TOX/MIN/2011/05

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

Minutes of the meeting held on Tuesday, 1st November 2011 in Aviation House, London.

Present

Chairman:	Professor D Coggon		
Members:	Mr D Bodey		
	Professor A Boobis		
	Dr R Brimblecombe		
	Professor J Cade		
	Dr R Dearman		
	Dr J Foster		
	Dr M Graham		
	Dr A Hansell		
	Professor D Harrison		
	Professor B Lake		
	Professor I Morris		
	Dr N Plant		
	Mr R Smith		
	Dr J Thompson		
Food Standards Agency (FSA) Secretariat:	Dr D Benford	Scientific Secretary	
	Mrs J Shroff	Administrative Secretary	
	Dr C Baskaran		
	Dr E Cemeli		
	Mr T Chandler		
	Mr J Elliot		
	Dr D Gott		
	Ms F Hill		
	Mr B Maycock		
	Ms C Mulholland		
	Dr D Parker		
	Dr J Shavila		
Health Protection Agency (HPA) Secretariat:	Mr J Battershill	Scientific Secretary	
	Dr L Hetherington		
Invited Experts:	Dr D Lovell	St Georges, University of London	Item 6
Assessors:	Dr P Holley	Department of Health	Item 5
	Mr S Fletcher	Veterinary Medicines Directorate	Items 4 & 5

External Observer:	Mrs C McAlinden	(Future) Advisory Committee on Animal Feedingstuffs (ACAF) member	Item 4
Officials:	Ms S Cossom	Food Standards Agency – ACAF Secretariat	Item 4
	Ms M Jumnoodoo	Food Standards Agency – ACAF Secretariat	Item 4
	Dr Clifton Gay	Food Standards Agency - Statistics	Item 6
	Dr P Edwards	HPA	
	Dr Tim Gant	HPA	
	Mr J Graves	Department of Health	Item 5
	Ms H McGarry	Health & Safety Executive (HSE)	Item 5

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Announcements

1. The Chairman, Professor Coggon, welcomed Members to the meeting. He also welcomed Dr Tim Gant (newly appointed Head of the Toxicology department at HPA), Mrs Christine McAlinden (who would shortly become a member of the Advisory Committee on Animal Feed (ACAF)), Dr David Lovell (Reader in Medical Statistics at St. George's, University of London), Ms Helen McGarry (HSE) and new member of the FSA Secretariat, Dr Eduardo Cemeli.

2. The Chairman reminded those attending the meeting to declare any commercial or other interests that they might have in any of the agenda items.

Item 1: Apologies for absence

3. Apologies for absence were received from Professors Konje and Houston.

Item 2: Draft minutes of the meeting held on Tuesday, 13th Sep 2011 – TOX/MIN/2011/04

4. The minutes of the 13th Sep 2011 meeting were agreed subject to the following amendments (in italics):

- Para 14 -18 and 21: ~~MoA~~ replaced by *MOA*

- Para 19: ~~One difficulty encountered with DBP was~~ *It was noted* that although ~~many consider it~~ *DBP is* an endocrine agonist, it ~~was observed to~~ *also* cause*s* other gene changes *in rodents*. Knowledge of the internal dose at the target site was important, but not necessarily straightforward to generate. *The internal dose could then be extrapolated to* ~~A~~ *a*n external dose ~~could be calculated~~ for use in risk assessment, for example using physiologically-based pharmacokinetic modelling.

- Para 22: ~~It was noted that microRNAs could have huge redundancy in pathways such that multiple pathways needed to be affected before functional effects would arise.~~

- Para 26: In some cases the original papers ~~of~~ *from* studies would be checked to clarify the way in which they were described.

- Para 34: Chemical contaminants had been measured in composite samples so that they were ~~evenly distributed~~ *representative.*

- Para 36: It was noted that *contaminating* herbicides had been considered *only* in the context of possible damage to crops. Similarly plant alkaloids were assessed *only* in the context of possible harm to livestock.

- Para 39: The allergens present were expected to be high molecular weight proteins. ~~No~~ *Very little* evidence was available on whether proteins could be taken up by plants, but ~~this seemed unlikely~~ *based on their physico-chemical properties, it was unlikely that proteins would be taken up by passive processes*. Exposure of operators to allergens through direct contact was more likely to pose a risk. It was noted that COMEAP (Committee on the Medical Effects of Air Pollutants) were ~~interested in the formation of~~ *planning to assess* bio-aerosols *formed* from compost.

Item 3: Matters arising

5. *Matters arising from the meeting of 28th June*

- Para 7: The COT response to the quinquennial review had been published on the COT website. It would be discussed by the General Advisory Committee on Science (GACS) on 9 November 2011.

- Para 10: The peer-review comments on 'Assessment of the COT uncertainty framework from a social science perspective' had been forwarded to Members. There were no further comments.

- Para 11: The proposed secure website for COT papers had been set up and Members had been provided with login details.

6. Item 4: *Use of toxicogenomics data in risk assessment*

Para 23: The Chairman thanked a Member who had provided advice on the proposed COT discussion paper. It was anticipated that the paper would be ready for discussion at the February 2012 meeting of COT.

7. Item 5: *Draft statement on a systematic review of the epidemiological literature on para-occupational exposure to pesticides and health outcomes other than cancer*

Para 26: The COT statement and lay summary had been published on the COT website.

8. Item 6: *Draft statement on the FSA-funded T05 research programme on phytoestrogens*

Para 29: It was anticipated that the revised draft statement would be ready for discussion at the December 2011 meeting of COT.

9. Item 7: *WRAP risk assessment on anaerobic digestates*

The agreed final version of the COT minutes would be forwarded to the authors of the report.

Item 4: Draft statement on FSA–funded research and other progress on mixtures of pesticides and similar substances – TOX/2011/28

10. Professor Boobis declared a personal specific interest as he had been a contractor for two of the research projects under consideration, T10004 and T10020.

11. The Committee agreed with the overall structure of the statement. A number of changes were requested to the text and some clarifications sought. A Member would consider the wording of two paragraphs in further detail after the meeting. One of the items in Table 2 would be updated and the table formatting amended.

12. The Committee agreed to split the current "Conclusions" section into "Conclusions" and "Research recommendations". The "Conclusions" would include: the support of the research project results for the default assumption of dose addition for combined exposure to chemicals with the same modes of action; the conclusions the Committee had drawn on the biomarkers research; and conclusions on the study of the effects of processing commodities on pesticide exposure. The "Research recommendations" section would include the development of parameters in vitro for incorporation into physiologically-based pharmacokinetic (PBPK) models and focusing of further development of biomarkers on the particular LC-MS assays of urinary metabolites that the Committee had identified as most promising.

13. A revised draft statement would be circulated to Members by email for their further consideration and comments. The statement would then be agreed by Chairman's action unless substantial changes were required.

Item 5: Restriction report: proposal for a restriction: bis(2-ethylhexyl)phthalate (DEHP), benzyl butyl phthalate (BBP), dibutyl phthalate (DBP) and diisobutyl phthalate (DiBP) – TOX/2011/29

14. Dr Dearman declared a personal specific interest arising from industry-funded research on phthalates, and did not participate in the discussions.

15. The Danish Environmental Protection Agency (EPA) had submitted a restriction report to the European Chemicals Agency (ECHA) in support of their proposals to restrict further the use of phthalates in Europe. The Health and Safety Executive (HSE) had requested advice from COT on the scientific basis for restricting the placing on the market of articles, intended for use indoors in unsealed applications and articles that may come into contact with skin or mucous membranes, containing one or more of the 4 phthalates (DEHP, BBP, DBP and DiBP) at a concentration greater than 0.1% by weight of any plasticised material.

16. Members had been provided with the following papers related to this item:

- TOX/2011/27 - *Update on regulatory and biomonitoring activities with regard to phthalate esters* - provided as an information paper at the September 13th COT meeting.

- TOX/2011/29, which included relevant sections of the Danish restriction report, the 2011 COT statement on dietary exposure to phthalates, and two published papers on the reproductive effects of DEHP and DiBP in rats.

- An addendum to TOX/2011/29, summarising estimates of dermal absorption of DBP, DEHP and BBP.

- Four published papers describing biomonitoring studies.

- Advance comments from two Members.

17. The COT had previously considered a report by the Danish EPA entitled 'Survey and Health Assessment of the exposure of 2-year-olds to chemical substances in Consumer Products' at its February 2010 meeting. The Committee had not thought that the information presented at that meeting (summary and conclusion of the report) raised concerns which required urgent action. The COT had subsequently published a statement in May 2011 on dietary exposure to phthalates, based on data from an FSA total diet study (TDS). At that time, the COT had concluded that the TDIs set for a number of phthalates by the European Food Safety Authority (EFSA) in 2005 could be used in assessing possible risks from dietary exposures to phthalates.

18. Members agreed with the reference doses for DEHP, DIBP and BBP established in the Restriction Report. In respect of DBP, there was agreement that the dose of 2 mg/kg bw/day in the study by Lee *et al.* (2004) should be the point of departure for establishing a reference dose. However, it was noted that in this study the effects on mammary glands in male rats, which were observed at this dose, would most likely reflect androgenic activity, whereas DBP was anti-androgenic. Moreover, the testicular effects, which were observed at the same dose, were reversible with continued dosing and lacked clear dose-dependence. Also, this apparent lowest observed adverse effect level (LOAEL) was much lower than the no observed adverse effect levels (NOAELs) observed in other developmental studies of the compound in which reproductive outcomes were investigated. Taking these reservations into account, members considered that the assessment factor of 300 applied in the Restriction Report was unduly conservative, and that the TDI for DBP of 0.01 mg/kg bw/day, which was established by the EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC), was a more appropriate reference dose for DBP than the derived no effect level (DNEL) proposed in the Restriction Report.

19. Although the reference doses for the four compounds were derived from studies of developmental toxicity, it was agreed that it was reasonable to apply them to all population groups, including infants and children. However, it was noted that whereas during pregnancy adverse effects might conceivably arise from over-exposure on a single day, in other circumstances it was the average exposure over at least several days that would be relevant. Thus, when deriving risk characterisation ratios (RCRs) for population groups other than women of child-bearing age, estimates should be made of potential average exposures over several days, and not of the highest exposures that might occur on a single day.

20. The Committee agreed with the values for gastro-intestinal absorption that were used in the Restriction Report. However, empirical evidence indicated that the default values assumed for dermal absorption of DBP and DEHP were likely to be overestimates.

21. As acknowledged by the authors of the Restriction Report, there was much uncertainty regarding their exposure estimates. Members recognised that the estimates did not take account of all possible sources of exposure. Nevertheless, they considered them to be highly conservative. This was because: a) they assumed that on a single day an individual would be highly exposed to each compound from each of the sources considered, which was unrealistic; and b) they focused on the highest exposures which might occur in a single day, whereas as argued above, in population groups other than women of reproductive age, exposures over a longer period would be more relevant. Furthermore, the recently completed TDS undertaken by the FSA indicated that in the UK, dietary intakes of the four phthalates under consideration were substantially lower than those assumed in the Restriction Report.

22. Members agreed that the biomonitoring studies to which the Restriction Report referred were adequately conducted, but noted that the calculated intakes reflected historical exposures prior to the introduction of EU wide regulatory controls on the use of phthalates. Also, the risk assessment again focused on the highest exposures which might occur in a single day, and made the assumption that an individual would be simultaneously exposed to high levels of all four compounds.

23. Members agreed that a dose addition approach to risk characterisation was appropriate.

24. Bearing in mind the sources of conservatism outlined above, Members viewed the RCRs derived in the Restriction Report as a first tier risk assessment. They were not so high that they necessarily required risk reduction measures, beyond those which were already in place. However, they did indicate a need for more refined risk assessment, and if necessary, more thorough consideration of the possible risks from use of alternative products, including estimation of potential exposures.

25. To refine the characterisation of risk, the Committee suggested that it would be most useful to collect new biomonitoring data reflecting current exposures in representative populations. Such studies should look at: a) the distributions of estimated exposures in a single day; b) the variation of exposures in individuals from day to day; and c) the inter-relationship of individual exposures to different phthalates. As a secondary objective they might also collect information about participants' activities as a means of exploring the major determinants of high exposure.

26. The main points from this discussion would be submitted in a summary statement to HSE and to ECHA via their website to meet the deadline of the 16th December 2011.

Item 6: EFSA opinion on Statistical Significance and Biological Relevance – TOX/2011/30

27. The EFSA Scientific Committee had published a scientific opinion on concepts related to statistical significance and biological relevance. Dr David Lovell, a member of the EFSA Scientific Committee, and Chair of the working group that drafted this scientific opinion had been invited to give a presentation to COT on his (personal) perspectives on the opinion and the relevance for committees conducting risk assessments.

28. Dr Lovell informed Members that the EFSA opinion had been developed to assist the EFSA Scientific Panels and Committee in assessment of biologically relevant effects. Assessment of the relevance of scientific studies to the work of EFSA was based upon critical assessment of the evidence they provided. Statistical analysis of the data was central to this assessment. However, confusion in the use of words such as “significance”, “relevance” and “importance” could hinder the assessment. The EFSA opinion had also addressed a number of statistical considerations, including null hypotheses versus equivalence testing, multiple testing, and significance testing versus use of confidence intervals.

29. Following the presentation, Members were invited to discuss the conclusions and recommendations of the opinion, and their relevance to evaluations conducted by the COT.

30. The Committee appreciated Dr Lovell’s presentation as it provided useful context to the EFSA opinion. Members noted that the opinion focussed on frequentist statistical techniques rather than Bayesian approaches, and aimed to guide those submitting and evaluating data. The utility of retrospective power calculations was questioned by the Committee, particularly when confidence intervals were available for consideration. It was noted that statistical power tests for epidemiological studies did not always take into account misclassification of variables. Members noted the importance of being clear about the number of tests that are done during multiple comparisons, and any methods used to adjust data. Members agreed that statistical planning and appropriate model selection were important considerations when designing new studies, as they would have an impact on the outcome. However, this was often not possible for completed studies that had been submitted for evaluation. It was noted that EFSA intended to carry out statistical reanalysis of some of the data submitted in dossiers.

31. Previously, biological relevance of data had not been discussed sufficiently in EFSA’s assessments. Failure to consider a lack of *a priori* evidence for many end points in toxicity testing had resulted in the significance of tests being misinterpreted. Difficulties were noted in defining the magnitudes of effects that were biologically relevant, particularly as some changes could be within natural variation. Confidence limits could have important implications for regulatory decisions at a population level. When estimating relative risks, wide confidence intervals should not necessarily be viewed as indicating a lack of information if the point estimation was high. Members agreed that less emphasis should be placed upon the reporting of statistical significance and more on estimation with confidence intervals.

32. The Committee agreed with the conclusions and recommendations of EFSA's opinion on statistical significance and biological relevance. The Chairman thanked Dr Lovell for assisting the Committee.

Item 7: FSA Scientific Advisory Committees (SACs) Update – TOX/2011/31

33. Members were provided with a paper outlining the headline topics that other Committees were discussing, and were advised that it would be possible to obtain details on any of the topics if required.

Item 8: Any other business

34. The Secretariat and Members did not have any other business to raise.

Item 11: Date of next meeting

35. The next meeting was scheduled to take place on Tuesday 13th December 2011 in Conference Rooms 4 & 5, Aviation House, 125 Kingsway, London WC2B 6NH*.

* The 13th December meeting was subsequently cancelled. Next meeting is 7th February 2012