

SCIENTIFIC OPINION

Statement on tolerable weekly intake for cadmium¹

EFSA Panel on Contaminants in the Food Chain (CONTAM)^{2, 3}

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ABSTRACT

The Panel on Contaminants in the Food Chain of the European Food Safety Authority (CONTAM Panel) was asked by the European Commission to confirm whether the current tolerable weekly intake (TWI) of 2.5 µg/kg body weight (b.w.) for cadmium is still considered appropriate or whether any modifications are needed in view of the provisional tolerable monthly intake (PTMI) of 25 µg/kg b.w. established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2010. Both assessments used the same epidemiological dataset and have two primary components, a concentration-effect model that relates the concentration of cadmium in urine to that of beta-2-microglobulin (B2M), a biomarker of renal tubular effects, and a toxicokinetic model that relates urinary cadmium concentration to dietary cadmium intake. The following methodological differences were identified: i) the identification of the reference point on the basis of the urinary cadmium and the B2M concentration data; ii) the statistical approach to account for the variability and uncertainty of the biomarker of exposure (urinary cadmium concentration) and the biomarker of response (B2M concentration) in the concentration-effect model; and iii) the methodology for transforming urinary cadmium concentrations into dietary intake values.

Following an evaluation of the two approaches, the CONTAM Panel concluded that the approach adopted for its previous opinion on cadmium in food was appropriate and hence the current TWI for cadmium of 2.5 µg/kg b.w. was maintained.

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KEY WORDS

Cadmium, dietary exposure, tolerable weekly intake, provisional tolerable monthly intake

¹ On request from the European Commission, Question No EFSA-Q-2010-01008, adopted on 18 January 2011.

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³ Acknowledgement: The Panel wishes to thank the members of the Working Group on cadmium modelling: Billy Amzal, Alan Raymond Boobis, Diane Benford, Clark Carrington, Eugenia Dogliotti, Lutz Edler, and Antonio Mutti for the preparatory work on this scientific opinion, and EFSA staff: José Cortinas Abrahantes and Claudia Heppner for the support provided to this scientific opinion.

SUMMARY

Foodstuffs are the major source of cadmium exposure for the non-smoking general population. Cadmium exerts toxic effects after long-term exposure mostly on the kidney but also on the bones. In 2009 the EFSA's Panel on Contaminants in the Food Chain (CONTAM Panel) established a tolerable weekly intake (TWI) of 2.5 µg/kg body weight (b.w.) for cadmium. In 2010 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) reviewed its previous evaluation on cadmium and established a provisional tolerable monthly intake (PTMI) of 25 µg/kg b.w. which corresponds to a weekly intake of 5.8 µg/kg b.w. In view of the differences in the two health based guidance values (HBGV), EFSA was asked by the European Commission to confirm whether the TWI of 2.5 µg/kg b.w. for cadmium established by the CONTAM Panel is still considered appropriate or whether any modifications are needed. The CONTAM Panel reviewed the approach taken in its assessment and carried out a comparison of the two evaluations on the basis of available information.

The assessments of the CONTAM Panel and the JECFA are based on a meta-analysis of the same dataset selected in a systematic review performed by European Food Safety Authority (EFSA) of epidemiological studies assessing the concentration-effect relationship between urinary cadmium and beta-2-microglobulin (B2M) levels. An increase of the latter is a biomarker of renal tubular effects. Both assessments have two primary components, a concentration-effect model that relates the concentration of cadmium in urine to that of B2M, and a toxicokinetic model that relates urinary cadmium concentration to dietary cadmium intake.

However, the following main methodological differences between the two assessments were identified: i) the identification of the reference point (RP) on the basis of the urinary cadmium and B2M concentration data; ii) the statistical approach to account for the variability and uncertainty of the biomarker of exposure (urinary cadmium concentration) and the biomarker of response (B2M concentration) in the concentration-effect model; and iii) the methodology for transforming urinary cadmium concentrations into dietary intake values.

The meta-analysis performed by EFSA for the CONTAM Panel linked reported summary values of urinary cadmium and B2M concentrations, assuming a log-normal distribution, within a Bayesian framework. A hybrid benchmark dose (BMD) approach, in which the Hill model was fitted to the data, was chosen to estimate the BMD and its lower one-sided 95 %-confidence bound for an extra risk of 5 % of producing a specified change in the urinary level of the B2M (BMDL5). B2M levels exceeding 300 µg/g creatinine in urine have been associated with an accelerated decline of age-related progressive loss of renal function and therefore this pre-specified biological cut-off was chosen together with a statistical cut-off to identify a RP from the respective BMDL5 values. An overall group-based BMDL5 of 4 µg cadmium/g creatinine was thus identified and the CONTAM Panel confirmed this as an RP for use in establishing a TWI.

The CONTAM Panel re-examined the need to apply an adjustment factor of 3.9 to the RP to account for variability in the concentration-effect relationship data. In a simulation exercise the estimated BMD and BMDL were compared when using summary data or individual data when fitting the concentration-effect model. It was confirmed that, when using summary data, the confidence band around the fitted model was narrower than when using individual data. Therefore, using summary data would lead to an overestimation of the BMDL. It was also noted that some of the inter-individual variability may have been accounted for already in the BMD analysis, but it was not possible to determine to what extent. Therefore, it was concluded that the BMDL5 value would need adjustment to account for this remaining source of variability. The CONTAM Panel reiterated its view that it was necessary to apply an adjustment factor to the RP to account for the variability in the concentration-effect relationship data in the absence of individual data, and reconfirmed a urinary cadmium concentration of 1 µg cadmium/g creatinine in urine as the modified RP.

The JECFA used the break point of 5.24 (confidence interval (CI): 4.94 - 5.57) µg cadmium/g creatinine in urine as its RP, obtained from a piece-wise linear model fitted to the data. The JECFA

used a combined approach to account for toxicodynamic and toxicokinetic variability in the relationship between urinary cadmium and dietary cadmium intake in a simultaneous two-dimensional (2D) Monte-Carlo simulation. The JECFA modelled the toxicodynamic variability by introducing a log-triangular distribution function with a fixed range of variation by a factor between 1 and 3 below and above the RP (break point) for both increased and reduced individual susceptibility.

To determine the dietary exposure corresponding to a cadmium concentration in urine, a one-compartment toxicokinetic model was used by EFSA. The data from a population-based Swedish cohort study, where individual data on urinary cadmium concentrations and daily dietary cadmium intake were available for 680 never smoking women of 56-70 years age, were used to estimate the critical dietary cadmium exposure. In order to remain below the modified RP of 1 µg cadmium/g creatinine in urine it was calculated that the average daily dietary cadmium intake should not exceed 0.36 µg/kg b.w., and this daily intake was used to derive the TWI of 2.5 µg/kg b.w.

The CONTAM Panel noted that the applicability of the 2D Monte-Carlo simulation approach used by the JECFA for its risk assessment of cadmium to address simultaneously variability and uncertainty of multiple components in hazard characterisation needs to be further explored. The CONTAM Panel noted that the choice of the toxicodynamic variability function has a major impact on the outcome (e.g. the HBGV) and that the differences in the other parameters involved have only a minor influence.

Based on the current state of knowledge, the CONTAM Panel concluded that for cadmium the current TWI of 2.5 µg/kg b.w. established in 2009 should be maintained in order to ensure a high level of protection of consumers, including subgroups of the population such as children, vegetarians or people living in highly contaminated areas. Taking non-dietary exposure into account, it is anticipated that the total exposure of some subgroups of the population could exceed the JECFA PTMI as well as the CONTAM TWI.

The CONTAM Panel reaffirmed its previous conclusion that adverse effects are unlikely to occur in an individual with current dietary exposure, but there is a need to reduce exposure to cadmium at the population level.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The Panel on Contaminants in the Food Chain (CONTAM Panel) adopted an opinion on cadmium in food on 30 January 2009. In this opinion a provisional tolerable weekly intake (PTWI) of 7 µg/kg body weight previously established by the Scientific Committee on Food was not maintained and a considerably lower tolerable weekly intake of 2.5 µg/kg body weight was established by the CONTAM Panel. In 2010, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) reviewed its previous evaluation on cadmium and set a provisional tolerable monthly intake of 25 µg/kg body weight which is in the range of the previously set PTWI of 7 µg/kg body weight.

Based on the outcome of EFSA's risk assessment on cadmium in food in 2009, the Health and Consumers Directorate-General is reviewing, together with the Member States, the currently established maximum levels for cadmium in relevant food groups in order to address the concerns raised by the CONTAM Panel. The discrepancies in the two toxicological thresholds and the consequences related to the dietary exposure assessment by the two bodies could have consequences for European farmers and producers as well as for international trade if levels proposed by the European Commission would deviate from Codex levels.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art. 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks EFSA to confirm whether the tolerable weekly intake for cadmium of 2.5 µg/kg body weight established by the CONTAM Panel in 2009 is still considered appropriate or whether any modifications are needed.

EVALUATION

1. Introduction

The consumption of food is the main source of cadmium exposure for the non-smoking general population. Cadmium is toxic primarily to the kidney, particularly to the proximal tubular cells, where it accumulates over time, leading to renal dysfunction.

In 1988 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessed the risks to human health related to the presence of cadmium in foodstuffs and established for cadmium a provisional tolerable weekly intake (PTWI) of 7 $\mu\text{g}/\text{kg}$ body weight (b.w.) that was subsequently endorsed by the Scientific Committee on Food.

In 2009 the EFSA's Panel on Contaminants in the Food Chain (CONTAM Panel) was asked to assess the risks to human health related to the presence of cadmium in foodstuffs, the outcome of which is referred to as the Opinion (EFSA, 2009a) in this document. On the basis of a systematic review of the literature, 35 epidemiological studies that measured biomarkers both of exposure and of effect in urine were compiled into an aggregated dataset made up of 165 groups with matched urinary cadmium concentrations and beta-2-microglobulin (B2M). Group geometric means (GMs) and standard deviations (GSDs) were meta-analysed using concentration-effect models (e.g. a piece-wise linear model and the Hill model, both on the log-log scale) which related B2M as the effect parameter to urinary cadmium concentration. The CONTAM Panel used the Hill concentration-effect model accounting for gender, ethnicity, study heterogeneity and the group sample sizes to determine a reference point (RP) using the benchmark dose (BMD) approach for hazard characterisation (for details see Section 3.1 and Table 36 in the Opinion (EFSA, 2009a)). To account for inter-individual variations in cadmium concentration within groups, not explicitly accounted for in the BMD modelling (i.e. when calculating the lower one-sided 95 %-confidence bound for an extra risk of 5 % of producing a specified change in the urinary level of the B2M, denoted BMDL5), the CONTAM Panel modified the BMDL5 value using an adjustment factor based on the estimated variance of within group cadmium concentration. After adjustment, the CONTAM Panel identified a critical cadmium concentration of 1 μg cadmium/g creatinine in urine as a modified RP on which to base a health based guidance value (HBGV) of cadmium dietary intake. Subsequently, a one-compartment population toxicokinetic (TK) model was fitted to 680 paired data of cadmium intake and urinary cadmium concentrations from the Swedish Mammography Cohort study (Amzal et al., 2009). This TK model showed that a dietary intake of no greater than about 2.5 $\mu\text{g}/\text{kg}$ b.w. cadmium per week would prevent 95 % of the Caucasian population from being above the modified RP of 1 μg cadmium/g creatinine in urine after 50 years of exposure (EFSA, 2009a). In order to remain below this modified RP it was calculated that the average daily dietary cadmium intake should not exceed 0.36 $\mu\text{g}/\text{kg}$ b.w., and this daily intake was used to derive the TWI of 2.5 $\mu\text{g}/\text{kg}$ b.w.

The approach taken by the CONTAM Panel for this assessment is summarised in Figure 1 showing how the various datasets, analyses and outputs of analyses were sequenced and combined to establish the HBGV for dietary cadmium.

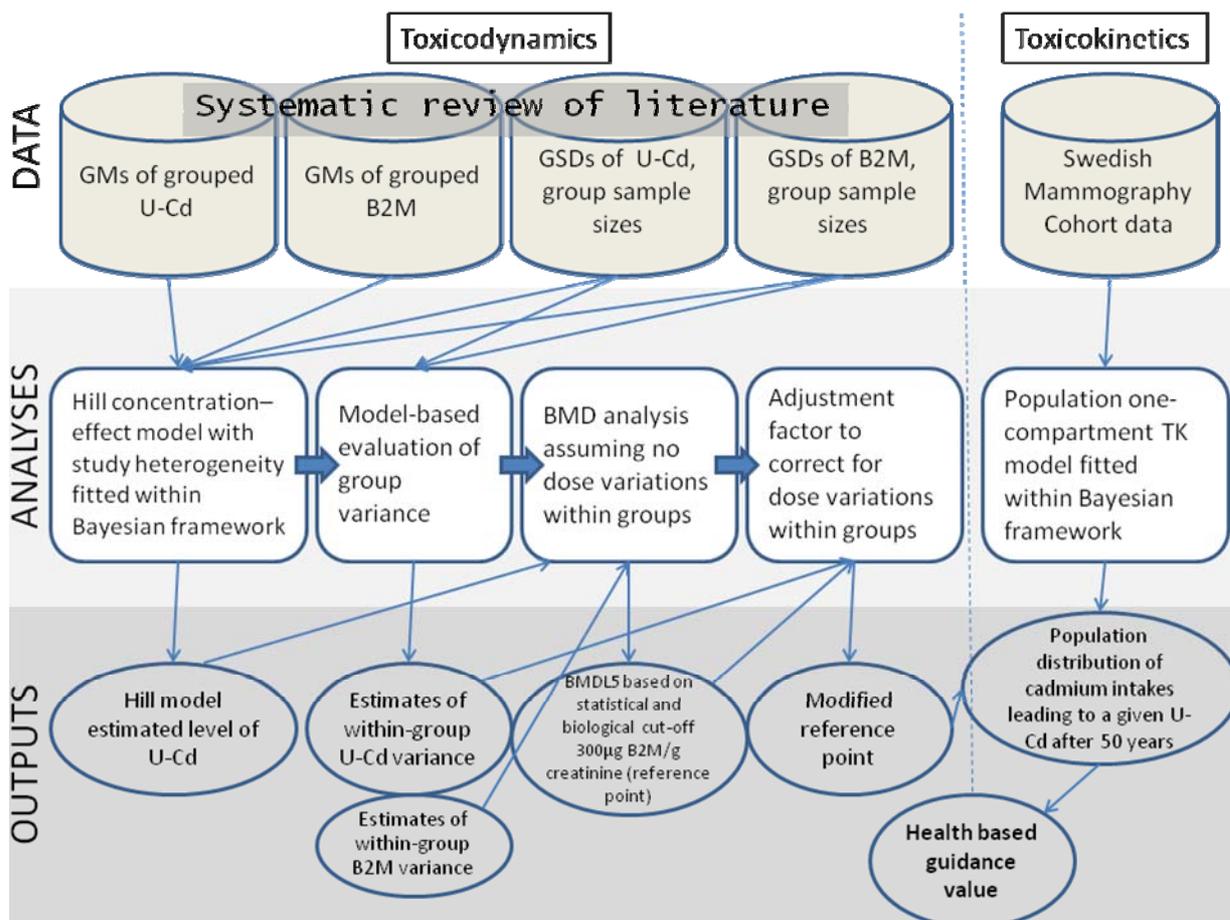


Figure 1: Graphical representation of the step-wise toxicodynamic/toxicokinetic assessment performed to derive the final HBGV for dietary cadmium reported in the Opinion (EFSA, 2009a). GMs and GSDs denote the geometric means and the geometric standard deviations of the urinary cadmium concentrations (U-Cd) and the B2M levels, respectively, in the groups used in the meta-analysis.

In 2010 the JECFA reviewed its previous evaluation of cadmium using the same epidemiological dataset as the CONTAM Panel but with some methodological differences (see Chapters 2 and 3). As a result, the JECFA withdrew its previous PTWI of 7 µg/kg b.w. and established a provisional tolerable monthly intake (PTMI) of 25 µg/kg b.w. The JECFA concluded that the tolerable dietary intake should be expressed as a monthly value because of the long half-life of cadmium (FAO/WHO, 2010, 2011). This PTMI corresponds to a weekly intake of 5.8 µg/kg b.w.

In view of the differences in the two HBGVs, the European Food Safety Authority (EFSA) was asked by the European Commission to confirm whether the TWI for cadmium of 2.5 µg/kg b.w. established by the CONTAM Panel is still considered appropriate or whether any modifications are needed.

2. Similarities in the CONTAM Panel and the JECFA assessments of cadmium

The assessments of the CONTAM Panel and of the JECFA are both based on the data identified by a systematic review conducted by EFSA of epidemiological studies that tabulated paired summary data for cadmium concentrations in urine and for B2M, a biomarker of renal tubular effects. The JECFA did not identify any additional studies to those included in the Opinion (EFSA, 2009a) for consideration in its recent assessment of cadmium. Both assessments have two primary components, a concentration-effect model that relates the concentration of cadmium in urine to that of B2M, and a

toxicokinetic model that relates urinary cadmium concentration to dietary cadmium intake. Both assessments endeavour to account for population variability in the concentration-effect relationship.

3. Methodological differences in the CONTAM Panel and the JECFA assessments of cadmium

Although both bodies used the same dataset (see Chapter 2) methodological differences can be identified at the following steps leading to the HBGV:

- the identification of the RP on the basis of the urinary cadmium and the B2M concentration data (see Chapter 3.1);
- the statistical approach to account for the variability and uncertainty of the biomarker of exposure (urinary cadmium concentration) and the biomarker of response (B2M concentration) in the concentration-effect model (see Chapter 3.2);
- the methodology for transforming urinary cadmium concentrations into dietary intake values (see Chapter 3.3).

3.1. The identification of the reference point on the basis of the urinary cadmium and the B2M concentration data

The CONTAM Panel used the BMD approach to calculate the critical urinary cadmium concentration as a RP, through a comprehensive analysis of all available concentration-effect data as illustrated by the first three steps of the “Analyses” track in Figure 1. A piece-wise linear model (PLM) and the Hill model, both on a log-log scale were fitted to the data as described in more detail in the EFSA Report (EFSA, 2009b). The CONTAM Panel then chose the Hill model and estimated the BMDL5 modified by an adjustment factor to serve as RP for the hazard characterisation. The JECFA used the break point of 5.24 (confidence interval (CI): 4.94 - 5.57) μg cadmium/g creatinine in urine obtained from a PLM fitted to the data as its RP.

The CONTAM Panel noted that EFSA recommends that, when possible, the BMD approach should be used for determining a RP, including the dose-response assessment of observational epidemiological data. EFSA Scientific Panels and Units are strongly encouraged to adopt the BMD approach as such or as otherwise specified in EFSA Scientific Committee Guidance on the use of the benchmark dose approach in risk assessment (EFSA, 2009c). The BMD approach makes use of all available dose-response data and is applicable to human dose-response data if the individual data are available, irrespective of whether the response (or effect) is on a continuous or quantal (dichotomous) scale. If continuous effect data are summarised by means and standard deviations of subgroups and if the samples sizes are known, the BMD approach can still be applied although its statistical validity depends on the assumed distribution. The CONTAM Panel noted that the application of the BMD approach as developed for a continuous effect using individual data was applicable to the data compiled in the systematic review. Calculation of a RP was therefore based on a hybrid type BMD analysis (see e.g. Sand et al., 2003; Suwazono et al., 2011) applied to the group summary data from the meta-analysis within a Bayesian framework, using a mixed-effects model and cut-off points based on relevant biological changes in the biomarker of renal damage. The CONTAM Panel chose two cut-off points in the hybrid approach: a biological cut-off of 300 μg B2M/g creatinine in urine and a statistical cut-off, which was determined during the hybrid analysis and corresponds to the 95th percentile of B2M distribution of background exposure (for details see EFSA, 2009a, 2009b). Exceeding B2M levels of 300 $\mu\text{g}/\text{g}$ creatinine in urine has been associated with an accelerated decline of age-related progressive loss of renal function (Nakagawa et al., 1993, 2006; Nishijo et al., 1994, 1995, 1999, 2006) and was therefore chosen, together with a statistical cut-off (associated with a B2M level of 211 and 374 μg B2M/g creatinine, for the whole population and for the focus population, respectively; see Tables 17 and 20 in EFSA 2009b for the calculation of the RP in the hybrid BMD analysis, see Table 36 in EFSA 2009a). The Hill model was chosen as the concentration-effect model since it uses more interpretable parameters than the PLM, has symmetrical properties on the log scale, leads to a more robust BMD estimate, and it showed an adequate fit (EFSA, 2009a). The PLM gave a

similar fit except at low cadmium concentrations in urine. The CONTAM Panel identified an overall group-based 95 % lower confidence bound of the BMD of 4 µg cadmium/g creatinine in urine as its RP (for details see Table 36 in EFSA, 2009a).

Although the JECFA used the same database as the CONTAM Panel, they assessed it differently. The JECFA considered the PLM of EFSA to characterise the concentration-effect relationship between urinary cadmium concentration and B2M (FAO/WHO, 2011). The JECFA recognised that this model showed an obvious transition or break point between the low dose slope and the slope at higher doses (as a marker of pathological changes in renal tubular dysfunction) and chose the break point value of 5.24 (CI: 4.94-5.57) µg cadmium/g creatinine in urine as its RP. This should be compared with the results of EFSA when the PLM was fitted to the data of the so-called focus population, i.e. groups of non-occupationally exposed individuals with mean age over 50 years, adjusted for ethnicity (see Table 11 in EFSA, 2009b; FAO/WHO, 2011).

The CONTAM Panel reviewed its risk assessment (EFSA, 2009a) in the light of choosing a cut-off level for B2M in the BMD modelling, recognising that B2M as a biomarker of cadmium-induced renal tubular effects is not *per se* associated with any symptom or objective sign of disease. Similar RPs had been obtained by EFSA (2009a) when using a biological cut-off of 300 or 1,000 µg B2M/g creatinine in urine, respectively, above which B2M excretion levels were considered as adverse, or as likely to be irreversible. Based on a statistical cut-off and a biological cut-off of 300 µg B2M/g creatinine in urine the CONTAM Panel confirmed 4 µg cadmium/g creatinine in urine as RP.

3.2. Accounting for the variability and uncertainty of the biomarker of exposure and the biomarker of response in the concentration-effect model

This section compares the CONTAM Panel and the JECFA risk assessments for differences in adjusting for variability and uncertainty in the biomarker of exposure (urinary cadmium concentration) and the biomarker of response (B2M concentration in urine) in the concentration-effect model, when transforming urinary cadmium concentrations into intake values.

For the analysis of the biomarker concentration-effect relationship, EFSA compiled a dataset for the CONTAM Panel by conducting an extensive literature search which covered publications of epidemiological studies from October 1996 until October 2008 on approximately 30,000 individuals. However, the relationship between urinary cadmium concentration and B2M in these publications was not based on individual data but on a total of 165 matched pairs of summary data (GMs and GSDs) on urinary cadmium concentration and B2M from a total of 35 eligible studies, mostly of a cross-sectional design, contributing from one to 16 dose groups and having sample sizes between $n=3$ and more than $n=1,300$ individuals. The CONTAM Panel identified the main sources of variability in its modelling approach: (i) inter-study variability; (ii) population variability of the effect given a urinary cadmium level; (iii) population variability of urinary cadmium within each dose group; (iv) variability of the BMD estimation; and (v) modelling uncertainty. The BMD approach applied to the 165 matched pairs of summary data within a Bayesian framework accounted for these sources of variability except that for urinary cadmium concentrations within each dose group, due to the fact that group means and not data points from individual subjects were used when identifying the BMDs and the BMDLs. It was concluded that the estimated BMDLs were likely to be greater than if calculated with individual data, which were not available. Therefore, an adjustment factor to allow for this was calculated based on the estimated coefficient of variation (100 %) of inter-individual variability of urinary cadmium concentrations within the sub-groups. This resulted in an adjustment factor of 3.9. Application of this factor to the BMDL5 value of 4 µg cadmium/g creatinine in urine resulted in a modified RP of 1.0 µg cadmium/g creatinine in urine (EFSA 2009a).

The CONTAM Panel re-examined the need for an adjustment factor in a simulation exercise conducted by EFSA (2011) that compared the calculation of BMD and BMDL when using summary data with an estimation based on individual data when fitting the concentration-effect model as in the

BMD analysis performed by EFSA (EFSA, 2009b). It was confirmed that, when using summary data, the confidence band around the fitted model was narrower than when using individual data and would lead to an overestimation of the BMDL. It was also noted that some of the inter-individual variability may have already been accounted for already in the BMD analysis, but it is not possible to determine to what extent (EFSA, 2011). Therefore it was concluded that the BMDL5 value would need adjustment to account for this remaining source of variability.

The JECFA used, for its analysis of the biomarker concentration-effect relationship, the break point value of 5.24 (CI: 4.94-5.57) μg cadmium/g creatinine in urine of the PLM model and concluded that toxicodynamic variability in the concentration-effect relationship was not taken into account by that modelling, because the data represented only population averages rather than individual data. The JECFA further concluded that, within a sub-group, it could not be assumed that urinary B2M concentrations would vary as a function of urinary cadmium concentration. Therefore the JECFA modelled the toxicodynamic variability in the PML assuming that individuals would have an individual break point (comparable to an individual threshold value) somewhere within a range around the estimated reference point of 5.24. The JECFA accounted for this by introducing a log-triangular distribution function with a fixed range of variation by a factor between 1 and 3 below and above the RP (break point) for both increased and reduced individual susceptibility. The JECFA used a maximum value of 3, the approximate default toxicodynamic sub-factor in the conventional 10-fold uncertainty factor, for inter-individual variability. Individual values were generated in a Monte-Carlo simulation approach for both increased and reduced individual susceptibility resulting in a distribution around the RP (see also Chapter 3.3). EFSA investigated the range and the shape of this distribution based on the computer program codes made available to EFSA and observed a low frequency of simulated data points in the range below the RP (EFSA, 2011). Only small portions of the data points were located in the lower part of that range when moving the factor accounting for toxicodynamic variability to its maximum value of 3. However, when the log-triangular distribution preferred by the JECFA was replaced by a function in which each value has the same probability of being drawn (use of a uniform distribution with the break point as centre and the same range of variation), values considerably lower than those reported by the JECFA were obtained. For further details see EFSA report (EFSA, 2011).

3.3. The methodology for transforming urinary cadmium concentrations into dietary intake values

In contrast to those hazard characterisations where the RP is based on a dose defined by intake data and a critical response by an adverse effect on health, the use of a biomarker dose-response relationship as in the case of cadmium, requires additional steps. Using urinary cadmium concentration as a biomarker of exposure requires the use of a toxicokinetic model to relate dietary intake to urinary cadmium levels. The CONTAM Panel and the JECFA took different approaches to address this problem.

The CONTAM Panel chose a one compartment model in which urinary cadmium concentration is proportional to dietary cadmium intake at all ages. That model was fitted to data from the population-based Swedish Mammography Cohort of 680 non-smoking women with ages ranging from 56 to 70 years (Amzal et al., 2009). The dietary cadmium exposure that corresponded to different urinary cadmium levels after 50 years of exposure was then estimated for different proportions of the population (see Figure 20 and Table 38 of EFSA, 2009a). In order to remain below 1 μg cadmium/g creatinine in urine in 95 % of the population by age 50, the daily dietary cadmium intake should not exceed 0.36 μg cadmium/kg b.w.

The JECFA also used the one-compartment model of Amzal et al. (2009) to characterise the relationship between urinary cadmium concentration and dietary cadmium intake, but included a statistical parameter for variation in apparent half-life and calculated the population distribution of the ratio of urinary cadmium concentration over cadmium intake with confidence intervals (see Figure 3

in FAO/WHO, 2011). This calculation was performed within the framework of the aforementioned two-dimensional (2D) Monte-Carlo simulation approach accounting simultaneously for variability in the break point, the toxicodynamics and the toxicokinetics, and assuming potential independent variation within sub-groups for the urinary cadmium concentrations and the B2M levels. The dietary cadmium exposure ($\mu\text{g}/\text{kg}$ b.w. per day) that equates to a concentration of $5.24 \mu\text{g}$ cadmium/creatinine in urine (break point) was estimated to be $1.2 \mu\text{g}/\text{kg}$ b.w. per day at the 5th population percentile, 0.8 and $1.8 \mu\text{g}/\text{kg}$ b.w. per day, corresponding to the break point CI 4.94 - $5.57 \mu\text{g}$ cadmium/g creatinine in urine, respectively. The JECFA used the lower bound of $0.8 \mu\text{g}/\text{kg}$ b.w. per day as critical dietary intake to account for particularly susceptible individuals to ensure that 95 % of the population will maintain urinary cadmium levels with 95 % probability below $5.24 \mu\text{g}$ cadmium/g creatinine, i.e. “below the point at which renal pathology is indicated by increased B2M levels” (FAO/WHO, 2011).

The CONTAM Panel noted that the applicability of the 2D Monte-Carlo simulation approach used by the JECFA for its risk assessment of cadmium to address simultaneously variability and uncertainty of multiple components in hazard characterisation needs to be further explored.

To explore the impact of the assumptions on the establishment of a HBGV, EFSA performed a number of simulations using varying assumptions (EFSA, 2011). On the basis of this sensitivity analysis, the CONTAM Panel concluded that the choice of the toxicodynamic variability function has a major impact on the outcome (e.g. the HBGV) and that the changes in the other parameters involved in the simulation have only a minor influence.

4. Consequences of applying the health based guidance value for cadmium from EFSA and the JECFA

For the current statement, the CONTAM Panel refers to the previous exposure estimates from 2009 (Table 30 in EFSA, 2009a), which took into account about 140,000 data points covering the period from 2003 to 2007 on cadmium occurrence in various food commodities received from 20 Member States.

As previously expressed by the CONTAM Panel, “the average dietary exposure to cadmium for adults across European countries was estimated to be between 1.9 and $3.0 \mu\text{g}/\text{kg}$ b.w. per week, and the high exposure adults have estimates in the range of 2.5 - $3.9 \mu\text{g}/\text{kg}$ b.w. per week” (EFSA, 2009a). The exposure for high consumers was estimated by summing the 95th percentiles (consumers only) for the two main contributing categories (cereal and vegetables) and the mean exposure (whole population) for the other food categories.

The CONTAM Panel reiterates its previous conclusions that the average dietary exposure in European countries is close to, or slightly exceeds, the TWI of $2.5 \mu\text{g}/\text{kg}$ b.w. and that subgroups of the population, such as vegetarians, children, and people living in highly contaminated areas, may exceed the TWI by up to 2-fold.

Table 1: Overview of weekly cadmium exposure estimates for the different exposure pathways (Table 30 in EFSA, 2009a).

Source	Pathway	Range ^{a)} of calculated or reported exposures [µg/kg b.w. per week]	
		Adults	Children
Dietary exposure	Food average	1.89 - 2.96	2.56-3.46
	Food high	2.54-3.91	5.49
	Food in industrial areas	3.3 - 5.8 ^{b)}	4.6 ^{b)}
	Extreme diets	2.87-4.64	
	Vegetarians	5.47	
Non-Dietary Exposure	House dust	0.076	0.607
	Air	0.0024	0.0033 ^{c)}
	Smoking	0.35-0.70 ^{d)}	-

^{a)} Estimated ranges of mean cadmium exposure according to individual European countries for which data were available;

^{b)} Estimated using a factor of 1.86 times average exposure derived from Vromman et al., 2008;

^{c)} Assuming a daily inhalation volume of 7 m³ and a body weight of 15 kg;

^{d)} Assuming the contribution from smoking can increase overall cadmium exposure by 15-30 % when smoking between 20-40 cigarettes a day. For this calculation the mean exposure estimate across European countries of 2.27 µg/kg b.w. per week was applied.

Comparing the European dietary exposure estimates to the PTMI of 25 µg/kg b.w. (equivalent to a weekly intake of 5.8 µg/kg b.w.) established by the JECFA in 2010, the CONTAM Panel noted that estimates of dietary exposure for some subgroups of the European population, such as people living in highly contaminated areas (e.g. close to non-ferrous metal plants), vegetarians, or children (95th percentile high consumers) are close to this HBGV. Taking into account non-dietary exposure it is anticipated that the total exposure of some subgroups could exceed the JECFA PTMI as well as the EFSA TWI.

Based on its previous risk assessment on cadmium in food, the CONTAM Panel reaffirmed its conclusion that adverse effects are unlikely to occur in an individual with such dietary exposure, but there is a need to reduce exposure to cadmium at the population level.

5. Uncertainty analysis

The assessment of uncertainty of this statement extends the earlier uncertainty analysis of the assessment of cadmium (EFSA, 2009a). Additional sources of uncertainty identified during the preparation of this statement and not expressed in the Opinion (EFSA, 2009a) are elaborated below and refer in particular to:

- mechanistic and modelling uncertainty;
- uncertainties related to the choice of the adjustment factor;
- updated assessment of the uncertainty of the HBGV proposed by EFSA.

5.1. Study and Data Selection

The CONTAM Opinion (EFSA, 2009a) did not address uncertainty in design of the human studies used in the meta-analysis. However, the CONTAM Panel noted that the summary data on B2M and urinary cadmium concentration mostly originate from cross-sectional studies. Such data may, according to criteria of evidence based medicine (Harbour et al, 2001), have similarly low level of evidence as those of ecological data; hence, the weakness of the study designs on which the summary

data are based, contributes to the uncertainty of the calculated RP. The weakness of this design therefore contributes to the uncertainty of the calculated RP values. This meta-analysis approach is different from standard practice in risk assessment when the most critical study out of a set of studies is identified and the individual dose-response data are used in a dose-response assessment. However, it was noted that the modified RP of 1 µg cadmium/g creatinine used by EFSA following a meta-analysis of all available data (not only GMs but also GSDs) within a Bayesian framework may be less affected by this type of uncertainty from study design. This conclusion is supported by individual studies reporting BMDLs as low as 1 µg cadmium/g creatinine in urine (see the supporting data reported in Section 8.5.1.2, EFSA, 2009a and in Suwazono et al., 2011).

Further uncertainty arises from the possibility that publication bias could have affected the systematic review. Uncertainty also arises from the use of parameters to describe log-normal distributions, when distributions are re-constructed from means and standard deviations or the observed range of the data, or when data were transformed because of obvious misreporting or erroneous measurement units in publications.

5.2. Biomarkers of kidney damage

The cross-sectional design of almost all published studies does not allow residual damage caused by past peak exposures to cadmium to be distinguished from effects resulting from much lower concurrent exposures. Moreover, owing to day-to-day variation in biomarkers of exposure, estimates of subjects' exposures that rely on single measurements would generally perform poorly in a regression analysis designed to examine effects resulting from chronic exposures (Symansky et al., 2001). Finally, intra-individual variability in early markers of renal damage recorded over three subsequent days typically ranges from 30 to 50 % (Mutti et al., 1992) and therefore it may be assumed to be even greater over longer observation periods.

Such uncertainties are particularly relevant to cadmium-induced changes in biomarkers of renal damage. Indeed, some of them, including B2M, are very sensitive to changes in renal function and are influenced *inter alia* by factors such as gender, age, body mass index, physical exercise, meat meals, and diurnal variation. The CONTAM Panel is aware that factors resulting in increased urinary excretion of serum proteins may also cause an increased urinary excretion of cadmium bound to those proteins, thereby interfering with exposure-effect relationships, and that – owing to the long half-life of cadmium – age is an important confounder, as most degenerative changes associated with aging, including a progressive reduction in renal function, are likely to be associated with cadmium accumulation. Nevertheless, a causal relationship between cadmium exposure and such degenerative changes cannot be ruled out and therefore an adjustment factor was identified, aimed at accounting for the several sources of uncertainty underlying the relationship observed in the meta-analysis:

- use of single point estimates for both urinary cadmium and B2M for each sub-group;
- use of parameters to describe log-normal distributions rather than individual data;
- extrapolating of GMs and GSDs from arithmetic means and standard deviations reported in some published studies.

5.3. BMD Modelling

The main uncertainty associated with the BMD modelling arises from the use of the hybrid approach with epidemiological data from cross-sectional studies with very wide intra-group dose ranges. Therefore, the CONTAM Panel used a specific mixed-effects model within a Bayesian framework. Factors potentially influencing the BMD calculation such as gender, ethnicity and age, have been controlled for in the analysis. No additional sources of uncertainty in the modelling assumptions than those already addressed in the Opinion (EFSA, 2009a) (e.g. lognormal population distribution, choice of one-compartment model, intra-individual variability not fully accounted for) were identified. Inter-individual variability within the dose groups was accounted for by applying an adjustment factor.

5.3.1. Hybrid BMD Model

In evaluating the hybrid model on the log-response scale any difference between the hybrid approach and other approaches may be related to the variance estimates (Sand et al., 2003). According to Sand et al. (2003) the hybrid BMD5 may be higher or lower than a BMD5 calculated using the individual continuous data, depending on the variance of the response at different dose levels. A non-constant variance can result in complications for the hybrid approach. For a fixed cut-off point (i.e. a certain fixed continuous response value) the BMD decreases with increasing variance whereas for a statistical cut-off, the BMD increases with increasing variance. Visual inspection of the data used in the meta-analysis suggests that the variance of the response is increasing with dose even after log-transformation. However, this could also result from inter-study and inter-dose group heterogeneity and it may not hold for the individual data, which were not available. Therefore, given the lack of individual data, the amount and direction of such uncertainty cannot be evaluated. The hybrid approach used by EFSA made the assumption that an excess risk of 5 % would give similar BMDLs as those that would be obtained with the same excess risk in an analysis of the original individual quantitative data, which were not available. Overall, the CONTAM Panel concluded that the use of the hybrid approach adds to uncertainty.

5.3.2. Missing individual dose information

Dose-response analysis using nonlinear models, with adjustment for covariates, is complex and the properties of such models are not completely understood when the dose levels are not fixed by design but are affected by measurement error. No easy-to-apply criteria exist which allow judgement as to whether ignoring errors in dose, e.g. due to the lack of individual data, would lead to over- or underestimation of the BMD or BMDL. One can assume that the effect of uncertainty in the dose values in this analysis was comparable to that occurring in linear regression and that as such it would tend towards overestimation. It is also likely that the BMDL values will be overestimated when using summary data (GMs and GSDs) and that the confidence bands around the dose-response model would be narrower than when fitting the model using individual data. As the CONTAM Panel did not have the individual data, it decided to account for this uncertainty and possible bias in the estimated BMDL values by using an adjustment factor, assuming a constant variance for inter-individual dose variability within each dose group, independent of the mean B2M and the mean urinary cadmium concentrations of the dose group. This assumption, necessary to perform the calculations in the approach chosen by the CONTAM Panel, adds to the uncertainty of the BMDL values.

5.3.3. Adjustment factor

The BMD approach used by the CONTAM Panel was implemented assuming no dose variations between individuals within each group. Then, in order to account for the existence of such variability, an adjustment factor of 3.9 was calculated based on within-group variability of urinary cadmium concentration. Some of the inter-individual variability may have been accounted for already in the BMD analysis, but it is not possible to determine to what extent.

5.4. Uncertainties in the comparison of the approaches taken by the CONTAM Panel and the JECFA

The CONTAM Panel noted that the approach taken by the JECFA also has intrinsic uncertainties. However, the JECFA did not explicitly address them in the monograph (FAO/WHO, 2011) or elsewhere, whereas the CONTAM Panel evaluates the inherent uncertainties in its assessment of exposure and the modelling for risk characterisation according to the guidance document on transparency in risk assessment issued by the EFSA Scientific Committee (EFSA, 2006, 2009d).

A comparison of the approach taken by the CONTAM Panel with that taken by the JECFA has been difficult because of the complexity of the methods used in both approaches.

The CONTAM Panel noted that their own approach involved complex statistical modelling of the concentration-effect data within a Bayesian framework, using a non-standard BMD model and a mixed-effects model to adjust for the type of data. The performance of the 2D Monte-Carlo simulation approach used by the JECFA was not explored by the JECFA and no detailed information was provided in the Monograph (FAO/WHO, 2011).

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

- The Joint FAO/WHO Expert Committee on Food Additives (JECFA) recently established a provisional tolerable monthly intake (PTMI) for cadmium of 25 µg/kg body weight (b.w.), which corresponds to a weekly intake of 5.8 µg/kg b.w. This value differs from the tolerable weekly intake (TWI) of 2.5 µg/kg b.w. established by the EFSA's Panel on Contaminants in the Food Chain (CONTAM Panel) in 2009.
- The assessments of the CONTAM Panel and the JECFA are based on a meta-analysis of the same dataset selected in a systematic review performed by European Food Safety Authority (EFSA) of epidemiological studies assessing the concentration-effect relationship between urinary cadmium concentration and beta-2-microglobulin (B2M) levels, an increase of which is a biomarker of renal tubular effects.
- The JECFA did not identify any additional studies to those included in the CONTAM Panel opinion.
- Both assessments have two primary components, a concentration-effect model that relates the urinary concentration of cadmium to that of B2M, and a toxicokinetic model that relates urinary cadmium concentration to dietary cadmium intake.
- The following methodological differences were identified between the two assessments:
 - the selection of the reference point for deriving the health based guidance value (HBGV);
 - the statistical approach to account for the variability and uncertainty of the marker of exposure (urinary cadmium concentration) and the marker of response (B2M) in the concentration-effect model;
 - the methodology for transforming urinary cadmium concentrations into dietary intake values.
- The CONTAM Panel used a hybrid benchmark dose approach to calculate a group based BMDL5 (the lower one-sided 95 %-confidence bound for an extra risk of 5 % of producing a specified change in the urinary level of the B2M) as a reference point (RP) using a Hill model within a Bayesian framework.
- The CONTAM Panel selected a statistical cut-off, and also a pre-specified biological cut-off of 300 µg B2M/g creatinine in urine in the hybrid approach because urinary B2M exceeding this value has been associated with an accelerated decline of age-progressive loss of renal function and reconfirmed 4 µg cadmium/g creatinine in urine as the RP.
- The JECFA used the break point of 5.24 (confidence interval: 4.94 - 5.57) µg urinary cadmium/g creatinine obtained from a piece-wise linear model fitted to the data as its RP.
- The CONTAM Panel reconfirmed the application of an adjustment factor of 3.9 to account for variability in the concentration-effect relationship data in the absence of individual data and reconfirmed a cadmium concentration of 1 µg cadmium/g creatinine in urine as the modified RP.

- The JECFA used a combined approach to account for toxicodynamic and toxicokinetic variability and uncertainty in a simultaneous two-dimensional (2D) Monte-Carlo simulation.
- The JECFA modelled toxicodynamic variability by introducing a log-triangular distribution function with a fixed range of variation by a factor between 1 and 3 below and above the RP (break point) for both increased and reduced individual susceptibility.
- Both the CONTAM Panel and the JECFA used a one-compartment toxicokinetic model to characterise the relationship between urinary cadmium concentration and dietary cadmium intake.
- While the CONTAM Panel used a deterministic approach, the JECFA introduced into its 2D Monte-Carlo simulation an additional variability function which together with the break point was used to account simultaneously for toxicodynamic and toxicokinetic variability and uncertainty.
- The CONTAM Panel noted that the applicability of 2D Monte-Carlo simulation approach used by the JECFA for its risk assessment of cadmium to address simultaneously variability and uncertainty of multiple components in hazard characterisation needs to be further explored.
- The CONTAM Panel noted that the choice of the toxicodynamic variability function has a major impact on the outcome (e.g. the HBGV) and that the differences in the other parameters involved have only a minor influence.
- Based on the current state of knowledge, the CONTAM Panel concluded that for cadmium the current TWI of 2.5 µg/kg b.w. established in 2009 should be maintained in order to ensure a high level of protection of consumers, including subgroups of the population such as children, vegetarians or people living in highly contaminated areas.
- Taking non-dietary exposure into account it is anticipated that the total exposure of some subgroups of the population could exceed the JECFA PTMI as well as the CONTAM TWI.
- The CONTAM Panel reaffirmed its previous conclusion that adverse effects are unlikely to occur in an individual with current dietary exposure, but there is a need to reduce exposure to cadmium at the population level.

RECOMMENDATIONS

- The use of probabilistic approaches to model variability and uncertainties in risk characterisation needs to be further developed.
- An internationally harmonised approach for the use of epidemiological data in dose-response assessment for the purposes of risk assessment is urgently required.
- Means to communicate non-standard statistical modelling techniques e.g. Bayesian methods or simulation methods need to be improved to allow risk assessors to judge the assumptions made and their limitations.

DOCUMENTATION PROVIDED TO EFSA

1. FAO/WHO (Food and Agriculture Organisation/World Health Organization), 2011. JECFA cadmium evaluation, draft toxicological monograph, as submitted by WHO, to be published as: Safety evaluation of certain contaminants in food. WHO Food Additives Series No. 64 (in preparation).

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ABBREVIATIONS

2D	two-dimensional
B2M	beta-2-microglobulin
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit; 95 %-confidence lower bound
BMR	benchmark response
BMDL5	benchmark dose 95 % lower (one-sided) confidence bound at the BMR=5 %
b.w.	body weight
C.I.	confidence interval, two sided at the confidence level of 95 %
CONTAM Panel	EFSA's Panel on Contaminants in the Food Chain
EFSA	European Food Safety Authority
GM	geometric means
GSD	geometric standard deviation
HBGV	health based guidance value
JECFA	Joint FAO/WHO Expert Committee on Food Additives
modified RP	reference point modified using an adjustment factor
PLM	piece-wise linear model
PTMI	provisional tolerable monthly intake
PTWI	provisional tolerable weekly intake
RP	reference point
TK	toxicokinetic
TWI	tolerable weekly intake