Establishment of a health-based guidance value - Statement on the effects of lead on maternal health

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24. The DR modelling and establishment of an HBGV have been reviewed and summarised in the COT statement (2013). The COT discussed the three endpoints assessed by EFSA (cardiovascular, renal and neurodevelopmental effects) and concluded that the most relevant were neurodevelopmental effects. This is summarised in brief in the following paragraphs.

Benchmark Dose Modelling

25. A study by Lanphear *et al.* (2005) (paragraph 28), was used by both EFSA and JECFA for DR modelling of neurodevelopmental effects (EFSA, 2010; and FAO/WHO, 2011). The raw data generated in the Lanphear *et al*. (2005) study was obtained and modelled by EFSA for use in their benchmark calculations. JECFA based their analysis on the pooled data presented by Lanphear *et al*. (2005) for

their benchmark calculations. The DR modelling was previously described in a COT statement in 2013 relating to Pb in the infant diet and has been summarised in the following paragraphs (COT, 2013).

26. Budtz-Jørgensen (2010) was commissioned by EFSA to calculate a BMDL for the association of lead with the development of intellectual function, by modelling of the raw data by Lanphear *et al.* (2005). The benchmark calculations used regression models with full IQ score as the dependent variable, and adjustment for birth weight, Home Observation for Measurement of the Environment (HOME) score (The HOME Inventory is an index that reflects the quality and quantity of emotional and cognitive stimulation in the home environment (Lanphear *et al.*, 2005)), maternal education and maternal IQ, all of which were significantly associated with IQ in the dataset. BMD and BMDL values were calculated for a 1 % change in full scale IQ score (a decrease in IQ by 1 point), taking concurrent blood lead, maximum blood lead, average lifetime blood lead and early childhood blood lead as alternative exposure metrics. The dose-response models applied were logarithmic, linear, and a piecewise linear function with breakpoint at 100 µg/L.

27. For the assessment of risk, EFSA took as a point of departure, the BMDL01 value of 12 µg/L from the piecewise linear dose-response model for concurrent blood lead. Concurrent blood lead concentration exhibited the strongest relationship with IQ, and the piecewise linear model showed a better fit to the data than the linear model. The logarithmic model generally gave an even better fit than the piecewise linear model, but the differences were small, and EFSA preferred the latter because, taking into account the mathematical properties of the models, they considered that it provided “less uncertain estimates of the BMDL01”. Using the US Environmental Protection Agency’s (EPAs) **Integrated Exposure and Uptake Biokinetic** (IEUBK) model, the blood lead BMDL01 of 12 µg/L was estimated to correspond to a dietary lead exposure in infants and children of 0.5 µg lead/kg bw/day (EFSA, 2010).

28. JECFA (FAO/WHO, 2011) also used data from the Lanphear *et al.* (2005) analysis for DR modelling based on the authors' pooled analysis. Models were based on concurrent blood lead levels since they showed the highest correlation with IQ. Initially, six different models were considered – four with linear form and two sigmoidal. From these, a bilinear model (unlike the piecewise linear model used by EFSA, this did not constrain the inflexion in the dose-response relationship to be at a pre-specified blood lead concentration) was chosen to characterise the relationship of blood lead to IQ, since it provided a better fit than

four of the other models, and it was considered that it would give better estimates of effect than the one other model with similar fit, when non-dietary exposures to lead were unknown or highly variable. Using this model, the chronic dietary exposure of a 20 kg child corresponding to a decrease of 1 IQ point was estimated to be 0.6 µg/kg bw/day with a 90 % confidence interval of 0.2 - 7.2 µg/kg bw/day.

29. The differences between the EFSA and JECFA analyses are small and reflect inevitable uncertainties in the specification of the mathematical models. The COT (COT, 2013) noted that both were influenced by an apparently steep dose-response at low levels of lead exposure (blood lead levels less than 75 µg/L), which was based on few data from a single study in Rochester, USA, and may have rendered the BMDL values conservative. The COT had based its risk characterisation on the EFSA BMDL01, which is between the EFSA BMD01 and the lower 90 % confidence limit for the BMDL01 calculated by JECFA. The EFSA BMDL01 corresponds to a dietary exposure of 0.5 µg/kg bw/day (COT, 2013).

30. As the BMDL was for a small effect (a one-point difference in IQ), derived from a pooled analysis of multiple cohort studies of exposures in infants and children, and is likely to be conservative (paragraphs 26-27), EFSA therefore concluded that a margin of exposure (MOE) of 10 or greater should be sufficient to ensure that there was no appreciable risk of a clinically significant effect on IQ. At lower MOEs, but greater than 1.0, the risk is likely to be low, but not such that it could be dismissed as of no potential concern. (EFSA, 2010)

31. In relation to women of childbearing age, the COT agreed that the BMDL01 and corresponding dietary exposure of 0.5 µg/kg bw per day should be used in the current risk assessment for risk characterisation purposes.