Comments by ICdA (International Cadmium Association)

Responses to comments 1-15, i.e. those referring to Part I of the Annex XV dossier for $CdSO_4$. Responses to comments 27, 36-37 are also given below.

The comments on Part II (comments 16-37) may, when relevant, be taken into account at later stages of the risk management process. Some of the comments in Part II are similar to those on Part I.

Section 12 of the Annex XV report contains references and citations from previous risk assessments by other authorities. These assessments have been included for information purpose and have not been evaluated. Therefore, no responses to comments on this section are given.

Comment 1

The justification for SVHC identification is based on the intrinsic properties of the substance, not on exposure and risk. In the case of $CdSO_4$, the justification for articles 57(a), 57(b) and 57(c) is based on the harmonized classification (Carc. 1B, Muta. 1B, Repr. 1B). Also for 57(f) the harmonized classification, in this case as STOT RE1, is of high relevance.

We agree that intentional uses of $CdSO_4$ contribute to a very low extent to the total exposure of cadmium. However, as effects on eg. bone can be seen in the general population in EU today, all contributing parts of the total exposure, even small ones, need to be diminished, when possible. An important aim of the authorization system in REACH is that SVHC substances should be progressively replaced with technically and economically viable alternatives. Since the registered uses of $CdSO_4$ are exempted from authorization, we realize that the substance may not be prioritized to Annex XIV in the near future. However, inclusion in Annex XIV would decrease the probability of new uses of this SVHC.

Comment 2

The justification for SVHC identification is based on the intrinsic properties of the substance, not on exposure and risk. The text on p.7, referring to the Council resolution from 1988, should be considered as background information. It is of course good that several actions in order to diminish the use and emissions of cadmium have been taken since 1988, but nevertheless the problem is not yet solved.

Comment 3

It is true that the observed effects on kidney at very low exposure to cadmium have recently been questioned, in particular when exposure and effects have been assessed using the same matrix (urine). However, the toxic effects in the kidney at higher exposures have not been questioned. Instead other effects, eg. bone effects and cancer, have recently gained more interest and

evidence. Such effects can be seen in the general population, thus at comparably low exposures to cadmium, i.e. at lower exposure than that corresponding to 1 μg/g creatinine. A review on non-renal effects and risk assessment of environmental cadmium exposure was published in Environmental Health Perspectives earlier this year. This publication is available via the following link: http://dx.doi.org/10.1289/ehp.1307110

The TDI established by EFSA is based on a urinary Cd level of 1 μg/g creatinine at the age of 50. Since Cd accumulates in the body younger individuals have lower values (at the same intake of Cd). The median value for European women referred to in the comment is for woman < 45 years of age.

Comment 4

The estimation of annual costs in the KemI report mentioned is actually based on data on dietary intake of cadmium (not urinary Cd) and effects on bone (fractures) in two Swedish population-based prospective cohorts.

Comment 5

Please see response to comment 1.

Comment 6

We do not agree with the statement that *"the current observed dietary intakes of cadmium in the EU can be considered safe in a life time perspective",* nor do EFSA, as referred to in section 3.2 of the Annex XV report. This conclusion is not solely based on the 95th percentiles in the EFSA report. When it comes to estimations of dietary intake this can be done using different methods, this is one reason for different studies showing different results. As background information for the present SVHC proposal, we consider the estimations presented by EFSA, covering most EU countries, as appropriate.

Comment 7

The TWI value established by EFSA, and the rationale behind this value, should be regarded as background information in the SVHC proposal. Although this assessment may be interesting to discuss, it is not relevant for the SVHC proposal. As already mentioned the SVHC identification is based on the intrinsic properties of the substance, not on risk.

However, we agree with the EFSA 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*". It is of great concern that a significant fraction of the population exceeds the TWI. The size of this proportion is somewhat uncertain; depending on country and method used, estimates between 2 and 42 % were recently reported (Sand et al (2013) Food Chem Toxicol 62, 7-15).

Comment 8

For a response, see comment 3. Although details in single scientific studies may be relevant to discuss and assess further, the results referred to in the comment do not change the overall conclusion concerning the ability of cadmium to cause kidney toxicity. Further, it should always be kept in mind that non-significant correlations in small groups should not be considered as showing lack of effect, rather the results are equivocal.

Comment 9

The use of urinary cadmium in studies on non-renal effects has not been questioned. Below is a citation from Åkesson et al (2014), which is available at: http://dx.doi.org/10.1289/ehp.1307110.

Most bone studies have used U-Cd to explore associations. Although these associations were present at very low-exposure levels, it is not likely that they represent reverse causation, that is, that the bone effects cause the increased U-Cd (e.g., that bone-derived proteins bind Cd and are excreted into urine). In addition to the studies based on biomonitoring of exposure, two were based on dietary Cd exposure, combining individual food consumption data from a food-frequency questionnaire with data on Cd content in food. Both Engström et al (2012) and Thomas et al (2011) observed associations with osteoporosis and/or fracture incidence, even though the exposure misclassification is likely to be larger than for the biomarkers with this method. Decreased bone mineral density with increasing B-Cd has been described in a few studies. In Alfvén et al (2002), B-Cd was < 1 µg/L (corresponding to an average U-Cd < 1 µg/g cr), but the study population included subjects who had previously had higher Cd exposure. In a study by Nordberg et al (2002), the exposure levels were very high (> 20 µg/L). Nevertheless, the fact that associations between Cd and effects on bone were observed by the use of three different exposure assessment methods (urine, blood, and dietary intake) reduces the likelihood that the results were due to confounding.

In the section on bone toxicity (fractures) some recent prospective population based studies are briefly described (Swedish Mammography Cohort and Cohort of Swedish Men). In these studies, where increased fracture risk was significantly elevated in individuals above the median dietary exposure to cadmium compared to those below the median, the exposure was assessed using food frequency questionnaires in combination with measurements of cadmium content in the various food items. In a subset, urinary cadmium was measured in approximately 2700 women. The median concentration was 0.34 (5-95th percentile 0.15-0.79) µg Cd /g creatinine (Engström et al 2011), thus even lower than 0.5 µg/g. As already mentioned urinary Cd is considered a good measure of body burden of cadmium suitable for correlations with eg. bone effects.

Engström, A., Michaëlsson, K., Suwazono, Y., Wolk, A., Vahter, M. and Åkesson, A., 2011. Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. *J Bone Miner. Res.* **26(3)**, 486-495.

Comment 10

The statement comes from the KemI report (No 1/11), in “Bilaga 3”, written by cadmium researchers from the Karolinska Institutet in Stockholm.

In a recent report from the Swedish National Food Agency vitamin D intake was estimated as 8.3 μg/day, in line with the recommended intake of 7.5 μg/day (http://www.slv.se/upload/dokument/rapporter/kemiska/2012_livsmedelsverket_7_market_basket_2010.pdf).

Further, in the reference given below it is concluded that *"the low levels of cadmium exposure present in the studied women, although high enough to be associated with lower bone mineral density and increased bone resorption, were not associated with lower serum concentrations of 1,25(OH)(2)D. Hence, decreased circulating levels of 1,25(OH)(2)D are unlikely to be the proposed link between cadmium-induced effects on kidney and bone."*

Engström A, Skerfving S, Lidfeldt J, Burgaz A, Lundh T, Samsioe G, Vahter M, , Åkesson A. Cadmium-induced bone effect is not mediated via low serum 1,25-dihydroxy vitamin D. Environ. Res. (2009) **109(2)**, 188-192.

The recommended intake of calcium is 800 mg/day and approximately 60 % comes from milk, yoghurt and cheese, which are common food items in Northern Europe (Swedish National Food Agency).The calcium intake of women in the Swedish Mammography Cohort are above this recommended level (Michaelsson et al, 2014).

Michaelsson K, Wolk A, Byberg L, Ärnlöv J, Melhus H. (2014) Intake and serum concentrations of α-tocopherol in relation to fractures in elderly women and men: 2 cohort studies. Am J Clin Nutr **99**, 107-114.

Comments 11-15

See responses to comments 1- 4.

Comment 27

Concerning time trends, there are no firm indications that the exposure to cadmium has decreased in more recent years. For short-term time trends of cadmium data from young individuals are of particular relevance. Please find below a citation from a recent study reporting data from the German Environmental Survey (GerES (Becker et al. (2013) Int J Hyg Environ Health, 216, 250-254).

Also for cadmium (Cd) in urine neither ESB nor GerES no obvious and prolonged trend of decreasing concentrations could be shown (Wiesmueller et al., 2007; Schulz et al., 2007a). Regarding Cd in blood no time trends were found in GerES for children. In ESB the concentrations in young adults remained unchanged over time between the year 2000 and 2005 and the geometric means were in the range of 0.25 μg/l (Wiesmueller et al., 2007). It can be assumed that the major source for Cd in German non-smokers is nutrition (HBMC,

2011), and exposure through this pathway might not have changed that much in the time period observed. The observed significant time trend in GerES in blood of adult smokers and non-smokers in the total of Germany found between 1990/92 and 1998 can mainly be explained by the decrease of exposure in East-Germany after reunification (Schulz et al., 2007a).

Comment 36

Urinary cadmium is considered a good marker for body burden of cadmium and may be used for studies on eg. developmental effects. It is only in connection with kidney effects, measured as increased protein levels in the urine, i.e. in the same matrix, that urinary cadmium has been questioned.

Comment 37

In recent years, data indicating endocrine disrupting effects of cadmium have been published. This is briefly mentioned in Annex I. This effect has however not been used for the SVHC identification.