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Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

Paper for information

COT response to the EFSA Consultation on a draft scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs

Secretariat
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General

COT members considered the draft opinion to be an impressive document, and generally agreed with the conclusions. Discussion focussed on changes that would improve the clarity of the opinion, and the rationale for some of the decisions that had been made in its drafting.

It is unclear if this part of the draft opinion will ultimately be merged with the exposure part. If not, it would be important to include a diagram of the chemical structure of bisphenol A also in this part.

As indicated on page 533, the abbreviation DAF has been used twice with different meanings, which needs to be resolved.

Section 2. Methodology applied for performing the risk assessment for bisphenol A

In general, the COT supported the weight-of-evidence approach that had been adopted. Six categories of “likeliness” had been used to classify possible hazards. Hazards classed as “likely” or “very likely” had been taken forward to the hazard characterisation stage. However, the classification system used was a little unusual, and it was unclear how a hazard would be classified if there was no evidence. Where evidence was inadequate, it might be misleading to classify a hazard as being as “as likely as not”. It was unclear why a classification approach such as that employed by the International Agency on Research on Cancer had not been used, which would have included a category for “inadequate evidence”. The opinion should emphasise more strongly that the classification related solely to hazard identification and not to risk assessment, since there was a danger of misinterpretation.

Section 3. Hazard identification and characterisation

General comment relating to human studies:
The conclusions regarding epidemiological data were appropriate, but the text describing the data was not always consistent with the conclusions. Furthermore in evaluating data from multiple epidemiological studies, the EFSA assessment appeared to have given much greater weight to results

from prospective cohort studies than to those from case-control studies, and it was unclear if the coherence of results between studies had been taken into account. A high quality case-control study could provide more useful data than a low quality cohort study, particularly if the exposure assessment in the case-control study was not based on recollection. Furthermore, the text implied that useful information could not be obtained from cross-sectional studies, which was incorrect. The text needed to be more specific about why greater weight had not been given to data from cross-sectional studies.

It was presumed that where the text referred to “no associations” in epidemiological studies it meant “no significant associations”. It would be helpful to provide confidence intervals when summarising the results of epidemiological studies to give an indication of whether the absence of significance could have been because the study was inadequately powered.

The EFSA opinion noted that the analysis of bisphenol A in serum samples in some of the epidemiological studies may have been unreliable due to contamination by leaching from plastic equipment in which they were collected and stored. However, it was not clear whether or how this had been taken into account. The argument about the reliability or otherwise of studies because of contamination of serum samples needed to be made clearer.

Section 3.1 Toxicokinetics and metabolism

The COT endorsed EFSA’s use of the human equivalent dose (HED) approach to extrapolate from experimental animals to humans, adjusting for the differences in toxicokinetics. A possible criticism was that the plasma Area Under the Curve (AUC) in humans had been estimated using a model, which had some uncertainties. However, the Committee considered that the approach to developing the model had been thorough, and they had no concerns about it. Plasma AUC was considered to be the most relevant dose metric, and preferable to administered dose or maximum blood level. An issue not addressed in detail was whether the lipophilicity of bisphenol A would alter the kinetics of the compound following chronic exposure, specifically with regard to the level of bisphenol A in tissues such as the brain. Using a physiologically-based pharmacokinetic (PBPK) model, the exposure of any tissue could be considered, but it was not clear if this had been done.

It was observed that there was no information in the draft opinion on the chemistry of bisphenol A, which was pertinent to the PBPK modelling. Whilst such information had been included in the previously published part of the

draft opinion on exposure, it would be important for the two parts of the opinion to be integrated.

A figure showing the chemical structures of key metabolites would be helpful.

Section 3.2 General toxicity

COT agreed that liver and kidney effects were “likely”. However, it was noted that hypertrophy is likely to be an adaptive response rather than “toxicity”.

Section 3.3 Reproductive and developmental effects

It would be helpful to more fully explore the reasons for conflicting results in studies of reproductive effects, both for animal studies and epidemiological studies.

COT broadly supported the conclusion that effects on fetal growth and thyroid function were “not likely”, but there could have been more attempt to understand the discrepancies between studies.

Section 3.4 Neurological, neurodevelopmental and neuroendocrine effects

COT agreed that neurological and neuroendocrine effects were “not likely”.

Section 3.5 Immune effects

COT agreed with the conclusion that immunological effects were “not likely”. The text of the opinion stated that, based on recent studies, there were indications that bisphenol A exposure may be linked to immunological outcomes in humans. However, the COT considered that the evidence for this was inconsistent.

Section 3.6 Cardiovascular effects

It was observed that different epidemiological studies had assessed different cardiovascular outcomes. The Committee agreed with the overall conclusion that cardiovascular effects were “not likely”. However, the description of the epidemiological studies was unclear. The draft EFSA opinion suggested that an association in one prospective study might be due to confounding by diet.

It was unclear what was meant by this, and the opinion should explain which specific aspect(s) of diet might have accounted for the association.

Section 3.7 Metabolic effects

COT agreed that metabolic effects were “not likely”. However, the criticism of cross-sectional studies was considered excessive. In addition, the wording that there was “no convincing evidence” of an obesogenic effect implied that the possibility of a hazard would be dismissed unless the evidence was overwhelming, which was not consistent with the weight of evidence approach that was being taken. Associations should not be dismissed simply because there could be confounding by other chemicals. There needed to be co-exposure to other specific chemicals that could reasonably be expected to cause the effect.

Section 3.8 Genotoxicity

COT agreed that genotoxicity was “not likely”. Since bisphenol A had produced negative results in tests for mutagenicity, it would be more appropriate for the text to state that “bisphenol A has been shown not to be mutagenic” rather than “bisphenol A has not been shown to be mutagenic”.

Section 3.9 Carcinogenicity

COT agreed that carcinogenicity was “not likely” and that the effects on mammary gland proliferation or differentiation were “likely”. COT considered that the implications of such effects were unclear, since they might result in tumour promotion but not necessarily be sufficient to lead to carcinogenicity.

Section 4. Health-based guidance value

COT considered the proposed temporary tolerable daily intake was appropriate. The difficulty with benchmark dose (BMD) modelling of the mammary gland hyperplasia was noted. The study had not been designed for dose-response modelling and the wide range of BMDs and BMDLs generated by different models demonstrated that the data were not suitable for such modelling. It would be useful to make clear in the text that there was a wide range in the modelled BMDs as well as in the BMDLs.

It was queried why the data for left kidneys and right kidneys had been modelled separately, rather than together using hierarchical methods to account for similarities between two kidneys from the same animal. If that

were possible, it might have resulted in tighter confidence limits around the BMD10 and thus a slightly higher BMDL10.

A total uncertainty factor of 25 had been used. COT agreed that adjustment of the critical BMDL10 in mice to a human equivalent dose addressed toxicokinetic variation between mice and humans, and therefore the inter-species factor of 1 for toxicokinetics was appropriate. The factor of 25 comprised a factor of 2.5 for remaining interspecies variation, the component of the default 10-fold uncertainty factor which is assumed to allow for toxicodynamic differences, together with a full 10-fold uncertainty factor for inter-individual variation in the human population. There needed to be discussion of the adequacy of the remaining sub-factors when one of more of the sub-factors was removed from the total default uncertainty factor of 100.

It was agreed that the approach to modelling dermal absorption was conservative. It was noted that absorption through the fingers may be lower due to a thicker stratum corneum.

Section 8. Recommendations

COT agreed that further good-quality research addressing possible non-monotonic dose-response relationships for bisphenol A would be helpful. Further work on dermal absorption, and the metabolism of bisphenol A following dermal absorption, would also be useful. One of the recommendations in the draft EFSA opinion was for further investigation of the toxicokinetics of bisphenol A in mice. The COT considered that this should be extended to include also further investigation of the toxicokinetics of bisphenol A in humans. PBPK models could be developed to explore the time-course of bisphenol A concentrations in tissues.