as a whole (sum of Cd-industry emissions + emissions from incineration <1% x 0.42, cfr figure 5.1).

It is emphasised that the assessment given above relates to all uses of Cd and Cd compounds. Cadmium sulphate as such is not directly used by consumers. Therefore, the contribution from CdSO₄ production and use to general population Cd exposure is considered insignificant, and consequently any measures related to this source are considered insignificant and not proportional too.

The major sources of Cd to atmosphere are detailed in comment 5. The dossier provides no support of how these sources would relate to CdSO₄.

Comment 2

Page 6, section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH”, heading “equivalent level of concern”, 4th paragraph, 4th line -

Reference is being made to the Council resolution on cadmium of 25 January 1988 -25 years ago- to justify further action on cadmium. The Annex XV fails to consider a) extensive EU legislation that was implemented since then on restrictions of the main cadmium uses, b) the extensive work that has been undertaken by the Commission since then on cadmium, with the EU risk assessment, as a result of which further measures were decided, c) the marked progress that was achieved on limiting documented Cd-emissions to air, water and soil. As such, the annex XV document ignores the significant reduction that has been observed since 1988 related to the cadmium exposure of the general population through the atmosphere (see comment 5 for data).

Comment 3

Page 8, section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH” (cont.), 3rd paragraph -

The annex XV document mentions rightfully that there is a continuous publishing of new information on cadmium. It states that this demonstrates that “what can be considered as a safe exposure level is steadily decreasing”. This statement however ignores a number of recent publications that challenge the significance of Cd-U as a marker of cadmium exposure in situations of very low exposure (e.g. at or below Cd-U = 1 µg Cd/g creatinin) for both kidney and bone effects (see comment 8 for details). It is emphasized that the current exposure of the general population is below this very low level (EU mean value for female adults \approx 0.22µg/l), as is demonstrated by recent Cd-U monitoring data in the EU (see comment 33 for details).

Comment 4

Page 8, section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH” (cont.). 6th paragraph -

The estimation of annual costs of cadmium exposure in Sweden is based on the lowest estimation of the safe exposure level, measured by Cd-U. Cd-U is however recently challenged by academic research as a biomarker of Cd-exposure in situations of very low exposure (see comment 8). The estimation of annual costs therefore needs to be considered with great caution.

For the use of cadmium in pigments a detailed critical review has been made of the economic analysis in the KEMI report (KEMI 2013) and the underlying studies from which the KEMI’s final economic figures were derived (EFTEC 2014).

Comment 5

Page 12, section 3.1, Anthropogenic and natural sources of cadmium exposure

As follows from the analysis under comment 1 on sources of cadmium to general population exposure, the Cd inputs to atmosphere are an important contributing factor, because they are a direct source of crop/food cadmium content. The annex XV fails to make a quantitative analysis of the relative weight of the different origins of cadmium going into the atmosphere and being deposited on/taken up by the crops. As such, Annex XV fails to assess the importance of the different atmospheric Cd-sources in the perspective of human exposure. This analysis is presented here.

The current atmospheric emissions from the different sources in the EU are presented in figure 5.1 (EMEP inventory (2012)). From this inventory, the relative contributions of deliberate uses of cadmium and cadmium as impurities to atmospheric depositions can be determined:

It follows from figure 5.1 that the main Cd sources to atmosphere are: a) public power generation, b) industrial combustion, c) small combustion; d) industrial processes, e) waste incineration. These sectors emitted 20, 50, 5, 30, and 13,8 Tonnes of Cd per year into the atmosphere in 1990, respectively.

In 2010, they were (with the exception of waste incineration) still the main sources, but important decreases in emissions were observed by that time: Cd-emissions for these sectors were by then 7,

19, 6.6, 10.4, and 0.45 T/y respectively (EMEP 2012). The significant decrease of waste incineration emissions is noted (-97% compared to 1990 emissions).

Overall, Cd emissions to the atmosphere decreased by >60% over the period 1990-2010 (EMEP 2012). It follows from these data that the major part of cadmium emissions to atmosphere is from anthropogenic use where Cd is an impurity. The emissions from deliberate Cd production and use are further discussed below.

It should be noted that the EMEP inventory does not report natural emissions. These have been estimated at ca. 15T/yr (Cd/CdO RAR ECB 2008).

The emissions from the company’s manufacturing Cd-products (Cd-production, Cd-recycling, production of Cd compounds, manufacture of NiCd batteries, pigments, and thin-film photovoltaic panels) are very low. They are given in table 5.1., based on recent company data reported by industry.

Figure 5.1.: Cd-emissions to the atmosphere (T/y) by sector in the EU-15 during the period 1990-2010 (EMEP 2012).

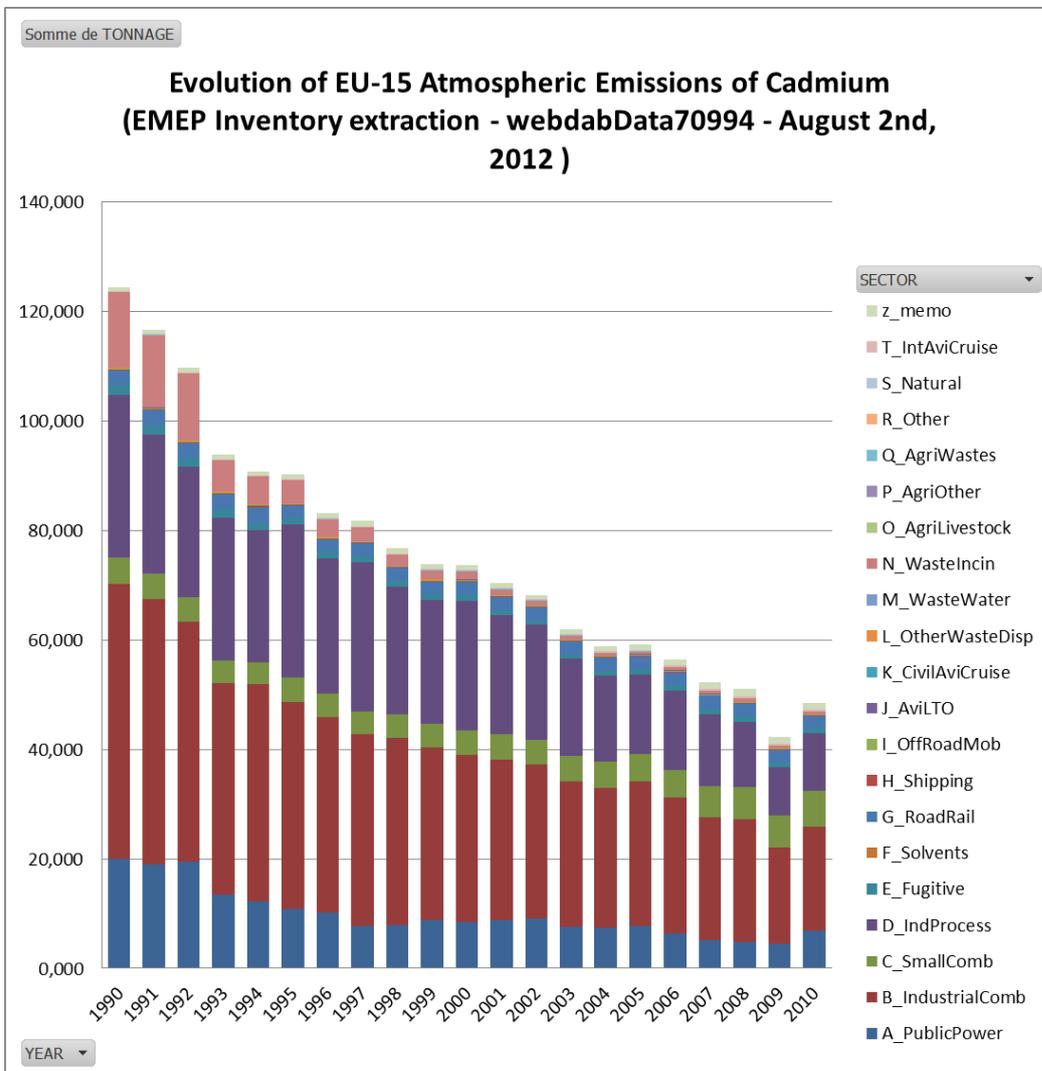


Table 5.1.: Industry supplied data (2012) on Cd emissions to air (T/y) in the EU covering all EU sites with deliberate uses of cadmium (Cd refiners, specialty cadmium compounds manufacturers, Ni-Cd battery manufacturers, thin film PV manufacturers, recyclers).

Industrial activity	Emission to atmosphere (kg Cd/y)
Cd-production	53.6*
Cd-compound production	5.1
Cd recycling	1.1
Cd-products manufacture	26.3
Total EU Cd-industry	86.1

*data from 4 out of 6 EU producers; for 2 missing companies, an emission factor following from the available data was used.

The data presented above all relate to cadmium and cadmium compounds in general. They demonstrate that the contribution from the whole of the Cd-related industry (production, processing to compounds, manufacturing into products, recycling) to the total anthropogenic atmospheric Cd-emissions are minimal (0.18% of EU total). Consequently the contribution of this industrial activity to the total anthropogenic Cd-exposure of the general population is 0.08% (= 0.18 x 0.42; cfr fig 1.1).

Considering the above, it is emphasised that the production and use of CdSO₄ is only a small fraction of this industrial activity related to cadmium in general. Therefore, the contribution of the CdSO₄ production and use to cadmium exposure of the general population is entirely insignificant.

During service life, emissions from Cd-containing products are negligible: e.g. with NiCd batteries, the main application, there is no emission or consumer exposure at all. Cd-pigments and Cd-compounds for photovoltaic applications are also contained in a matrix and do not cause emission or consumer exposure, neither (see also comment 26).

At end of life, most of the Cd in products is recycled (e.g. industrial NiCd batteries, photovoltaic panels). A small amount ends up in the municipal waste stream and can be incinerated, thus resulting in Cd-emissions to atmosphere, together with Cd from other sources. The total Cd-emissions from municipal waste incinerators in the EU was 453 kg/y in 2010 (EMEP 2012). It is noted a significant part of this Cd is of natural origin, e.g. the contribution from food and garden waste is estimated to be recently of the order 15% (Arche 2012). Moreover, part of the emissions originates from Cd-traces in non-Cd products. Considering this, the Cd emissions from incineration of Cd-products/impurities can be estimated to be <85% of total, which is <0.8% of total Cd-emissions to the atmosphere (48.4 T/y; EMEP 2012). It is noted that CdSO₄ containing products are only a very small fraction of the waste stream related to cadmium in general. Therefore, the contribution of the CdSO₄ production and use to cadmium emissions from waste is considered entirely insignificant.

In general, the decrease of the Cd-emissions from municipal waste incineration is partly due to the decrease of the Cd-content in municipal over the last decades, e.g. in a study from the French agency on environment and energy, it was observed that the Cd-content of MSW in France (which can be taken as relevant for the EU), decreased from 4 mg/kg DW in 1993 to 1.3 mg/kg DW in 2007 (ADEME 2007).

All EU Cd-emissions taken together i.e. from production, processing, use and end-of-life incineration of Cd products account for <1% (= 0.18% + <0.8%) of the anthropogenic Cd-emissions to the atmosphere and, accordingly, for <0.42% of the Cd-exposure of the general population (sum of Cd-industry emissions + emissions from incineration <1% x 0.42, cfr figure 1.1).

In other words, the emissions from deliberate Cd production and use are minimal compared to the total emissions. Notably the emission from the production and use (as an intermediate) of CdSO₄ is very low and therefore its impact on general population exposure is considered negligible.

In conclusion, a) emissions to atmosphere from Cd-production, processing and use are minimal, b) most Cd in products is recycled and emissions from incineration of municipal solid waste are also limited. Since all combined emissions related to deliberate anthropogenic cadmium activity amounts only to less than 0.42% of general population exposure, the effect of measures taken against the use of Cd-products on general population as a whole and, notably, the effects of measures taken against CdSO₄ are considered to be insignificant and disproportionate.

Comment 6

Page 13, section 3.2: "food"

This paragraph makes reference to a recent EFSA report to conclude that "children and adults at the 95 percentile exposure can exceed health-based guidance values". As is indicated in the EFSA report itself, this 95 percentile estimate is "speculative and potentially unrealistic" (section 3.2 page 17 of EFSA 2012) because it is based on the unlikely assumption that the same individuals retain the same high exposure throughout their whole life. This 95 percentile should thus be considered as clearly overestimated. The average Cd intake value calculated in this EFSA study is considered conservative as it is higher than recently published values in EU countries. However, it remains below the EFSA dietary intake standard, which is itself lower than the WHO dietary intake standard. Therefore, even following conservative assumptions, current observed dietary intakes in the EU can be considered safe in a life time perspective. See comment 33 for more detail.

Comment 7

Page 13, section 3.2: "food"

The Annex XV document makes reference to the current TWI of 2.5 µg/kg bw as defined by EFSA (EFSA 2009, 2012).

Both WHO's Joint expert committee on food additives (JECFA 2010) and the European food safety authority (EFSA 2012) have derived a provisional tolerable weekly intake (PTWI) value for cadmium. In spite of the fact that the same epidemiological dataset was used by both organisations, and that they use similar toxicokinetic models to relate urinary cadmium to dietary cadmium intake, the outcome of both exercises is different: while JECFA derives a tolerable weekly intake of 5.8µg Cd.kgBW.w, EFSA sets the limit at 2.5µg Cd/kg BW.w. EFSA (2012), on request of the EU Commission, re-evaluated the evidence and models and identified a number of differences possibly explaining the different outcome. One of those is the methodology used for transforming urinary cadmium concentrations into dietary intake values. We will here comment further on this aspect of the assessment.

To determine dietary exposure corresponding to a (critical) Cd-U, EFSA used the paper by Amzal et al (2009), based on the data from a Swedish population based study on non-smoking, post-menopausal women. Using a reference point (RP) of 1µg/gC for Cd-U, EFSA calculated that the average daily intake should not exceed 0.36µg/kgBW.d, and this daily intake was used to calculate the tolerable weekly intake of 2.5µg/kgBW.w.

When looking at the Amzal et al paper in more detail, it can be observed that the RP of 1µgCd/gC is exceeded in only 2 individuals of the 680 participating in the study. The maximum intake observed in the study is 0.4µg/kg.BW. In other words, at this highest intake, only 2/680 or <<1% of the population is exceeding the RP, while the critical intake following from the analysis is set at the 95% protection level. At the same time we observe that the highest dietary intake (0.4µg/kgBW.d) is equal to the critical intake value derived to protect the 95percentile of the population.

So, there are reasons to assume that the Amzal et al assessment is overly conservative. The main reason for this seems to be the assumption, in Amzal et al (2009), and taken over in EFSA (2009) that the highest Cd-intake can correspond to the highest bioavailability in the body, resulting in the highest Cd-body burden (measured as Cd-U). As indicated below, this assumption does not correspond to measured Cd-uptake (as Cd-B or Cd-U) data, as follows from the detailed overview made in the EU risk assessment RA (ECB 2007).

The EU risk assessment report (ECB 2007) discussed in detail the evidence related to the relationship between Cd-intake and Cd-uptake in the body. The evidence suggested that higher Cd intake due to a higher consumption of food groups with elevated Cd-content, e.g. shellfish and mushrooms, is not reflected in a proportional increase in systemic dose of Cd. The data show that other factors than food Cd-content, e.g. iron status and fiber intake, have a more important effect on Cd-B. Some case examples:

- In the duplicate meal study of Vahter et al. (1996), a group of 17 non-smoking women, consuming shellfish at least once a week, was compared with a group of 34 non-smoking women with a mixed diet low in shellfish. The average dietary Cd intake in the shellfish group was 28 µg Cd while it was 11 µg Cd for the mixed diet group. The Cd-B was not significantly different between both groups (0.28 µg/l and 0.24 µg/l respectively). The Cd-concentration in the blood was strongly influenced by the body iron stores of the test persons and increased sharply when serum ferritin was below about 20 µg/l.
- A study from New Zealand on oyster consumers showed that, in spite of very high Cd intake via oysters (group averages 15-233 µg/day), Cd-B and Cd-U were significantly elevated, however, not to the same extent as the dietary intake (McKenzie-Parnell et al., 1988). Smoking had a more pronounced effect on Cd-B than intake of Cd via oysters.
- The gastrointestinal availability of Cd from mushrooms is most probably also low. The Cd concentrations in blood, urine and faeces was monitored daily for eight adults (5 male and 3 female, 2 moderate smokers) that consumed 290-500 g wild mushrooms (*Agaricus* species) daily during three consecutive days (Schellman et al., 1984). Monitoring started 2-3 days before the mushroom consumption and was continued for 4 days after the last mushroom meal. The extra Cd intake due to the mushroom consumption varied between 315 and 908 µg Cd/day. The faecal excretion of Cd sharply increased on the first day of mushroom consumption and, although it decreased progressively the following days, it was still elevated up to four days after the last mushroom meal. In contrast, Cd-B did not show any trend during the whole experimental period for any individual. The Cd-B varied between 0.2 and

2.9 µg/l and the Cd-B variance among individuals was larger than that within individuals. No increase in Cd-U was found during or after mushroom consumption.

- By analysing data on observed Cd-U, the RA concluded that model calculations assuming a GI absorption rate of 10% at $t_{1/2}=13.6$ years are generally overestimating uptake by the body. Moreover, the largest calculated Cd-U at the GI absorption rate 5% (at same $t_{1/2}$) is 0.76 µg Cd/g creatinine, which is still >2 fold above the largest observed value. Citing the RA (ECB 2007): *“This indicates that either the 5% GI absorption rate also overestimates the body burden in this group or that groups with the largest Cd intake have a lower average GI absorption rates as often found in feeding studies. The latter suggestion effectively means that it would be inappropriate to estimate upper percentiles of Cd-U from upper percentile of dietary Cd with average toxicokinetic parameter values”*

The RA noted *“that the upper ranges are best described when selecting a 3% GI absorption rate for a kidney Cd half-life of 13.6 years. This might reflect the fact that, while increased GI absorption rates up to 10% may exist during certain periods of iron deficiency (e.g. late pregnancy), this status does not persist constantly during the whole life. Considering a constant f_u of 10% during 50 years would therefore be inadequate for a risk characterisation.”*

Considering the above, it is concluded that the accumulation of worst case assumptions (highest intake together with highest bioavailability) used in the EFSA paper to set the PTWI does not seem to be valid and results in an overly conservative PTWI.

It is noted that the assumption of combined high intake with high bioavailability was not validated in the Amzal et al paper (2009); actually, it is contradicted by the observed Cd-U values presented in fig 5 of the paper. In other words, the toxicokinetic model parameters used in Amzal et al. are dependent of dietary intake, and not independent as assumed in the paper.

Based on the elements above, it is concluded that the EFSA derived PTWI value of 2.5µg Cd/kgBW.w is overly conservative. This has consequences for the annex XV statement that ‘the margin between the average weekly intake of cadmium from food by the general population and the health-based guidance values is too small (EFSA 2009)’.

Comment 8

Page 16, section 4.2.1 Kidney toxicity, para 2

Annex XV makes reference to Kemi (2011), in which a number of studies were cited, “showing significant associations between cadmium in urine and/or blood and markers of impaired kidney function, mostly impaired tubular function”.

However, recent evidence, questions the causality of these associations between U-Cd and biomarkers of kidney effects (urinary proteins) in populations with low levels of exposure.

Recent literature, as discussed in Annex XV, is showing that the association between Cd and protein excretion probably represents normal variability in renal physiology resulting in a temporarily increased or decreased Cd excretion, independent of kidney cadmium concentration (Kidney Cd) (Chaumont et al., 2012, Akerstrom et al., 2013a). The excretion of Cd and proteins is assumed to change in the same direction due to temporary changes in the renal activity, since Cd bound to metallothionein and LMW proteins share the same tubular binding site (Christensen et al., 2009), thus resulting in an association between U-Cd and urinary proteins excretion.

Overall, Akerstrom concludes that “these associations are unlikely to be caused by Cd toxicity but rather reflect temporary changes in urinary flow or other sources of normal physiological variability that affect the excretion of U-Cd and urinary proteins in the same direction, resulting in an overestimation of the risk of renal toxicity from low-level Cd exposure” (Akerstrom et al. 2013a). These recent findings suggest that at low environmental exposures, U-Cd would be more a reflection of the functional integrity of the nephron than of the Cd exposure or of the Cd body burden (Chaumont 2012).

These reverse causality mechanisms might have important implications in the risk assessment of Cd for the general population, which currently largely relies on the use of U-Cd as exposure indicator (Chaumont et al 2012).

See also comment 28 for more details.

In conclusion, the scientific debate on the causal effect of low Cd exposures (measured as Cd-U) on kidney function is ongoing. Taking this debate into account, 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.

Referring to the recent study of (Åkerström et al, (2013b) showing a strong association between kidney Cd and urinary Cd (healthy kidney donors), we would like to emphasize this study should be interpreted very cautiously.

In summary, in the study of Akerström et al (2013b), the associations shown between concentrations of Cd in urine (or in blood) and the concentration of Cd in kidney are based on the whole population with no distinction between never and ever smokers. The association in ever-smokers is certainly confounded by the influence of recent exposure as the authors have not considered separately current and former smokers. The study would have been much more conclusive by showing that U-Cd correlates with K-Cd when considering only former smokers. The authors have not excluded the possibility that the association in smokers is mainly driven by the current exposure to tobacco smoke. The only place where a correlation appears between U-Cd and K-Cd in never-smokers is in Table 3, model 2. This correlation is based on only 31 subjects and is shown with U-Cd expressed per 24 h (output and not concentration) and with K-Cd expressed in total amount of Cd. As these important results are not illustrated by a Figure, it is difficult to judge of the robustness of this association based on few data and perhaps some outliers. These units are not those classically adopted in most studies. What determines the risk is the concentration of Cd in kidney cortex and not the total amount of the metal in the kidney (estimated using the body surface).

The authors have not reported the correlations calculated with U-Cd in $\mu\text{g/g}$ creatinine and with K-Cd in ppm or $\mu\text{g/g}$ kidney weight, which are the units commonly used in biomonitoring for deriving thresholds of Cd toxicity. By using these more classical units, the authors would have eliminated the influence of body size/surface which thus determines the uptake and the kidney weight.

Furthermore, it is interesting to note that U-Alb emerges as a determinant of U-Cd in this study of Akerstrom et al, confirming the physiological link between U-Cd and protein excretion reported now by several authors. This is an important point as urinary protein excretion and in particular albuminuria has recently been found to be a significant predictor of bone disease (Barzilay et al. 2013). Further studies should check whether the associations between U-Cd and bone persists after adjustment for albumin excretion.

And in conclusion, if one takes the study by Akerstrom et al. 2013b as an evidence that U-Cd reflects reliably the body burden of Cd and in particular the K-Cd, then one has to take also into

consideration that in another study by the same group (Wallin et al. 2013) based that time of the concentration of Cd in kidney cortex, there was no significant association between K-Cd and bone mineral density after adjustment for confounders. In other terms if one assumes that U-Cd reflects the K-Cd, according to Wallin et al. (2013) U-Cd would reflect an indicator that does not correlate with the BMD.

Comment 9

Page 17, section 4.2.2. Bone toxicity, para 1, line 9

Annex XV suggests “that even a urinary concentration around 0.5 µg/g creatinin is associated with increased risk of osteoporosis and fractures”.

It is emphasized (see also comments 8, 28) 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 2013a). 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 creat 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 2013a). 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.

Comment 10

Page 17, section 4.3 Bone toxicity, para 2: osteoporosis and fractures, line 14

The Annex XV document mentions: “it is concluded that the differences cannot be explained by differences in risk of slipping, low calcium intake, vitamin D deficiency or by inactivity”. No references are given to explain this statement. We anticipate that “slipping risk” and “inactivity” are rather comparable between countries. However, the parameters low Ca and VitD are very important for the bone effect, so clear references should be provided for this statement.

Comment 11

Page 20, section 6.2.2, 2nd paragraph, 4rd line.

Section 6.2.2 is largely similar to section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH”. The comments 1 to 4 formulated above on this section, are also relevant here. Notably the sentence in paragraph 2, 4rd line “Deposition from air is an important source to the input of cadmium to soil and must therefore be reduced. In order to achieve this all uses of cadmium and cadmium compounds should wherever possible, be substituted” is misleading,

since (a) it ignores the main single source of Cd to general population exposure, i.e. the use of P-fertilizer on agricultural land (see also comment 1), and (b) the fact that cadmium (REACH) uses do not contribute to the cadmium deposition from air on crops and soil (see comment 5).

We note that the percentages provided in comment 1 are averages for the EU, and that differences between countries in Cd-sources to soil can occur. Yet, the averages are quite consistent throughout EU member states (OJ 2008/C 149/03), see for more detail comment 1.

Comment 12

Page 20, section 6.2.2, 2nd paragraph

Again, this section 6.2.2 is largely similar to section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH”. Comment 1 formulated above on this section, is also relevant here.

Comment 13

Page 20, section 6.2.2, 3rd paragraph.

Again, this section 6.2.2 is largely similar to section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH”. Comment 2 formulated above on this section, is also relevant here.

Comment 14

Page 21, section 6.2.2, heading “uncertainties on safe exposure” 1st paragraph.

Again, this section 6.2.2 is largely similar to section “summary of how the substance meets the criteria set out in article 57(a) and 57(f) of REACH”. Comment 3 formulated above on this section, is also relevant here, see also comment 8 & 9 for more details.

Comment 15

Page 22, section 6.2.2, heading “societal concern and impairment of quality of life”.

See comment 4 made above

Comment 16

Page 23, section 7.1 “Imports and exports of the substance into and from the EU”.

From the co-registrants under EU REACH, we have no confirmation of any imports or exports into or from EU.

Comment 17

Page 23, section 8.1. "Overview of uses"

PROC 21 and PC20 are effectively not appropriate; they are remainders in co-registrants dossier and will be rectified in the next update of the dossier.

Comment 18

Page 25, section 8.3. "Substance use as laboratory reagent"

One co-registrant of CdSO₄ includes the use as laboratory reagent. The SU09 and SU24 are remainders in this co-registrant dossier. Use as a laboratory reagent is a formulation with the following use descriptors: PROC 15, PC 21 and ERC2. This will be rectified in the next update of the dossier.

Comment 19

Page 26, section 8.4. "Non-registered use- use for battery restoring"

No information confirmed from co-registrants under EU REACH of that type of use.

Comment 20

Page 26, section 8.5. "Non-registered uses- metal electroplating"

No information confirmed from co-registrants under EU REACH of that type of use. If CdSO₄ would be used in electroplating, it is typically an intermediate use.

Comment 21

Page 26, section 9.1. "Introduction"

We confirm CdSO₄ is indeed only registered as intermediate use. The C&L notifications probably refer to use as laboratory reagent.

Comment 22

Page 27, section 9.2. "Industrial uses"

We confirm there are only industrial formulations (intermediate processes).

Comment 23

Page 27, section 9.3. "Professional uses"

Indeed we confirm there are no professional uses of cadmium sulphate

Comment 24

Page 27, section 9.4. "Consumer uses"

Indeed we confirm there are no consumer uses of cadmium sulphate

Comment 25

Page 27, section 9.5. "Releases from use of articles"

Cd pigments are today strictly quality controlled by a special leaching test for releases of Cd soluble salts eg CdSO₄.

"Cadmium sulphate in restoring of acid lead batteries": this alleged use has not been confirmed by co-registrants.

Even without the above mentioned uses, Cd being a natural element, there will be always an exposure to the general population.

Comment 26

Page 32, section 12.1 EU RAR & 12.2, Work environment –SCOEL assessment

In addition to the information provided in Annex XV, ICdA wishes to provide the following additional information.

Risk management measures have been developed by industry in two stages.

Stage ONE: adopting and disseminating the Swedish legislation throughout the EU

As the RAR covering Cd/CdO (ECB, 2007) was in the process of getting near to completion, it became apparent that a conclusion would be reached indicating that there was a need for limiting the risk to workers. Industry therefore decided to build an Industry Guidance for its members explaining how to reduce and control this risk.

Industry (ICdA) built its Guidance on the basis of the Swedish legislation developed by ARBETSMILJÖVERKETS FÖRFATTNINGSSAMLING (the Swedish Work Environment Agency), amended and published in MEDICINSKA KONTROLLER I ARBETSLIVET (Medical Surveillance in Occupational Setting) publication AFR 2005:6.

Implementation of this legislation had been on-going (under version 2005, following previous versions) in a large industrial Ni-Cd battery manufacturing plant since its inception, and has proven excellent at keeping exposure of workers extremely low.

This Industry Guidance (available upon request) was published in 2006, dissemination followed, and implementation started in 2007.

Industry sectors who have committed to implementing this program are Zn producers, Cd refiners, specialty cadmium compound manufacturers, pigment manufacturers, Ni-Cd battery manufacturers, thin-film PV panel manufacturers, Ni-Cd battery recyclers.

This industry Guidance is built along three pillars;

- keeping the workplace clean,
- implementing collective and individual hygiene policies,
- ensuring individual exposure is properly controlled by means a medical surveillance program which takes advantage of:
 - exposure bio-markers: [Cd-U] for cumulated exposure and [Cd-B] for recent exposure,
 - as well as effect biomarkers: measurement of the urinary excretion of specific proteins.

CdB and CdU based action levels, taken over from this Swedish regulation, determine what added surveillance must be implemented should an employee exceed these action levels. Removal from exposure is decided should a certain threshold be exceeded.

Stage TWO: selecting risk based OEL (set by SCOEL) as the DNEL for workers

As mandated after the conclusion of the Cd/CdO RAR (ECB 2007), a COM Risk Reduction Strategy was agreed, and the setting of an OEL (and possibly a BLV) was decided. SCOEL was therefore tasked with developing a health based proposal.

SCOEL published its (health based) OEL recommendation of [Cd-air] = 4 µg/m³ (respirable fraction) in February 2010. The recommendation of SCOEL was introduced by the following comments:

Setting an OEL

Beside a BLV, an OEL is necessary to protect workers against long-term local effects. Chronic inhalation of Cd-containing dusts and fumes is associated with the development of local respiratory effects, including lung emphysema and cancer. Cd is considered as a lung carcinogen in experimental animals and upon occupational exposure.

- experimental studies have reported the induction of tumours in rats exposed to low concentrations of Cd (12.5 µg/m³).
- in humans, no sufficiently valid epidemiological data exist to perform a working-life risk assessment for the cancer risk when exposure is to Cd alone. When an increased risk was observed, co-exposures did appear to play a central role
- the mechanism of the carcinogenic activity of Cd is not exactly known, but involves, at least in part, genotoxic events mediated by indirect mechanisms for which a threshold can be identified (Category C, Bolt and Huici-Montagud, 2008)
- a threshold of 1000 µg/m³x years (or 25 µg/m³ during 40 years) has been reported for genotoxic effects in workers exposed to Cd by inhalation
- there is also some epidemiological evidence that Cd does not seem to induce an excess of lung cancers at exposure levels sufficient to cause renal and respiratory toxicity (Sorahan and Esmen, 2004).

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Industry therefore decided to take this OEL forward as its worker DNEL in the cadmium registration dossier.

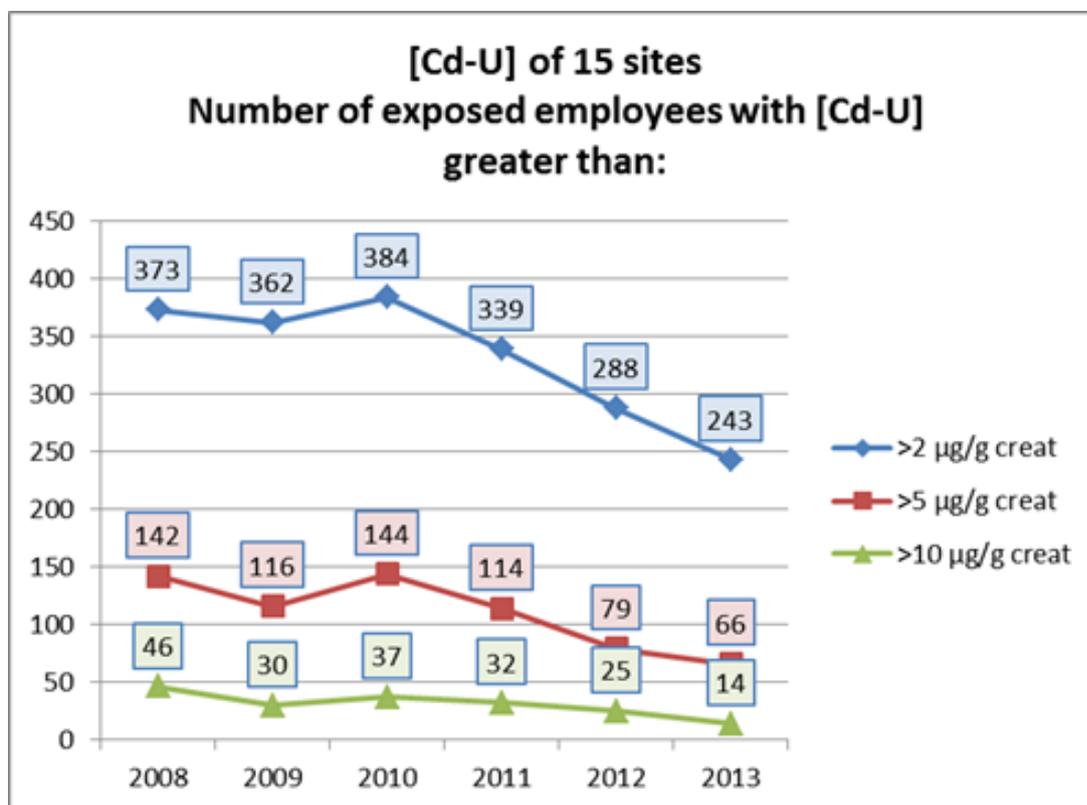
Since that date this is the workplace air quality standard that industry is legally bound to comply with.

Results of Industry Guidance implementation; current exposure of workers in industry deliberately using cadmium

Two sets of Cd-U distributions (the biomarker which integrates all routes of exposure) are tracked.

First set of data:

This data tracks the distribution of exposure of workers from 15 industrial sites (deliberately using cadmium) whose occupational doctors have started reporting anonymous data since the inception of the program in 2008. The size of this exposed workforce is 2,293 workers.



This data shows that 2.88% of workers have a [Cd-U] greater than the maximum value allowed under the Swedish regulation (5µgCd/g creatinine).

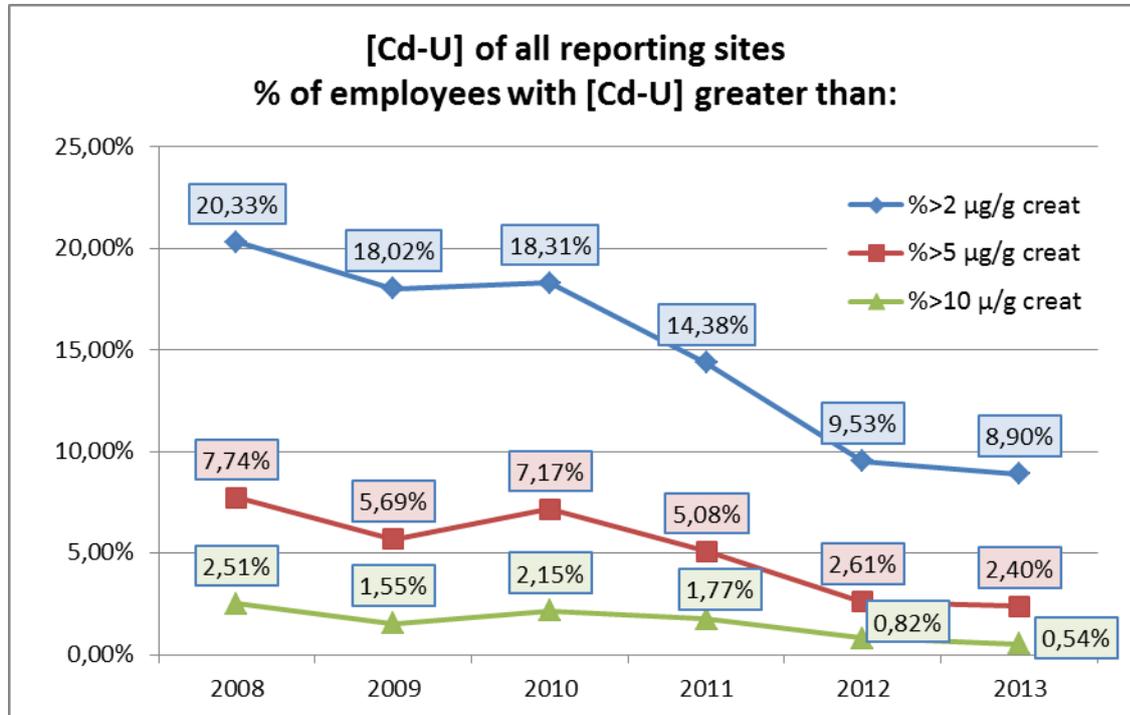
As strongly recommended by the Swedish regulation, most of these workers are removed from exposure. Only in limited cases will the occupational doctor allow such employees to continue work in exposed positions.

This data also shows that 10.59% of workers have a [Cd-U] greater than the BLV proposed by SCOEL in February 2010.

Both numbers are being reduced at a rapid pace.

Second set of data:

This data tracks the distribution of exposure of all workers from all industrial sites (deliberately using cadmium) whose occupational doctor have started reporting anonymous data, either in 2008 or at a later date. 24 sites have reported for 2013. The size of the corresponding exposed workforce is 2,956 workers. It is estimated that the whole industry employs ca. 3,500 workers.



This data also shows a strong decrease between 2008 and 2013 of both categories of workers, respectively from 7.7% down to 2.4%, and from 20.3% down to 8.9%.

It can be concluded from this data that as of 2013, 8.9% of the workforce exposed to cadmium in a deliberate use of this substance have a biomarker in exceedance of the SCOEL health-based threshold of 2 µg Cd/g creat. In this respect, it is noted that Cd-U is a marker for life time accumulated exposure; in other words the higher Cd-U levels observed today can be a reflection of higher exposure in the past. Nevertheless, within the framework of the OCdBio (Observatory of cadmium biomonitoring in the European industry) program, industry has set clear objectives towards a further reduction of occupational exposure of the employees in the cadmium industry:

- **95% of European employees** subject to medical surveillance and bio-monitoring should have a urinary cadmium level below **2 µg Cd/g creatinine by the end of 2017,**
- **98% of European employees** subject to medical surveillance and bio-monitoring should have a urinary cadmium level below **2 µg Cd/g creatinine by the end of 2020**

Based on the progress observed at present, and the continued implementation of strict risk reduction measures, it is expected that cadmium exposure at the workplace will continue to decrease and that these objectives will be met.

It is stated that “a critical review of the database on biomarkers of Cd-exposure provides no evidence for a decrease in Cd exposure over time during the last 2-3 decades in Sweden”.

The reader of this Annex XV document is referred to Keml Rapport Nr1/11 (2011). Based on this report the above statement is challenged, not only for Sweden, but also for the EU, as there is clear indication for decreasing exposure, as follows from the information below:

For Sweden, there are 3 studies available on kidney-Cd content of general population. Most relevant for comparing the general exposure are the data on the “ever non-smokers”, since the smokers/ever smokers data are dominated by smoking behaviour. The “never smoker” data show that between the 1970s and 1990s, there was a rather significant decrease in Cd-content of forensic autopsy kidney samples (compare Elinder et al 1976) with Friis et al 1998). Kidney Cd values were subsequently evaluated by Barregard et al 2010), related to the period 2003-2006. These samples had Cd content that was not different from the Friis data, and, while still lower, the differences with Elinder et al (1976) were smaller in the comparable age groups. When considering these kidney Cd data, it needs to be taken into account that the number of samples was small (order of magnitude ~10) in all studies. Moreover, the time lapse between the period considered by Friis et al 1998 (period 1995-1996) and Barregard et al 2010 (period 2003-2006) was probably too small to allow indication of any further trend.

- No dietary intake data are presented in this section at all, so it is impossible to check this part of the statement.
- The interpretation of the Swedish Cd-U data presented in figure 4 of Annex XV is odd: of the 12 populations, where a comparison was made in Cd-exposure (measured via Cd-U) between 2002-2004 and 2008-2009 (in the areas of Västergötland, Stockholm, Västmanland och Norrbotten), a decrease was observed in 10 out of 12 cases; while in 2 cases there was an increase. The decreases are sometimes quite large (reductions can amount to -40%), but are put in doubt because of “analytical differences that are still under investigation”. We consider this a weak argument to refuse the data. Moreover, we consider that nowadays differences in analytical performance between labs leading to such differences would be unacceptable.
- In the section Cadmium exposure over time, second paragraph p48: the lack of trend in Cd-B levels in Sweden is mentioned. However, this statement probably (no reference given) refers to table 2 in Bilaga 3 ‘Health effects of cadmium in Sweden’, in Kemi 2011, where Cd-B data are summarized as a function of time. It is noted that the data in this table are not comparable, since a) smokers and non-smokers, b) rural and urban populations and c) different age groups are all mixed.

In conclusion, and in contrast to what is concluded in this section of Annex XV, the data show that the exposure of the general population in Sweden to Cd has decreased over the last 2-3 decades.

The question of time trends should however also be considered in a broader EU context. In this respect, the review of Schultz et al (2007) is particularly relevant.

Schulz et al (2007) reviewed data on urinary Cd-levels in the general population of Germany, obtained by the German Environmental Survey (GerES). These are nationwide population studies that have been repeatedly carried out in Germany since the mid-1980s. The survey monitored a.o. urinary Cd levels in adults, over the periods 1985-1986 (W-Germany only), 1990-1992, and 1998 (more recent studies focus on children only). The studies provide the absolute levels observed in the

general population and allow to check on possible time trends over the period 1990-1992 to 1998. The data are considered highly representative for the EU population, given the high number of monitored persons, the wide area over which they were spread, and the care taken in analytics and the selection of representative individuals.

Comparable data for non-smokers are summarized in table 27.1. The data show a clear decrease in Cd-U over the observed time period (6-8 years). P50 values decrease with 19% and geometric mean values with 14% over this relatively short period. P95 values show the same time trend (-18%), and all P95 values are below 1µgCd/l. In smokers, a similar decrease in time is observed; all parameters are 50-70% higher than for non-smokers; the P95 values are >1µg Cd/l (Schulz et al 2007).

Table 27.1: Cd-U levels (µg Cd/l) in the non-smoking adult population in Germany (after Schulz et al 2007)

period	N	P50	P95	Geometric mean
<i>Non-smokers</i>				
1990/1992	2745	0.26	0.94	0.244
1998	2758	0.21	0.77	0.209*
% decrease		-19	-18	-14
<i>smokers</i>				
1990/1992	1257	0.44	1.66	0.421
1998	1293	0.33	1.30	0.334*
% decrease		-25	-22	-21
<i>total</i>				
1990/1992	4002	0.30	1.27	0.290
1998	4052	0.24	0.99	0.243
% decrease		-20	-22	-16

*significant difference between data of 1990/1992 and 1998 ($p \leq 0.001$)

The Cd-U levels observed in children are, as expected, lower than in adults (table 27.2). Also for the children, a significant decreasing time trend in Cd-U levels is observed over the period 1990-1992 to 2003-2006. The relative decrease is 18-20% over this 11-16 years' time period. The Cd-U levels observed in the German children are very similar to the Cd-U levels recently observed for children in 17 EU countries (see comment 33 below).

Table 27.2: Cd-U levels (µg Cd/l) in children in Germany (after Schulz et al 2006)

period	N	P50	P95	Geometric mean
1990/1992	732	0.1	0.27	0.087
2003/2006	1354	0.08	0.22	0.071*
% decrease		-20	-18	-18

*significant difference between data of 1990/1992 and 2003/2006 ($p \leq 0.001$)

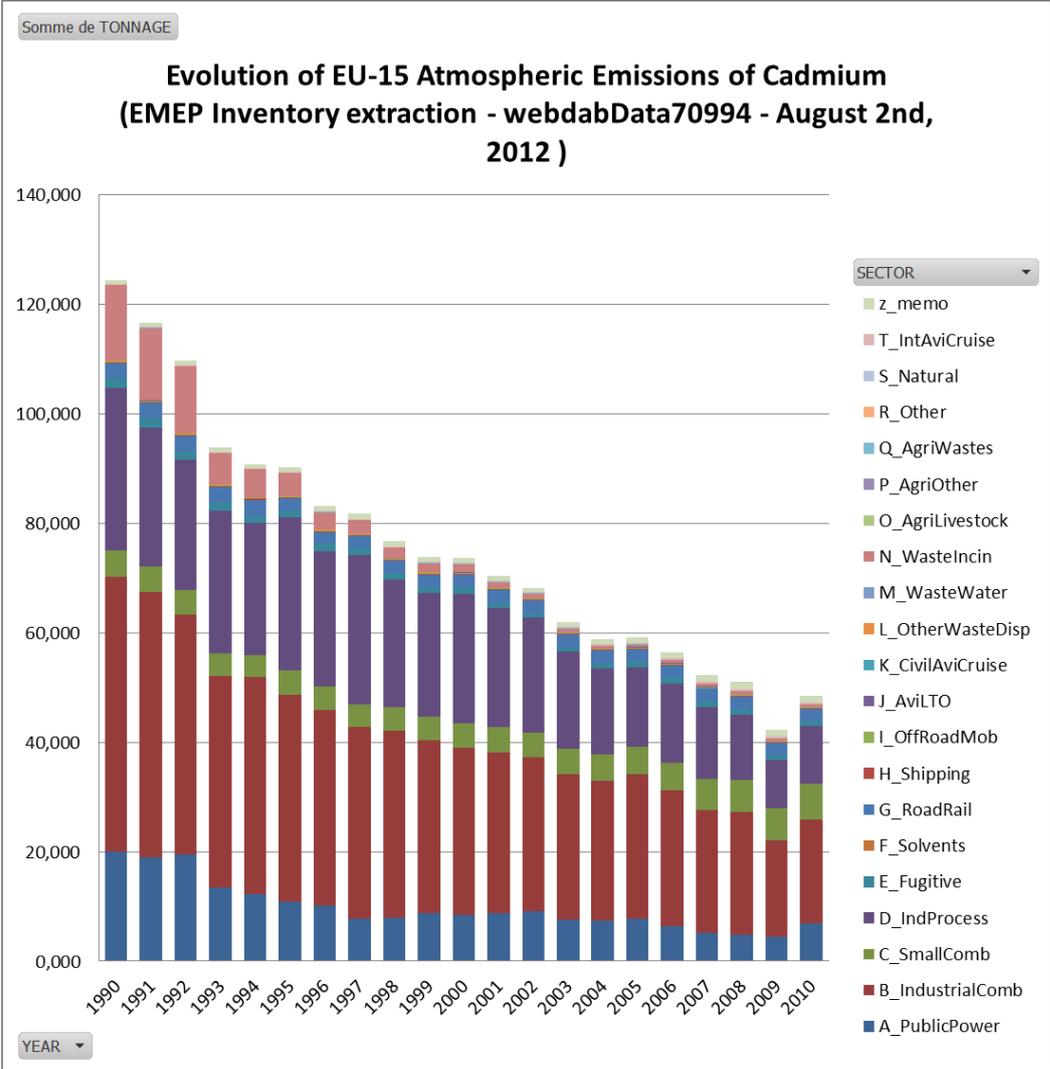
In conclusion, the studies presented above show that average Cd-U in adults in Europe is at the level of $\sim 0.22 \mu\text{g Cd/l}$. The data also show that P95 levels of the non-smoking adults are $< 1 \mu\text{g Cd/l}$. Moreover, time series data show that the internal exposure to Cd of the general population is decreasing, as demonstrated by significant reduction of Cd-U levels. This observation is consistent

with the observed decrease in Cd in major foodstuffs and in the diet that has been commented earlier by ICdA (ICdA 2014). So, the Cd-U data mentioned above confirm this decreasing trend of Cd exposure to the general population in Europe.

Dietary Cd-intake data are also an indication of the exposure of the general population. In contrast to what is stated in the Annex XV document, there is evidence showing that the dietary intake of Cd has decreased over the last decades.

This decrease in Cd exposure of the general population can be explained by the parallel decrease of Cd-emissions to atmosphere, observed over the same period. Over the period 1970-1995, the atmospheric deposition of Cd to mosses in Sweden decreased with 75%, due to the decreasing emissions from industry and fossil fuel combustion in Northern and Western Europe (Rühling and Tyler 2001). These data demonstrate the direct relationship between atmospheric Cd emissions and deposition of Cd from the atmosphere on exposed edible plant parts. Cd emissions to atmosphere have decreased significantly in the EU over the last decades as follows clearly from the yearly data between 1990 and 2010 from EMEP (2012), see figure 5.1.

Figure 5.1.: Cd-emissions to the atmosphere (T/y) by sector in the EU-15 during the period 1990-2010 (EMEP 2012).



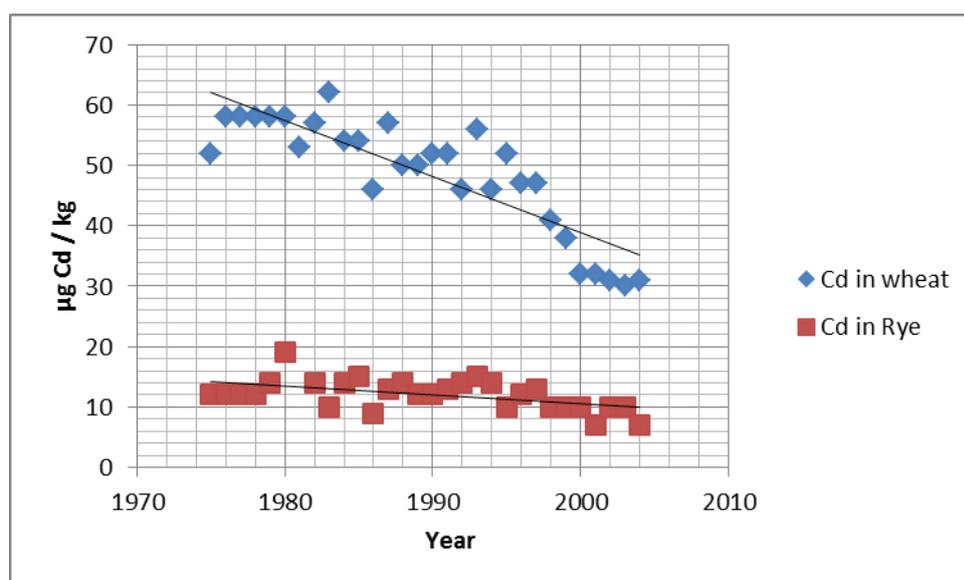
Referring to the effect observed on Scandinavian mosses, the general decrease of atmospheric Cd-emissions in the EU (>60% reduction) over the last 2 decades is anticipated to have resulted in a decrease of Cd-deposition on exposed edible plant parts, and, as a result, in a general decrease of Cd-content of food in the EU, and consequently, a decrease in Cd-intake through food in the EU.

This progressively lower Cd-intake is confirmed by crop data over time from Sweden and Germany: the Cd content of main cereal crops show consistently a decrease of 40-50% of the Cd content since the 1990s (BfR 2009, Kirchman et al 2009). Cereals are a general basis for food products, and a main source (33% of total) of dietary Cd intake by the general population (BfR 2009). The continuing decrease of the Cd content measured in 2 base cereals (wheat and rye) with about -40% over the period 1975-2004 is clear (figure 27.1). The observed decrease in these cereals is anticipated to have also resulted in a general decrease of the dietary Cd-intake of the European population.

This observation is also the result of the decreasing input of P-fertilizer (see below).

Given the central geographical position of Germany in the EU, notably the German data put the time trend of Cd-exposure to the general population in a broader EU-perspective.

Figure 27.1: Cd-content of cereal crops in Germany, measured during the period 1975-2005 (after BfR 2009).



Regarding the time trend of Cd-exposure in the future, it is expected that the phenomena leading to a decrease, as described above, will continue, due to a further progressive reduction of Cd-emission from point sources.

Moreover, with respect to future exposures, the annex XV document ignores an important prediction that was recently made by the author of the EU risk assessment on Cd and CdO. After updating the information and scenarios on Cd-inputs and outputs in EU agricultural soils with recent information, it was concluded that the current net balance of Cd in EU soils is negative, mainly due to i) decrease of P-fertilizer use, ii) decrease of atmospheric deposition, and iii) refinement of the leaching component (Six & Smolders, 2014).

Following the revision, the authors concluded that under current practice, the average Cd concentration in EU-27 + Norway soils will **decrease with 15% over the next 100 years**. Key in this

conclusion are the well-documented data on the pH of EU soils, studied in a systematical way with a same representative method over the whole EU area (NGU 2012).

Taking into account the prediction of -15% decrease of Cd content of agricultural soils, discussed above, the expectation is that the Cd-content of main crops and, consequently, the human Cd intake through food, will further decrease in the future.

In conclusion, the statement in annex XV that “there is no evidence for a decrease in Cd exposure over time during the last 2-3 decades in Sweden” is in conflict with the consistent evidence indicating a decrease of Cd-exposure to the general population in the EU and also in Sweden. A major factor for this is most probably the general decrease of atmospheric Cd-emissions observed all over the EU, having resulted most probably in a decrease of Cd content of food and thus of intake through the diet. The main cause for this decrease in atmospheric emissions is the decrease of industrial Cd-emissions to the EU atmosphere. Another important factor is the decrease in Cd-input to agricultural soils via P-fertiliser. Both Phenomena are expected to continue in the future. In other words, a decrease of environmental exposure to Cd through the diet (the objective of the current Annex XV exercise) is ongoing in the EU, and is expected to continue in the future.

Comment 28

Page 33, section 12.3, para 5

Annex XV states that “There is the debate concerning the causality and the health significance of the associations between urine-based biomarkers of cadmium exposure and kidney effects that occur at very low cadmium concentration. Thus, it is difficult to ascertain the exact lowest effects dose for a clear adverse effect. However, several recent mechanistic studies support effects at low exposure.”

It is emphasized that there is indeed recent debate on the significance of Cd-U as indicator of exposure at very-low Cd-exposure levels: (Chaumont 2012, Akerstrom 2013a) concluded that “There is evidence of non-causal associations between low-level urinary Cd and urinary proteins. The co-variability observed between Cd-U and urine based biomarkers would have a strong physiological basis. This evidence is suggesting that low-level urinary Cd (e.g. for Cd-U at or below 1 µg Cd/g creatinine) in the general population would be more a reflection of the recent intake and of the physiological variations in the urinary excretion of creatinine and of the renal function (diuresis, renal handling of proteins and glomerular filtration rates). This is relevant for all studies using U-Cd as cumulative exposure indicator.

In conclusion, the threshold for kidney effects of Cd < 1 µg/g creatinine for the general population exposed by the oral route should be questioned because of the non-causal associations between low-level U-Cd and urinary proteins mentioned in recent reports.

Consequently, the major hypothesis of the Annex XV document that there may be risk of impaired kidney function already at urinary Cd-levels below 1 µg/g creatinine has also to be questioned.

Comment 29

Page 33, section 12.3, para 7, line 4-5

The threshold for bone effects of cadmium concentration in urine around 0.5 µg/g creatinine for the general population exposed by the oral route should be questioned because of the non-causal

associations between low-level U-Cd and low Cd-exposure mentioned in recent reports (see also comment 8-9)

Consequently, the major hypothesis of the Annex XV document suggesting that already a cadmium concentration in urine of around 0.5µg/g creatinine is associated with increased risk of osteoporosis and fractures and the estimated societal cost related to that (see comment 4) has also to be questioned.

Comment 30

Page 34, section 12.3 (cont.), para 2, line 4-6

Annex XV suggests that results from experimental and epidemiological studies are raising concern that cadmium might have oestrogen-like effect and possibly increase the risk of hormone-related cancers. It is emphasized that although there are indications that this is the case, this needs to be confirmed by other studies, for several reasons (see also comment 37 for more details):

-most positive in vivo studies were conducted with acute Cadmium exposures. Kortenkamp (2011) emphasized in his review that a key issue that needs to be resolved in the context of human risk assessment is whether the estrogenic effects of Cd occur at dose levels that are lower than those known to be associated with kidney dysfunction or pulmonary carcinogenesis.

-most studies apply non-physiological routes of Cd-administration e.g. peritoneal injection. When relevant physiological routes of exposure (e.g. oral) were used, no positive effects were observed (Höfer et al 2009)

-CdCl₂ is used for most studies; however no effects were observed after oral administration of dietary Cd

-Finally, it is noted that in the general environment, humans are simultaneously exposed to metals (cadmium and others), but also to organic compounds that might also be endocrine disruptors. There is a need to study the possible additive, synergistic, or antagonistic effects on the endocrine system following exposure to such substances.

Comment 31

Page 34, section 12.3 (cont.), para 4, line 3-4

Annex XV states: « Causal relationships are supported by mechanistic experimental studies”.

No references are given. In comment 8, references are given which strongly suggest non-causal relationships.

Comment 32

Page 34, section 12.3 (cont.) para 4, line 4-6

Annex XV emphasises on bone effects of cadmium and their relationship with Cd-U as a marker for cadmium exposure.

As indicated, the significance of Cd-U as a biomarker of exposure in situations of very low Cd exposure (like in general population) is currently under scientific debate. Therefore the relationship between bone effects and Cd-U levels in the general population is questioned.

Comment 33

Page 36, section 12.4. risk via food intake-Abstract (EFSA 2012)

The Annex XV document presents the abstract of the EFSA study on dietary Cd intake in the European population (EFSA 2012). Calculated lifetime cadmium dietary exposure was estimated at a middle bound overall weekly average intake of 2.04µg Cd/kg BW, and a potential 95 percentile value of 3.66µg Cd/kg BW.

The following comments are made on the EFSA study:

- The dietary intake was calculated from food Cd-content data and dietary information. It has been observed that such approach may overestimate the Cd-intake, since considerable loss of Cd can occur during food preparation (Fouassin & Fondu 1981).
- The authors of the EFSA-report themselves note that the 95 percentile estimate is “speculative and potentially unrealistic” because it is based on the unlikely assumption that the same individuals retained the same high exposure throughout their whole life”. The 95 percentile should thus be considered with caution, since it appears that it is clearly an overestimation.
- The EFSA-report notes also that “many of the reported results for meat and edible offal category have been sampled under directive 96/23 and might include a high proportion of samples targeting potential problem areas and thus might not reflect an average situation” (EFSA 2012, page 8). This suggests that the average may be biased towards higher levels.

When comparing the EFSA average intake value with recent (post 2000) Cd-intakes for EU countries (including Sweden) reported from different literature sources, the values are indeed generally a factor 1.5-2 lower than the EFSA calculations (table 33.1). The points raised above may explain why. Even for a country like Belgium, which has a historical contamination of Cd, the 95 percentile value is only just at the level of the EFSA-average. These country data suggest that the EFSA average is overestimating current dietary Cd-intake.

Table 33.1. Recent (post year 2000) values reported for weekly dietary intake in EU member states.

Country	Year	Cd intake (µg/kg BW.week)	reference
The Netherlands	2003	1.0-1.14	RIVM 2003
Germany	2006	1.41-1.65	BfR 2006
Belgium	2006-2008	0.98 (mean) 2.02 (95P)	Vrommann et al 2010
Spain (Canary islands)	2000	1.12	Rubio et al 2006

Spain (Catalonia)	2000	1.57 (male adults) 1.40 (female adults)	LLobet et al 2003
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It is noted that the EFSA average Cd intake was an update from an earlier survey reported in 2009 (EFSA 2009). At that time, the average middle bound mean dietary intake of adults was calculated to be 2.27 µg/kgBW.w; in the update (with somewhat more recent and more complete data), a middle bound mean value of 1.77µg/kgBW was calculated for the same age group. This is 22% lower than the earlier estimate (EFSA 2012).

The weekly intake data mentioned above are general figures, which are related to the average exposure of general populations. Such data make sense for a cumulative toxicant such as cadmium, where critical exposure levels relate to chronic Cd accumulation at the level of the kidney cortex and therefore relate well to chronic average exposures. For that reason also, worst-case estimates may not be realistic, since such situations are unlikely to proceed for longer time. Yet, situations of consistent enhanced exposure can occur in particular related to specific dietary habits involving systematic consumption of high-Cd food.

With respect to the latter, the EU RAR discussed notably the more than average consumption of seafood (molluscs, crustaceans,...) that is observed in some local communities, e.g. of oyster cultivators. However, in spite of the fact that the Cd content of such foodstuff, and the corresponding estimated dietary Cd-intake of individuals can be quite high, it was found out that this does not translate in increased internal exposure (McKenzie et al 1982), most probably due to limited bioavailability of the Cd in these food sources. As a result, elevated dietary Cd intake due to preference of these food products may not necessarily result in proportional internal exposure.

In conclusion, recent (post-2000) weekly dietary Cd-intakes in the EU are rather at the lower end of the range 1 -2 µg/kg BW. and as such below the WHO PTWI standard of 5.8 µg Cd/kg BW, and below the more stricter EFSA standard of 2.5 µg Cd/kgBW. Calculations of dietary intake based on life-time continued worst case is considered unrealistic.

With respect to exposure of the general population , the recent EU DEMOCOPHES study is also of relevancy (DEMOCOPHES 2014). In this EU wide study, human biomonitoring data on e.g. Cd-U were compiled using a consistent methodology over 17 EU member states (Belgium, Cyprus, Czech Republic, Denmark, Germany, Hungary, Ireland, Luxembourg, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom). The study used a common EU protocol, and the laboratories analyzing the samples were selected through a strict quality assurance process, comprising Interlaboratory Comparison Investigations (ICI) and External Quality Assessment Schemes (EQUAS). Important to mention in a Cd-exposure context is that the adult populations in the DEMOCOPHES study include smokers and non-smokers , and don't make distinction between both groups in the first reports that are available on the study.

The results (European average) for children aged 6-11 years and their mothers aged up to 45 years are given in table below.

Table 33.2: Cd-U levels (µg Cd/l) in children and adults in 17 EU countries (after DEMOCOPHES 2014)

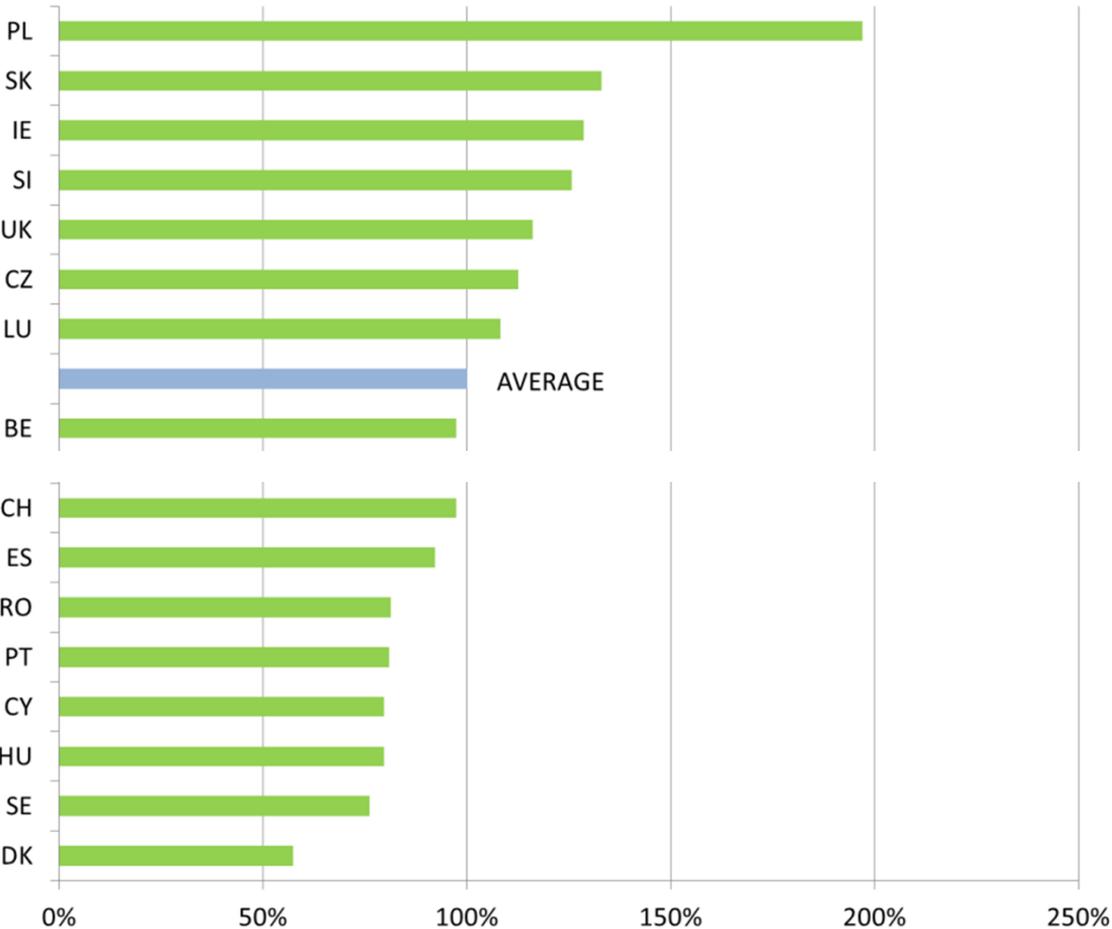
period	N	mean	P90
Sept 2010-Nov 2012	1844 "mother-and-child pairs"		
	children	0.07	0.22
	mothers	0.22	0.62

The mean EU result for the children corresponds very well with the P50 value observed in the German GerES study (see comment 27). The P90 for the 17 EU countries is similar to the P95 in Germany.

The adult mothers have a mean value that is also very similar to the P50 observed on the "total" = smokers + non-smokers) of the German study in 1998 (Schulz et al 2007). It is noted that the mothers in the EU study were as group younger than the German group. The P90 and P95 of both studies are not really comparable; the higher P95 observed in 1998 in Germany could be explained by the 12-14 years difference in time of sampling (considering the decrease that is observed in Cd exposure all over the EU), and the older age of the German population.

Important is that the DEMOCOPHES report explicitly mentions that "not one mother in this study had a cadmium level in her urine which indicates an adverse health effect on the kidneys".

The Cd-U data for each country in the study, as normalized towards the average at 100%, are presented in figure below (taken from DEMOCOPHES 2014).



The variability between countries is rather limited (+/-25-30%), with as exceptions the lowest exposure (60% of EU-average in Denmark), and the highest exposure (almost 200% of EU-average observed in Poland). The report considers that “the main reason for this might be that farmers are still using fertilizers with high cadmium content” (DEMOCOPHES 2014).

Conclusion

Based on the extensive analysis of Cd in food and diet, EFSA (2009) stated that the margin between Cd exposure through food and the EFSA limit value is small and that limited segments of the population may exceed the value. This EFSA assessment of Cd-intake through food in the EU is challenged, because of lower values currently observed in EU countries. In addition, the limit value set by EFSA (2011) for human daily intake has been evaluated as being overly conservative (see comment 7). A main point in the latter critique was that the accumulation of worst cases (highest intakes combined with highest uptake rates) applied by EFSA for the calculations, is not corresponding to reality. As is demonstrated by the recent Cd-U data observed in the EU, average Cd-U levels are consistently well below the value used as critical for Cd exposure 1µg Cd/l) and even P95 values of non-smokers are below that level.

Comment 34

Page 37, section 13.2 « uses »

‘Two non-registered probably low volume uses... ‘

This is not being confirmed by co-registrants.

Comment 35

Page 37, section 13.3 « Releases from manufacture and use

Indeed but this is not being confirmed by co-registrants

Comment 36

Page 42, Annex I Additional information on hazard and risk- Developmental toxicity, para 2

The studies of Ciesielski et al (2012) and Kippler et al (2012), showing associations between low-level environmental cadmium exposure in children (measured as Cd-U) and adverse neurodevelopmental outcomes should be interpreted with caution, in light of the recent literature data challenging the significance of U-Cd as biomarker of cumulative exposure in situations of low exposure (see comment 8).

Comment 37

Page 42-43, Annex I Additional information on hazard and risk- Endocrine effects

The Annex XV document mentions experimental studies that suggest that cadmium may have oestrogen-like effects. Swedish epidemiological studies have shown associations between estimated dietary exposure and increased risk of hormone-related cancers (endometrial, breast cancer). However, as noted in Annex XV, this needs to be confirmed by other studies (see also comment 30), for the following reasons:

To date, most cadmium *in vivo* studies have largely focused on acute cadmium exposures and there are only two studies on the effects of *chronic* exposure to low levels of cadmium. They suggest breast cancer development and progression (Alonso-Gonzales et al., 2007, Höfer et al 2009).

The observed effects are very much dependant not only of dose but also of route of administration. In the *in vivo* study from Höfer, it was explained that when cadmium was administered by physiological relevant routes (oral ingestion by gavage or drinking water), no effects were seen. The effects were seen only when cadmium was administered by non-physiological routes (e.g. intraperitoneal injection). It should be noted that only few studies used the main relevant human exposure route, i.e. ingestion, as the route of Cd administration. Most studies apply non-physiological routes of exposures, e.g. intraperitoneal injection.

It is noted that the studies of Ali et al (2013), as cited on page 43, para 3 in which the mechanism of the oestrogen-like effects of cadmium were investigated, are also acute exposure cadmium studies, in which transgenic ERE-luciferase reporter mouse were exposed subcutaneously for 3 days. This study design might be questioned in examining whether chronic, low-level exposures to cadmium can directly result in the development and progression of hormone-related cancers.

Moreover, in most *in vivo* studies to date, the estrogenic effects of Cd were estimated after exposure to inorganic Cd salts dissolved in a buffer or saline by injections or gavage (Höfer et al 2009, Ali et al 2010; 2012), while human populations are exposed to Cd mainly through diet. This difference was shown in the study of Ramachandran et al (2011) where oestrogen-like effects were only observed after oral administration of CdCl₂ and not after dietary exposure.

The Annex XV report mentions for the association between dietary cadmium exposure and breast cancer only the data from one epidemiological study (Julin et al., 2012a) although 4 additional studies were recently published investigating the association between dietary Cd intake and breast cancer (Adams et al., 2012, 2014; Itoh et al., 2014; Sawada et al., 2012). None of these additional studies reported statistically significant increased risks among postmenopausal women for the highest quintile/quartile/tertile after the most complete adjustments. The Annex XV report did not refer to nor mention these studies.

The Annex XV report mentions “.....dietary cadmium intake was positively associated with overall breast cancer tumors. The risk ratio when comparing the highest tertile with the lowest was 1.21 (95% CI 1.07–1.36 (Julin et al 2012).”

In this multivariate analysis, adjustment for smoking is not included. However, one single sentence in the result section of the paper (Julin et al 2012a) is stating that “Additional adjustment of the models for smoking status (never, former, current) or by multiple imputation of missing data did not change the results (data not shown).” Knowing that active smoking is associated with increased breast cancer (Gaudet et al, 2013) , it is a pity that the data on the additional adjustment for smoking status is not included and discussed since it is an important confounding factor in relation to breast cancer.

In conclusion, the elements listed above show the need for more basic, physiologically relevant research is needed (a) on the mechanisms of interaction between Cd and oestrogen signalling, (b) biologically active species of Cd, and (c) biomarkers of oestrogen-like effects of Cd *in vivo*, before conclusions on possible hormone disruptive effects of Cd can be drawn.

The Annex XV report refers to a recent meta-analysis (of four studies) showing a statistically significant positive association between dietary cadmium intake and breast cancer risk, RR= 1.15 (95% CI 1.04-1.28) (Cho et al 2013).

It has to be stressed that this meta-analysis (Cho et al. 2013) did not focus on postmenopausal women. Included data from the Japanese studies (Itoh et al (2014) ; Sawada et al. (2012)) were for all women. Rerunning the meta-analysis including only data for postmenopausal women and including the most recent American study data (Adams et al 2014) (not published at the time of the publication of the meta-analysis of Cho et al., 2013) did not show statistically significant increased risk of breast cancer (see annex 1). As Cho et al have combined epidemiological studies of different design (case-control and cohort studies) and as partial redundancies may have occur between the 2 Japanese studies (Itoh et al 2014; Sawada et al 2012) and between the two American studies (Adams et al 2012; 2014), sensitivity analyses (including only studies with the same design, excluding potentially redundant studies) have been performed and none of these meta-analyses has shown significant results (Annex 1). However, results of these meta-analyses have to be taken with caution due to the low number of included studies.

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ANNEX 1: Table: meta-analyses concerning the association between dietary cadmium exposure and postmenopausal breast cancer

Stratifications	N. studies	Meta-RR	[95% CI]	χ^2 Woolf	P-value	I ² (%)	95% UI
(1) All studies	5	1.05	[0.87-1.28]	14.988	0.473×10^{-2}	73	33-89
Study design							
(2) cohort	4	1.02	[0.84-1.25]	13.336	0.396×10^{-2}	77.5	39-92
(3) case-control	1	/	/	/	/	/	/
ER status							
(4) ER+	3	1.14	[0.93-1.38]	10.075	0.649×10^{-2}	80	37-94
(5) ER+ cohort only	2	1.08	[0.91-1.27]	5.833	0.0157	83	28-96
(6) ER-	3	1.02	[0.76-1.36]	4.765	0.0923	58	0-88
Sensitivity study							
(7) All studies minus Adams et al., 2012*	4	1.07	[0.85-1.34]	14.963	0.185×10^{-2}	80	47-92
(8) All studies minus Itoh et al., 2014**	4	1.02	[0.84-1.25]	13.336	0.396×10^{-2}	77.5	39-92
(9) All studies minus Adams et al., 2012 and minus Itoh et al., 2014**	3	1.02	[0.8-1.3]	13.322	0.128×10^{-2}	85	56-95

Notes : where studies reported results for tertiles/quartiles/quintiles, the data for the highest were used. Where results were reported for several levels of adjustment, the data adjusted for the largest number of parameters was used. *: as redundancy between some data from Adams et al., 2012 and Adams et al., 2014 can not be excluded, sensitivity analysis was performed omitting the study of Adams et al., 2012. **: as redundancy between some data from Itoh et al., 2014 and Sawada et al., 2012 can not be excluded, sensitivity analysis was performed omitting the study of Itoh et al., 2014.

Included studies were:

- (1) : Adams et al., 2012; Adams et al., 2014; Itoh et al., 2014; Julin et al., 2012a; Sawada et al., 2012
- (2) : Adams et al., 2012; Adams et al., 2014; Julin et al., 2012a; Sawada et al., 2012

- (3) : Itoh et al., 2014
- (4) : Adams et al., 2012; Itoh et al., 2014; Julin et al., 2012a
- (5) : Adams et al., 2012; Julin et al., 2012a
- (6) : Adams et al., 2012; Itoh et al., 2014; Julin et al., 2012a
- (7) : Adams et al., 2014; Itoh et al., 2014; Julin et al., 2012a; Sawada et al., 2012
- (8) : Adams et al., 2012; Adams et al., 2014; Julin et al., 2012a; Sawada et al., 2012
- (9) : Adams et al., 2014; Julin et al., 2012a; Sawada et al., 2012