COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

First draft updated statement on the tolerable daily intake for perfluorooctanoic acid

Questions on which the views of the Committee are sought

1. Members are invited to consider the structure and content of the draft update statement.

Secretariat
June 2009

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Note: This is a draft statement for discussion. It does not reflect the final views of the Committee and should not be cited.

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Introduction

1. The Food Standards Agency commissioned an analysis of perfluorooctane sulfonate (PFOS) and other structurally similar perfluorochemicals, such as perfluorooctanoic acid (PFOA), in the 2004 Total Diet Study and, in 2005, the Committee assessed the toxicity of PFOA and PFOS and the results of the study.

2. Subsequently, a COT statement on PFOA was published in which the Committee derived a tolerable daily intake (TDI) of 3 µg/mg/kg body weight (bw) (COT, 2006b).

3. PFOA can occur as a contaminant in both raw and drinking water and, in 2006, prior to publication of the COT statement, the Health Protection Agency (HPA) provided toxicological advice on PFOA at the request of the Drinking Water Inspectorate (DWI). In 2007, following the COT consideration, the HPA gave further advice and proposed a "maximum acceptable" concentration in drinking-water of 10 µg/L, which was adopted by the DWI as a non-statutory limit in drinking water.

4. In 2008, the European Food Safety Authority (EFSA) derived a TDI for PFOA of 1.5 µg/mg/kg bw/day (EFSA, 2008).

5. Subsequently, the Office of Water of the US Environmental Protection Agency (US EPA) has recently developed a Provisional Health Advisory Value[1] for PFOA of 0.4 µg/L, which is lower than the proposed UK "maximum acceptable" concentration in water (US EPA, 2009). The US EPA recommendation used uncertainty factors in the derivation of the TDI which were derived from toxicokinetic data, rather than the default values previously used by the other committees.

6. DWI has now asked the HPA whether the "maximum acceptable" concentrations of PFOA in drinking-water should be lowered in light of the USEPA advice and hence the COT was invited to re-evaluate the TDI recommended in 2006.

7. As part of this review, the COT also reviewed the previous TDI for PFOS and confirmed its previous advice (COT, 2006a).

[1] Provisional health advisory values are developed to provide information in response to an urgent or rapidly developing situation. They reflect reasonable, health-based concentrations above which action should be taken to reduce exposure to unregulated contaminants in water.

2006 COT evaluation

8. For PFOA, the COT modelled the data from a number of studies, including absolute and relative liver weights in a 13-week study in male ChR-CD rats (Perkins et al., 2004), hepatocytic megalocytosis in a 104 week dietary study in rats (Biegel et al., 2001), and absolute liver weight in a two-generation rat study (Butenhoff et al., 2004a). The COT also assessed a developmental toxicity study by Lau who administered PFOA to mice by oral gavage. Following a request of the Committee, the authors modelled the data to derive a $BMDL_{10}$ (lower 95% confidence limit of the benchmark dose for a 10% response) of 0.46 mg/kg bw/day for maternal liver weight at term, which was considered to be the most sensitive endpoint (COT, 2006b; Lau et al., 2006).

9. From the above studies, the Committee identified a dose of 0.3 mg/kg bw/day as a suitable point of departure based on a number of the most sensitive endpoints in mice and rats. In deriving the TDI, the default uncertainty factor of 100 (for inter- and intra-species differences) was considered to be appropriate (COT, 2006b).

10. The COT stated that "due to the long half-life of PFOA in humans, the risk assessment for PFOA could be based on a comparison of the internal dose of PFOA from animals, for a specific endpoint, with the internal dose in humans…. However, the toxicokinetics of PFOA in rodents and humans are not yet fully understood…. Therefore, the use of internal doses for the risk assessment was not considered appropriate on the basis of available data" (COT, 2006b).

11. Overall, in 2006 the Committee recommended that a TDI of 3 μg/kg bw/day should be established, based on a range of effects on liver, kidney haematological and immune systems. It was considered that the TDI was adequate to protect against other potential effects such as cancer.

Derivation of health based guidance values by EFSA and US EPA

12. The CONTAM panel of EFSA reported the $BMDL_{10}$ values of between 0.3 and 0.7 mg/kg bw/day, which were also cited in the COT statement, based on liver effects in mice and rats. EFSA noted that although PFOA is a peroxisome proliferator, not all of the liver or developmental effects could be attributed to this activity. The lowest $BMDL_{10}$ was selected as the most appropriate point of departure for deriving the TDI. The panel applied an uncertainty factor of 100 for inter- and intra-species differences and an additional uncertainty factor of 2 to compensate for uncertainties relating to the internal dose kinetics, hence an overall uncertainty factor of 200 was used, resulting in the TDI of 1.5 μg/mg/kg bw/day (EFSA, 2008).

13. The US EPA based its derivation of the Provisional Health Advisory Values on the developmental toxicity study carried out in mice (Lau et al., 2006). The $BMDL_{10}$ of 0.46 mg/kg bw/day for increased maternal liver weight at term was selected as the point of departure (US EPA, 2009).

14. In order to better approximate internal doses for PFOA, the US EPA developed data-derived extrapolation factors for toxicokinetics. They were deemed important due to the marked differences in retention time among humans and the test species in the critical study. The US EPA concluded that measures of internal exposure

should be used as the basis for interspecies extrapolation, although there were limited area under the curve or clearance data (US EPA, 2009).

15. A one-compartmental model was used to convert half-life data to clearance data, assuming steady state has been reached, using the equation:

Half life = (ln 2) x vol. of distribution / clearance

16. A volume of distribution of 198 ml/kg for PFOA was estimated from a study in female monkeys (Butenhoff et al., 2004b). This study was assessed by the COT in its 2006 statement (COT, 2006b). The US EPA deemed it appropriate to use the same volume of distribution of 198 ml/kg bw for mice and humans (US EPA, 2009). Olsen had cited a number of studies that stated that PFOA is highly bound to plasma proteins in rats, monkeys and humans, and that PFOA showed primarily an extracellular distribution volume (Olsen et al., 2007).

17. The internal dose of PFOA was approximated by using clearance data from mice and humans. The limited data available indicated that the half life of PFOA in mice and humans is 17 days and 3.8 years (1387 days), respectively.

18. Half lives of 17 and 1387 days converted to a clearance of 8.07 ml/kg/day and 0.10 ml/kg/day for mice and humans, respectively, using the volume of distribution of 198 ml/kg bw calculated from female monkeys. The toxicokinetic portion of the interspecies difference was calculated to be 81, (the ratio between mouse and human clearance). Overall, the total uncertainty factor used by USEPA in deriving its Provisional Health Advisory Value was 2430 based on 3 for toxicodynamics, 81 for toxicokinetics and 10 for intraspecies extrapolation (US EPA, 2009). However, the advisory value was not overtly expressed as a TDI or reference dose.

Discussion

19. The difference in the assessments was not in the toxicological endpoints used to derive the TDIs, but in the uncertainty factors used and their derivation.

20. The critical difference between the three assessments was the uncertainty factor used for interspecies toxicokinetics. The US EPA used 81 compared with an uncertainty factor of 4 or 8 used by COT or EFSA, respectively. The uncertainty factor used by the US EPA represented the ratio between mouse and human clearance of PFOA, based on the volume of distribution in monkeys, with the assumption that other species have the same volume of distribution because PFOA is tightly bound to plasma proteins and shows primarily extracellular distribution. However, we regard the US EPA approach as unsatisfactory because it makes too many assumptions which cannot be supported robustly by the available data.

Conclusion

21. Although an interspecies uncertainty factor of 4 was included in the COT's previous evaluation of PFOA, we conclude that an additional factor is appropriate to account for interspecies toxicokinetic differences in view of the large difference in half life and clearance of PFOA in humans and mice. We therefore recommend that an additional interspecies uncertainty factor of 2 should be used and a TDI of 1.5 µg/kg bw adopted. This should remain provisional and be reviewed as new information

becomes available. We consider that, on the basis of available information, this provisional TDI is adequate to protect against the range of identified effects.

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