SCIENTIFIC OPINION

Statement on tolerable weekly intake for cadmium

EFSA Panel on Contaminants in the Food Chain (CONTAM)

European Food Safety Authority (EFSA), Parma, Italy

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.

1 On request from the European Commission, Question No EFSA-Q-2010-01008, adopted on 18 January 2011.
2 Panel members: Jan Alexander, Diane Benford, Alan Raymond Boobis, Sandra Ceccatelli, Jean-Pierre Cravedi, Alessandro Di Domenico, Daniel Doerge, Eugenia Dogliotti, Lutz Edler, Peter Farmer, Metka Filipič, Johanna Fink-Gremmels, Peter Fürst, Thierry Guérin, Helle Katrine Knutsen, Miroslav Machala, Antonio Mutti, Josef Rudolf Schlatter and Rolaf van Leeuwen. Correspondence: contam@efsa.europa.eu
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 Abrantes and Claudia Heppner for the support provided to this scientific opinion.

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.