TOX/MIN/2014/04

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

Minutes of the meeting held on Tuesday, 2nd September in Aviation House, London.

Present

Chairman:	Professor D Coggon		
Members:	Mr D Bodey		
	Dr R Brimblecombe		
	Prof J Cade		
	Dr M Graham		
	Dr C Harris		
	Prof D Harrison		
	Prof R Harrison		
	Prof B Lake		
	Prof I Morris		
	Prof R Smith		
Food Standards Agency (FSA) Secretariat:	Dr D Benford	Scientific Secretary	
	Ms H Gbormittah	Administrative Secretary	
	Ms R Acheampong		
	Ms L Buckley		
	Dr D Hedley		
	Ms F Hill		
	Ms L Kent		
	Dr M Kurzawa-Zegota		
	Mr B Maycock		
	Ms C Mulholland		
	Mr A Sbaiti		
	Dr J Shavila		
Public Health England (PHE) Secretariat:	Ms F Pollitt	Scientific Secretary	
Officials:	Professor Guy Poppy	FSA Chief Scientist Adviser	Items 8-12
	Dr Penny Bramwell	FSA Director of Science, Evidence and Research	Items 8-12
	Dr J McElhiney	FSA Scotland	Item 7
	Mr Robin Clifford	FSA - Statistical Team	Item 7
	Dr Christina Baskaran	FSA – Agricultural, Process and Environmental Contaminants Team	Item 4
	Mr Richard Burden	FSA – Agricultural, Process and	Item 4

		Environmental Contaminants Team	
	Mr Charles Hickson	FSA Summer Student - Scientific Methods and Laboratory Policy Branch	
	Ms Alette Addison	Department of Health (DH)	
	Mr Stephan Knight	DH	
Assessors:	Prof Tim Gant	Public Health England (PHE)	
	Ms Michaela Benton	Health and Safety Executive (HSE)	
External Observers:	Rebecca-Lea Korinek	Research Fellow Social Science Centre, Berlin	Items 1-6
	Prof Erik Millstone	University of Sussex, Science Policy Research Unit	Items 1-6

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Announcements

1. The Chairman, Professor Coggon, welcomed Members and assessors to the meeting.

2. The FSA Scientific Secretary updated members on changes in the organisational structure of the FSA. Professor Guy Poppy of the University of Southampton had been appointed as external Chief Scientific Advisor, working for FSA three days per week. He would provide advice to the FSA Chief Executive and challenge to the FSA's use of science and evidence. In addition, Dr Penny Bramwell, had been appointed as Director of Science, Evidence and Research, and Deputy Chief Scientific Advisor. She was head of a new division of Science and Evidence, which included the FSA COT secretariat. Professor Poppy and Dr Bramwell were expected to attend the COT meeting during the afternoon.

3. 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

4. Apologies had been received from Dr Rene Crevel, Dr Anna Hansell, Prof Brian Houston, Prof John Thompson, Dr Nick Plant and Prof Faith Williams. Four members had submitted written comments. Apologies had also been received from an assessor, Sam Fletcher (Veterinary Medicines Directorate).

Item 2: Draft minutes of the meeting held on 13th May, 2014: TOX/MIN/2014/03

5. The minutes were agreed subject to minor editorial amendments.

Item 3: Matters arising

Item 3: Matters arising from previous meetings

6. The Secretariat updated Members on discussions at the Scientific Advisory Committee on Nutrition (SACN) Subgroup on Maternal and Child Nutrition (SMCN) of the COT statements on toxicity of chemicals in the infant diet. SMCN were planning that a complete report, incorporating the COT statements, would be issued for consultation at some time in 2015, but the exact timing was still to be decided. A further step would then be to consider dietary advice for children aged 1-5 years. SMCN were due to discuss their approach to these matters at their meeting on 10 September. SMCN had asked whether the COT statements could include definitive conclusions on the safety of breast milk. Members agreed that conclusions should be

definitive where scientific evidence was convincing, but that where evidence was weaker or less consistent, statements should make clear the nature and extent of uncertainties.

7. The Chair informed Members about recent correspondence regarding the COT's 2013 position paper on contaminants in the cabin air of commercial aircraft. In particular, Mr Ian Panton, had asked whether the COT's conclusions related only to adults of working age, and did not apply to children, infants or the unborn fetus. The Chair had emailed Members seeking comment on his view that the COT conclusions related to all population groups. Members confirmed that although the COT position paper made no specific mention of children or pregnant women, there was no reason to expect them to be markedly more sensitive when exposed short-term to chemicals of the type that occur in fume events, and therefore the conclusion that "Many different chemicals have been identified in the bleed air from aircraft engines, but to cause serious acute toxicity, they would have to occur at very much higher concentrations than have been found to date (although lower concentrations of some might cause an odour or minor irritation of the eyes or airways)" should be taken to apply generically. So too would the caveat that "uncertainties remain, and a toxic mechanism for symptoms cannot confidently be ruled out".

8. The Chair told Members that he had been invited to review a book by John Hoyte, entitled 'Aerotoxic Syndrome: Aviation's Best Kept Secret' in which he noted text, quoting from a House of Lords debate in March 2014, that appeared to give an unbalanced summary of the COT's views. The Secretariat would check the record in Hansard and report back to the COT at the next meeting so that a more accurate reflection of the COT's position could be minuted if appropriate.

9. The Chair also reported that he would be attending an Aviation Health Conference on 23 September in Paris, to give a presentation on the COT's consideration of cabin air and its findings.

10. Para 9: The COT statement on endosulfan isomers, pentachlorobenzene and chlordecone and its lay summary had been published.

11. Para 10: The paper on the aspartame research had still not been published in a scientific journal. In answer to a question about publication of FSA-funded research, the Chair stressed that if research commissioned by FSA indicated a need for urgent action to protect public health then it would be published as quickly as possible. In other circumstances contractors were given reasonable time to publish their results in the peer-reviewed literature, giving the benefit of external review and more effective dissemination. However all final reports of FSA-funded research were published on the Agency's website, and this could not be delayed indefinitely.

12. Para 12: The Chair had attended a meeting of the Veterinary Products Committee to present the COT statement on long-term neurological, neuropsychological and psychiatric effects of low-level exposure to organophosphates in adults. In addition, following correspondence on this topic between the Chair and Dr Sarah Mackenzie Ross, a COT Member had suggested it would be useful for the COT to produce guidance, setting out its approach to the assessment and synthesis of epidemiological evidence in its reviews. This proposal would be discussed again at a future meeting. The Chair noted that he and the Scientific Secretary would be attending an expert workshop on "Implementing systematic review techniques in chemical risk assessments: challenges and opportunities" at the Royal Society of Chemistry on 18 November 2014.

13. Para 13: An update on progress on evaluation of the risks and benefits associated with consumption of *Lactobacillus rhamnosus* GG as a component of fully hydrolysed formula would be provided at the October COT meeting.

Item 4: Assessment of the adequacy of the 10-fold uncertainty factor to allow for interspecies variation in developmental toxicity

14. It was expected that a draft paper would be presented to the COT later in 2014, and it would address the questions raised by COT members that were noted in paras 30 and 32.

Item 7: SACN Review of vitamin D. Adverse effects of high levels. Additional information on single dose vitamin D and changes in serum 25(OH)D levels

15. Para 60: Members were informed that the National Institute for Health and Care Excellence (NICE) was developing a public health guidance document on vitamin D supplements in vulnerable groups; and that NICE observers would be attending relevant meetings of SACN working groups.

Item 8: Third arm results from FSA-funded research study T05029 – the effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized double blind crossover study

16. A draft COT statement was being prepared for discussion at a future meeting.

Item 4: Consultation of the European Food Safety Authority on a Draft Scientific Opinion on Acrylamide in Food - TOX/2014/23

17. No interests were declared. Members were informed that the Scientific Secretary was Chair of the European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM), which had endorsed this draft opinion for consultation. It was agreed that she could present the paper.

18. The draft opinion from the EFSA CONTAM Panel provided an extensive evaluation of dietary exposure to acrylamide, and the possible effects of such exposure. The FSA had invited the COT and Committee on Carcinogenicity (COC) to respond to the EFSA consultation, providing an independent view that would help to underpin the FSA policy in this area, and at the same time assisting EFSA in finalisation of the opinion. Members were provided with a copy of the draft minutes of COC's discussion, concerning aspects of the draft opinion relevant to carcinogenicity.

19. The COT was invited to make general comments on the draft opinion, and to give views on its sections relating to: human exposure assessment; toxicokinetics; biomarkers of exposure/effects; toxicity in experimental animals; observations in humans; considerations of critical effects and possibilities for derivation of a health-based guidance value; risk characterisation; uncertainty; and conclusions, recommendations and summary.

20. The Committee commented on the high quality and comprehensive nature of the scientific opinion and was broadly in agreement with the evaluation and conclusions.

21. The use of the scenario modelling was considered appropriate, but the baseline scenario was not sufficiently explained. The exposure estimates shown in Table 8 appeared very similar and it was not possible to determine whether levels were really different. Members asked if it was possible to comment on the uncertainties around the means. The section on non-dietary sources of exposure could usefully be expanded with inclusion of more quantitative data where possible. This would allow a better understanding of the relative contribution of dietary exposure and would assist in interpretation of the epidemiological studies and risk characterisation. In particular, it would be helpful to estimate levels of exposure to acrylamide from active smoking and from environmental tobacco smoke.

22. Greater consideration could be given to potential variation in the activity of CYP2E1 because of genetic polymorphisms and its being highly inducible by alcohol.

23. It was noted that the section on observations in humans focused mainly on the marginal impact of relatively small and imperfectly measured variations in dietary intake, with smoking (including the additional exposure to acrylamide that it entails) treated as a potential confounding factor. It would be worthwhile also to consider the human evidence on risks in relation to total exposure to acrylamide from all sources. The epidemiological studies were predominantly based on data from food frequency

questionnaires, which were not very reliable and their limitations should be explained. In relation to the case-control studies, there should be discussion about potential biases. It was suggested that consideration should be given to the levels of exposure that had resulted in documented neurotoxicity, to check that they were higher than the $BMDL_{10}$ value that had been used when calculating margins of exposure. If this was not possible, the reasons should be explained.

24. The characterisation of risk, including for reproductive and developmental outcomes, should take into account evidence from human studies on acrylamide exposure from all sources. Depending on relative dose levels, background data on associations of relevant outcomes with smoking might provide an upper estimate of risk for effects from dietary exposures to acrylamide.

25. Given the effects on the rodent testis, a comment on the possibility of transgenerational effects would be useful, together with a recommendation for research in this area. It was noted that other potential sources of exposure should be taken into account when attempting to correlate urinary metabolites with dietary exposure.

26. Further comments from COT members, along with the views of COC, would be incorporated into a draft joint response, which would be circulated to Members before submission to EFSA by the deadline of 15 September.

Item 5: Scoping paper on the potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet - TOX/2014/24

27. No interests were declared.

28. In support of a review by the SACN of Government's dietary advice for infants and young children, the Committee had been asked to consider possible risks of toxicity and allergic disease from chemicals in the infant diet. An initial paper (TOX/2012/03), highlighting specific topics that might merit consideration, had been discussed by the COT in February, 2012. Members had agreed that brominated flame retardants (BFRs), including hexabromocyclododecanes (HBCDDs), should be considered as part of that body of work.

29. The Committee had previously produced statements in 2003 and 2006 concerning HBCDD in fish and shellfish. In addition, an evaluation of HBCDDs in food had been published by EFSA in 2011. Paper TOX/2014/24 provided information from the COT and EFSA reviews; summarised findings from relevant toxicokinetic, toxicological and epidemiological studies that had been published subsequently; and presented estimates of the exposures of infants to HBCDDs from breast milk, food and non-dietary sources.

30. The Committee commented on limitations of the method by which EFSA had used results from a single administration study to estimate the effects of repeated dietary exposures that would give rise to a similar body burden. It was noted that EFSA had expressed reservations about the methodology used in the study, but had accepted it since it exhibited the most sensitive effect.

31. A more recent repeat dose toxicity study in mice (Yanagisawa *et al.,* 122: 277-83, 2014) appeared to show significant hepatic effects at doses of HBCDDs much lower than those in the study used by EFSA to derive its lower confidence limit for a benchmark response of 10% ($BMDL_{10}$). Members agreed that they would review the study in detail to determine whether it should be used to establish an alternative reference point to that employed by EFSA in its Margin of Exposure (MOE) approach. Effects on bone that had been reported by van der Ven *et al.* (Toxicological Sciences, 94: 277-83, 2006) and cited in the EFSA opinion, would likewise be considered further, to check that they should not be used as a critical endpoint for risk assessment.

32. An epidemiological study by Kim and Oh (Environmental Pollution, 184: 193-200, 2004) would also be examined in more detail.

33. Clarification was requested on HBCDD levels in UK drinking water, infant formula, and food supplements such as cod liver oil. Exposures from dust were identified as an area of uncertainty because of the variability in reported data. Members requested additional information about the sources of the dust samples that had been measured, and if possible, on airborne concentrations of HBCDDs in both the gaseous and particulate phases, and on levels in settled dust.

34. It was noted that the EFSA $BMDL_{10}$ had been derived from a study in which the test material was predominantly γ-HBCDD, whereas estimated exposures were higher for α-HBCDD than for the other isomers. This was considered to be another source of uncertainty in the risk assessment.

35. The Committee was not yet able to comment on whether there was a concern regarding infants' exposure to HBCDDs, or on priorities for further research. It was agreed that the available information was sufficient to justify drafting a statement, to be discussed at a future COT meeting.

Item 6: First draft statement on adverse effects of high levels of vitamin D - TOX/2014/25

36. Dr Harris noted that her employer, Exponent, was involved in work on cholecalciferol as a rodenticide. This was considered to be a personal non-specific interest, but not a conflict. No other interests were declared.

37. The SACN were reviewing dietary reference values for vitamin D, and the COT had been asked to consider possible adverse effects of high intakes. This topic had been discussed in a number of earlier COT papers, and a first draft of a COT statement was now presented to the Committee in paper TOX/2014/25.

38. Some of the information included in the draft statement (for example, on serum levels of 25-hydroxyvitamin D (25(OH)D) in the National Diet and Nutrition Survey) had been updated to reflect the most recent findings, and additional data had been included from a paper by Markestad *et al*. (American Journal of Clinical Nutrition, 46:652-8, 1987). The latter concerned serum calcium and 25(OH)D levels in infants given large doses of vitamin D_2 as part of a prophylactic programme, and might be relevant to the potential effects of high, single doses of vitamin D.

39. SACN had asked for a brief document to attach to their report, and it was envisaged that this would be based on the final section of the draft statement (paragraph 130 onwards), although the full statement would be provided to SACN and published on the COT website in the usual way. The Committee was asked to comment on the draft statement.

40. Members made a number of suggestions and comments on the overall structure and content of the draft statement. A second draft of the statement would be prepared in line with the Committee's comments. Members were advised that depending on when SACN wished to publish their report for consultation, it might be necessary to finalise the summary and conclusions in advance of the rest of the statement.

Item 7: First draft statement on domoic acid in king Scallops (*Pecten maximus*) - TOX/2014/26

41. No interests were declared.

42. At its March and May 2014 meetings, the Committee had considered the evidence that was available to support shucking (removal of non-edible parts) as a scientifically robust and effective method for managing the health risks associated with toxins in King Scallops that cause amnesic shellfish poisoning (ASP). Data on the distribution of domoic acid (DA), the major ASP toxin, in different tissues from whole King Scallops had now been analysed to estimate an upper concentration for DA in whole scallops, at which consumption of a large portion of the shucked product would not result in intakes that exceeded the acute reference dose of 30 µg/kg bodyweight that had been established by EFSA in 2009. It was anticipated that the analysis would provide a basis for future risk management decisions.

43. The Committee discussed a first draft statement on DA in King Scallops, which incorporated the new analysis and took into account previous COT discussions. Members indicated that they were content with the overall structure of the statement, but proposed some editorial changes.

44. It was confirmed that the reported measurements in scallop tissues were for DA and did not include the related isomer, epi-DA. Members noted the variability of tissue DA levels in different studies and that the estimated centiles of DA tissue concentrations were based on only a limited number of data points. Increasing the number of data points by combining datasets from different studies did not add value to the assessment, and therefore results obtained in that way should not be included in the next draft of the statement. A Member agreed to seek specialised statistical advice on the implications of the limited number of data points for the robustness of derived centiles of DA concentrations, and on ways of characterising the associated uncertainty.

45. The Committee agreed that a paragraph summarising the main sources of uncertainty should be included in the statement. This should also reflect the uncertainties associated with variations in the efficiency of shucking, even among trained operatives. Members were informed that the FSA was commissioning research on shucking practice to inform its enforcement regime.

46. A second draft statement would be prepared for discussion at the next meeting.

Item 8: First draft statement on the potential risks from polybrominated diphenyl ethers (PBDEs) in the infant diet - TOX/2014/27

47. No interests were declared.

48. At the May COT meeting, Members had discussed a scoping paper on PBDEs in the infant diet, as part of a continuing series of investigations in support of the SACN review of Government recommendations on infant feeding. It had been concluded that it would be reasonable to take an MOE approach to risk assessment for selected congeners for which there were both exposure and toxicological data.

43. Paper TOX/2014/27 included a first draft statement that took into account the previous discussion and summarised available information on the toxicology of PBDEs, the BMDLs calculated by EFSA for BDEs 47, 99, 153 and 209, and estimates of infants' exposure to PBDEs from different sources.

49. Members noted that varying regulations and industrial practices, together with the global use of flame retardants, meant that PBDEs could be present in consumer

products imported into the EU/UK, with potential for their release to the environment during disposal, and that it was not possible to predict future trends in exposure.

50. The Committee asked for a more detailed critique of the method by which findings from a study using a single administration had been used to assess risk in humans following repeated exposures that would produce a similar body burden. It was noted that higher tissue levels would be expected in the period immediately after dosing, before redistribution to adipose tissue, and that this could make the approach conservative. However that would depend on whether the timing of the single dose coincided with the most sensitive developmental stage.

51. The dietary exposure data were very limited, especially in relation to infant formula and commercially produced infant foods. Although currently available data suggested that infant exposure to PBDEs from breastfeeding and complementary foods did not represent a risk, there was a possible concern related to exposure from dust.

52. Members agreed that the approach adopted in the draft statement was reasonable given the limited database. Some editorial changes and clarifications should be made, including mention of possible combined effects from multiple PBDEs. A short summary of the main sources of uncertainty should be included.

53. A second draft statement reflecting the discussion would be presented at the next meeting.

Item 9: Paper for information: COT review of risks arising from the infant diet and the development of atopic and autoimmune disease – TOX/2014/28

54. This paper was provided for information only.

Item 10: Paper for information: FSA Scientific Advisory Committees (SACs) update – TOX/2014/29

55. This paper was provided for information only.

Item 11: Any other business

56. Members were informed that a combined FSA risk assessment research workshop and COT meeting on toxicokinetics in the obese would be held on the 18th March 2015, following the COT meeting on 17th March. Further information would be provided in due course.

57. There was no other business.

Item 12: Date of next meeting

58. Date of next meeting – 28th October 2014, Conference Rooms 4 & 5, Aviation House, 125 Kingsway, London. WC2 6NH.