TOX/MIN/2015/01

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

Minutes of the meeting held on Tuesday, 3rd February 2015 in Aviation House, London.

Present

Chairman:	Professor D Coggon		
Members:	Mr D Bodey Dr R Brimblecombe Dr M Graham Dr A Hansell Dr C Harris Prof D Harrison Prof R Harrison Prof B Lake Prof I Morris Dr N Plant Dr J Thompson Prof F Williams		
Food Standards Agency (FSA) Secretariat:	Dr D Benford Ms H Gbormittah Ms R Acheampong Ms L Buckley Dr D Gott Dr D Hedley Ms F Hill Dr L Kent Mr B Maycock Ms C Mulholland Ms C Potter Mr A Sbaiti Dr J Shavila	Scientific Secretary Administrative Secretary	
Public Health England (PHE) Secretariat:	Ms F Pollitt	Scientific Secretary	
Invited experts and Contractors:	Dr Ken Ong	Medical Research Council (MRC)	
Officials:	Ms Wendy Dixon	FSA, Food Additives Policy Branch	Item 7
	Ms Nathalie Shapiro	FSA, Allergy and Novel	Item 1

		Foods Branch
Assessors:	Professor Tim Gant	PHE

Contents

Announcements

1. The Chairman, Professor Coggon, welcomed Members, assessors and Dr Ong who was representing the Scientific Advisory Committee on Nutrition (SACN) Subgroup on Maternal and Child Nutrition (SMCN) at the meeting.

2. The Chairman announced the appointments, with effect from 1st April 2015, of Professor Alan Boobis as Chairman and Dr James Coulson as a Member. The Chairman also announced the reappointments of Professors Roy Harrison, Brian Lake and Faith Williams.

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 were received from four members – Professors Robert Smith, Brian Houston and Janet Cade, and Dr Rene Crevel. Written comments had been submitted by two members. Apologies were also received from assessor Sam Fletcher (Veterinary Medicines Directorate).

Item 2: Draft minutes of the meeting held on 9th December 2014 – TOX/MIN/2014/06

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

Item 3: Matters arising

Item 3: Matters arising from previous meetings

6. Para 5: This item related to the Hansard record of a statement by Baroness Kramer (Minister of State for Transport) during a House of Lords debate in March 2014 on aircraft cabin air, which had not adequately reflected the COT's views. On 12th November 2014, the Chair had written to the Permanent Secretary at the Department for Transport, copied to Sir Mark Walport (Chief Scientific Adviser to HM Government), to express the Committee's concerns and to ask that where possible, future briefings for Ministers be checked with the Committee's Secretariat. As there had still been no reply, the PHE Secretariat would speak to the Permanent Secretary's Office to ensure the Chair's correspondence had arrived. If necessary, the Chair would write to the Permanent Secretary again, copying the correspondence to Sir Mark Walport.

7. A communication received by the Chair from Mr Ian Panton concerning this topic was noted. Members agreed that no further actions should be taken at this stage.

8. Para 6: The paper on aspartame was in the final stages of publication.

9. Para 7: The Chair's perspectives following the workshop on systematic review had been circulated to the Committee on 18th December.

10. Para 8: Dr Hansell introduced a paper on the proposed subgroup to review approaches that the Committee takes to the synthesis of epidemiological evidence. It was agreed that the subgroup should reflect on whether the output from their work should be guidance for the Committee, or a communication to the public about the approaches currently employed by the Committee (members of COT favoured the latter). The Members of the subgroup and dates of proposed meetings would be confirmed after discussions between the COT Secretariat and prospective Members.

11. Para 10: A draft paper on interspecies variation in developmental toxicity would be considered later in the meeting (Item 8).

12. Para 11: Professor Morris had attended the European Food Safety Authority (EFSA) stakeholder meeting on acrylamide on 10th December, and he provided a brief verbal report to the Committee.

13. Para 13: Papers on the local lymph node assay would be included in a follow-up paper for discussion later in the year.

14. Para 17: The statement and lay summary on the adverse effects of high levels of vitamin D had been published.

15. Para 18: The statement and lay summary on domoic acid in King Scallops had been published.

Item 5: Potassium-based replacements for table salt and sodium additives

16. Para 45: A revised statement was being prepared for the March meeting.

Item 6: First draft statement on polybrominated biphenyls (PBBs) in the infant diet

17. Para 51: As editing had been more extensive than expected, a revised draft was being brought back to the Committee, and would be discussed later in the meeting (Item 9). The revised draft included clarification about the relevance to humans of toxicity mediated by the constitutive androstane receptor (CAR), and the reasoning behind the selection of certain congeners for analysis in dietary surveys.

Item 7: First draft statement on the effects of soya consumption on thyroid status

18. Para 56: A table summarising the effects on thyroid function that had been reported in studies of isoflavone exposure in humans had been included in the second draft of this statement, which would be discussed later in the meeting (Item 6).

Item 8: Third draft statement on the potential risks from polybrominated diphenyl ethers (PBDEs) in the infant diet

19. Para 61: A revised (4th) draft statement on PBDEs in the infant diet was discussed by SMCN on 29 January. There were no major comments on the content or detail of the statement, but there was a request to check some details. A general comment was made that a more standardised use of terminology could be developed between SACN and COT that would aid risk communication. Dr Ong highlighted a need for information on the levels of PBDEs in infant formula for comparison with those in breast milk.

Item 4: Potential future discussion items – horizon scanning – TOX/2015/01

20. Members noted a list of agenda items for 2015 that were planned or underway, and discussed several other topics that might also be considered.

COT review of risks arising from the infant diet and the development of atopic and autoimmune disease

21. The COT had been asked to provide advice on risks of toxicity from dietary exposures in infants, including possible effects on the development of atopic and autoimmune disease. Members noted that to inform this work, FSA had commissioned four parallel reviews of the relevant, published, scientific literature, and agreed to consider the reviews according to the following proposed timing:

- Systematic review A, which explored the evidence relating milk-feeding to children's future risk of developing atopic or autoimmune disease, would be considered in May 2015.

- Systematic review B, which explored impacts of the timing of introduction of allergenic foods into the infant diet during the first year of life, would be considered in December 2015, by which time the review would be able to incorporate the results from two new randomized control trials.

- Systematic review C, which explored the effects of avoidance or exposure to specific dietary patterns, food groups or nutrients during pregnancy, lactation and infancy would be considered in September 2015.

- Systematic review D, which explored evidence on infant formulae containing protein hydrolysates and the risk of developing atopic or autoimmune disease, would be considered in June 2015.

Potential discussion topics

Consultations of the European Food Safety Authority (EFSA)

22. Members noted that a number of new EFSA opinions/reports were expected during the next year, and would be brought to the attention of the Committee if they were relevant to the work of the FSA and COT.

Items carried forward from the 2014 horizon scanning

Update on Tox21 and ToxCast

23. A brief overview was presented of recent developments in these American initiatives. Members were asked for their thoughts on the work, which they had considered in previous years. The Committee noted the major challenges faced by the Tox21 project. In particular, there had been poor progress in the integration of data on metabolism with *in vitro* assays.

24. The Committee supported the objective of ToxCast to prioritise substances for *in vivo* testing, so that resources could be used more effectively. The Committee indicated that it would welcome a presentation on progress in this area in due course, and PHE undertook to lead in this.

Modelling Kinetics

25. New publications had become available stemming from a European-wide cooperative initiative on physiologically-based toxicokinetic modelling. The Committee agreed that it would be useful to keep abreast of developments in this area, particularly as it might be asked in the future to advise on risk assesments using such models. This would be discussed further after the COT symposium on the implications of obesity on the kinetics of persistent organic pollutants.

FSA's New Recipes Database

26. The Committee was informed that an information paper concerning a project to update compositional data for recipes and its use in dietary exposure assessment, would be presented to the Committee in due course.

Possible new discussion items

Human Biomonitoring in the UK and Europe

27. Members were informed that PHE would be updating the Committee in May 2015 on the progress of projects in this area. It would be helpful to establish the extent and scope of biomonitoring studies that were currently on-going in the UK, and it was agreed that a useful way forward would be to conduct a literature search looking for publications from such studies, and to contact funders who might be supporting research using biomonitoring. In addition, biomonitoring was carried out as part of routine health surveillance for some occupational hazards (e.g. in workers exposed to lead). Members were invited to send information on ongoing biomonitoring work, potential funders who could be contacted and an appropriate focus for the literature review.

Histamine in cheese

28. Members noted that histamine poisoning was a well-established phenomenon arising from consumption of foods which have become contaminated with high levels of the chemical, usually as a result of bacterial spoilage. This was most frequently observed in fish, and regulatory limits had been set for levels of histamine in fish. Histamine could also occur in fermented products such as cheese, and reports of high levels in cheeses were becoming increasingly common. There were currently no regulatory limits for histamine in cheese, and the FSA therefore provided pragmatic advice on levels in cheese. The COT agreed to comment on the FSA's advice regarding histamine in cheese, and on an EFSA opinion on biogenic amines in fermented foods. Members requested a discussion paper including information on the relationship between levels of histamine and salt content, data on the occurrence of poisoning, and information about potentially sensitive individuals including children and those taking angiotensin converting enzyme (ACE) inhibitors and other relevant drugs.

The microbiome

29. The Committee agreed that it would be helpful to have a presentation on emerging evidence concerning the effect of individual microbiomes on susceptibility to chemical toxicity.

30. The PHE assessor would be attending a meeting of the International Microbiome Consortium in March 2015, and would then provide a summary report for the Committee. That would subsequently be followed up with a presentation by PHE.

Synthetic Biology and its implications for the work of the COT

31. Members noted that synthetic biology was an importantant emerging area of research and development, but concluded that it did not have special implications for the toxiocological risk assessments carried out by the COT, and therefore was not a high priority for more detailed discussion at this stage.

Balance of expertise on the Committee

32. It was noted that additional expertise in occupational health epidemiology would be welcome. Given the dearth of senior researchers in the field, there might be a need to involve scientists who were at an earlier stage in their careers. It would also be useful to include a member with expertise in biomonitoring, perhaps in occupational settings.

Other potential future topics

33. Members discussed their approach to assessing risks from mixtures of congeners (e.g. in flame retardants) which was carried out on a case-by-case basis. Opportunities for extrapolating from one congener to others that might be present in a mixture were mentioned as a possible way of improving assessments, but this would depend on the availability of data. It was noted that while data on the toxicity of individual congeners that occurred in food and the environment were often sparse, understanding of the differing pharmacological effects of stereochemical isomers in medicines tended to be better because there was more knowledge about anticipated molecular targets.

34. The approach taken by the EFSA to the assessment of enantiomeric mixtures in pesticides might provide useful insights. In addition, it would be helpful to review the published literature on the toxicity of congeners alone and in combination. Members agreed to propose terms for inclusion in a literature search for that purpose.

35. Exposure to chemicals other than nicotine (e.g. additives and flavourings) from electronic-cigarettes (e-cigarettes) was identified as another possible area for future discussion. Exposure to chemicals from this source would also be relevant to bystanders, and it would probably be necessary to consider the role of nano-particles. PHE agreed to update the Committee on developments in this area in due course, and to circulate a presentation that the PHE assessor would be giving at an upcoming MRC conference on the composition of e-cigarettes.

Item 5: Second draft statement on the potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet – TOX/2015/02

36. No interests were declared.

37. At the December COT meeting, Members had discussed a first draft statement on the potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet, as part of a continuing series of investigations in support of the SACN review of the Government's dietary recommendations for infants.

38. Paper TOX/2015/02 included a second draft statement that took into account the previous COT discussion and summarised the available information on the toxicology of HBCDDs. Members were asked whether they agreed that the effects of HBCDDs on the thyroid hormone axis were likely to be secondary to increased hepatic clearance of T4 via glucuronidation, and whether they agreed with the content of the second draft statement.

39. The Committee decided that, on the evidence provided, it would be more accurate to state that the effects of HBCDDs on the thyroid hormone axis 'might be' secondary to increased hepatic clearance of T4 via glucuronidation rather than that this 'was likely'. Members also wished to include data in the statement on enzyme induction by HBCDDs.

40. Members agreed that, following the above amendments, the statement could be finalised by Chairman's action. A draft lay summary would be circulated to Members for comment.

Item 6: Second draft statement on the effects of soya consumption on thyroid status – TOX/2015/03

41. No interests were declared.

42. At several previous meetings, the COT had considered the potential effects of consuming soya products on various health outcomes investigated in FSA-funded studies. The Committee had concluded that it would be appropriate to produce a COT statement on the possible effects of soya phytoestrogens on thyroid function. A first draft statement had been presented to the Committee in December 2014. The second draft statement, TOX/2015/08, had been revised in light of the Committee's discussion in December.

43. Members asked that a number of editorial changes be made, including amendments to the table. The Committee also requested a more detailed introduction to the FSA-funded research.

44. Members discussed the target audience for the statement and agreed that, once finalised, copies should be sent to The Society for Endocrinology, The Royal College of General Practitioners and The Society for Paediatric Endocrinologists. The

Committee requested that the statement be disseminated in such a way that it would be readily identifiable in literature searches.

45. Members suggested that consideration should be given to further research investigating possible links between consumption of soya milk and thyroid function.

46. A revised draft statement would be prepared for discussion at the next Committee meeting in March 2015.

Item 7: Consultation of the European Food Safety Authority on a Draft Scientific Opinion on the safety of caffeine – TOX/2015/04

47. The EFSA had published a consultation on a draft scientific opinion on the safety of caffeine on the 15th January, requesting comments by the 15th March. The COT were asked if they wished to make comments on the draft opinion, and to respond to the consultation. They were also asked whether in light of the draft EFSA opinion, they wished to update or reconsider their recent conclusions in an overarching statement on the risks of chemical toxicity and allergic disease in relation to the infant diet, and especially their conclusions on lactating mothers.

48. Members felt that EFSA's overall conclusions relating to adults were broadly in line with their own, and that the available epidemiological studies supported these adequately. However, they had a number of comments regarding the structure of the document and the arguments supporting the final conclusions.

49. Members considered that the tables in the appendices were not very helpful – more details for each study would be useful, so that the studies could be compared by the reader without having to refer to other parts of the document or the original papers. Especially of note were the doses of caffeine and statistical significance of associations in each study. The uncertainties were not well described and the inclusion of some data plots would be useful.

50. The Committee considered that some of the nuances set out in the conclusions to individual sections of the opinion were not reflected in the overall conclusions at the end.

51. It was suggested that the effect of genetic differences on caffeine consumption should be brought out more strongly, and that the use of extremely low caffeine consumers as referents might be inappropriate, given that this group was likely to over-represent people who were unusually sensitive to caffeine. Members proposed that comparisons between high and low consumers of caffeine would be easier to interpret.

52. Members noted that the opinion discussed acute caffeine intakes with supporting studies in the main text, but did not mention this research in the conclusions, which gave no explanation as to why acute effects had been discounted.

53. Further clarification on the remit of the opinion was requested by the Committee, as they were not clear why common sensitive groups had not been considered, apart from one study looking at people with diagnosed hypertension.

54. Members suggested that the inclusion of data referring to interactions with other drugs, either prescribed or illicit, would be useful.

55. The summary of a case-crossover study (page 35, lines 1401-1412) was unsatisfactory in that the design described was not that of a case-crossover study.

56. Section 4.2 on pharmacodynamics was considered to be incomplete. Members concluded that there was very little information on behavioural effects of caffeine, that this might usefully be expanded, and that the opinion was inconsistent in its consideration of anxiety (pages 39 and 42)

57. Members agreed with the EFSA conclusions on adults and pregnant women. With regard to lactating women, members noted that the EFSA conclusions were based on exposure of the infant through breast milk and extrapolation of toxicity from adults, but they were concerned that the EFSA did not appear to have considered whether infants might be more susceptible to caffeine than adults, due to differences in their metabolism. The COT had previously noted that in the UK advice to pregnant women on limiting caffeine consumption to 200mg/day had been extended to lactating women and considered that this remained appropriate given the uncertainties about possible metabolic differences. Members considered that the EFSA's approach of extrapolating adult data to children and adolescents on a bodyweight basis was acceptable given the lack of direct data.

58. A draft Committee response to the consultation, including the points set out above, would be circulated to members for agreement before submission to EFSA by the deadline. The Committee response would be included in an information paper for the next meeting.

Item 8: Draft manuscript on developmental toxicity and the uncertainty factor for interspecies extrapolation – TOX/2015/05

59. The Committee had considered papers on this topic at its December 2013 and May 2014 meetings. It had concluded that there were strong indications that the 10-fold uncertainty factor for interspecies variation in developmental toxicity was not always adequate, and having considered data on effects other than in utero

developmental toxicity, extended this conclusion to non-developmental outcomes also. The Committee had agreed that a paper should be written for publication in a peer-reviewed journal. A short COT statement could then be produced, based on the paper.

60. The Secretariat had approached a possible co-author for the paper, who had wished to see a draft manuscript before deciding how to contribute. A manuscript had been drafted focussing on developmental toxicity. The potential co-author had subsequently provided comments on the draft manuscript, but had decided not to be included as a co-author. TOX/2015/05 included the comments received and sought the Committee's views on the way forward.

61. Members agreed that the comments received were very useful. The aim of the paper as drafted had been to identify the frequency of cases in which the 10-fold uncertainty factor would not be adequate. An alternative approach might be to start from the position that the 10-fold uncertainty factor was not adequate for thalidomide and then to assess the strength of evidence that there were other chemicals for which it was also inadequate. Thus the approach taken so far could be presented as a screening exercise to identify candidate chemicals. This would then be followed by more in-depth critical evaluation for those chemicals to assess the quality of evidence that they were developmental toxicants, and their relative potency in humans and laboratory animals.

62. The Committee debated how broad the definition of developmental toxicity should be, and agreed that it should not be restricted only to teratogenicity but should be limited to effects of in utero exposure that were manifest at birth.

63. One Member suggested that retinoids be considered separately as their mode of action was teratogenic.

64. It was agreed that once the candidate chemicals had been selected by the screening approach, the epidemiological data should be passed to an epidemiologist and the toxicology data to a toxicologist. They could then comment on the strength of the data and advise on what they considered to be the human LOAEL and the rat and rabbit LOAELs, respectively. The LOAEL would be defined as the lowest dose level at which they were reasonably confident that adverse effects occurred.

65. The comments received had queried the implication that aspirin and propranolol were teratogenic in humans. It was clarified that the human data for aspirin related to associations in an epidemiological study with decreased birth weight and increased perinatal mortality, and for propranolol to case-reports of intra-uterine growth retardation.

66. The paper should include more justification for comparison of LOAELs rather than no observed adverse effect levels (NOAELs) or benchmark doses (BMDs).

67. The Committee agreed that it was worth pursuing publication of a paper in the peer-reviewed literature, and that a toxicologist and an epidemiologist should be sought as collaborators to evaluate the data critically for the identified candidate chemicals.

Item 9: Second draft statement on polybrominated biphenyls (PBBs) in the infant diet – TOX/2015/06

68. No interests were declared.

69. At the December COT meeting, Members had discussed a first draft statement on polybrominated biphenyls (PBBs) in the infant diet, as part of a continuing series of investigations in support of a SACN review of Government's dietary recommendations for infants (paper TOX/2014/40). Members had concluded that it would not be possible to conduct a meaningful risk assessment due to the limited exposure data available, and that a position paper or statement should be drafted to explain this.

70. Paper TOX/2015/06 included a second draft statement that took into account the previous COT discussion and summarised available information on the toxicology of PBBs, points of departure agreed by the Committee at the October meeting, and the limitations of the available exposure data.

71. Members suggested some minor editorial changes, including further clarification of expected future exposures and reasoning for the expectation that polychlorinated biphenyls (PCBs) would have greater toxicity than their PBB counterparts.

72. As the requested changes were minor, Members agreed that the statement could be finalised by Chairman's action. A draft lay summary would be circulated to Members for comment.

Item 10: Draft 2014 Annual Report – TOX/2015/07

73. Members had no comments on the draft 2014 Annual Report.

Item 11: Paper for information: Update on actions taken subsequent to COT advice – TOX/2015/08

74. This paper was provided for information only.

Item 12: Paper for information: FSA Scientific Advisory Committees (SACs) update – TOX/2015/09

75. This paper was provided for information only.

Item 13: Any other business

Cyanogenic glycosides in bitter apricot kernels.

76. The COT had considered cyanogenic glycosides in bitter apricot kernels in 2006, establishing a nominal reference dose of 0.5 µg/kg bodyweight/day, based on the toxicity of hydrogen cyanide. This meant that in practice, no more than one kernel per day could be consumed without exceeding the reference dose. The FSA issued advice to the public on consumption of apricot kernels, informed by this evaluation.

77. The FSA had now become aware that bitter apricot kernels had become available in a powdered form, potentially increasing the risk of over-consumption. A limited search of the literature suggested that there were no new data on cyanide toxicity, although some additional case reports of toxicity from kernels were identified.

78. Members were informed that the matter was being discussed by the European Commission, who were seeking an EFSA opinion on cyanogenic glycosides. Members noted that the 2006 risk assessment would still apply as this had been established based on cyanide and no new data had been identified.

79. No other business was raised.

Item 14: Date of next meeting

80. Date of next meeting – Tuesday 17th March 2015, Jurys Inn, Birmingham.