TOX/MIN/2013/06

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

Minutes of the meeting held on Tuesday, 29th October 2013 in Aviation House, London.

Present

Chairman:	Professor D Coggon		
Members:	Mr D Bodey Dr R Brimblecombe Prof J Cade Dr R Crevel Dr A Hansell Prof D Harrison Prof R Harrison Prof B Lake Prof I Morris Dr N Plant Prof R Smith Prof F Williams		Items 1-5
Food Standards Agency (FSA) Secretariat:	Dr D Benford Ms H Gbormittah Dr E Cemeli Dr D Gott Dr M Kurzawa-Zegota Dr B Maycock Dr D Parker Ms C Potter Mr A Sbaiti Dr J Shavila	Scientific Secretary Administrative Secretary	
PHE Secretariat:	Dr L Hetherington Dr H Garavini	PHE Scientific Secretary PHE Toxicology Unit, Imperial College	
Co-Opted Member:	Prof P Aggett	Vice Chairman, Scientific Advisory Committee on Nutrition (SACN)	
Invited Experts and Contractors	Dr N Dowdall	Civil Aviation Authority (CAA)	Item 4
	Prof A Piersma	National Institute for Public Health and the Environment – Netherlands	Item 8
	Prof S Atkin	Hull York Medical School	Item 10
	Prof R Hammersley	Hull York Medical School	Item 10

	Dr A Rigby	Hull York Medical School	Item 10
	Dr T Sathyapalan	Hull York Medical School	Item 10
Officials	Ms Kate Jennings	Department for Transport	Item 4
	Mr J Richardson	Department for Transport	Item 4
	Dr Tim Marczylo	Public Health England	Item 6-8
	Ms Joanna David	Food Standards Agency	Item 10
	Dr Mark Willis	Food Standards Agency	Item 10
Assessors	Dr T Gant	Public Health England (PHE)	
	Dr M Benton	HSE Chemicals Regulation Directorate	

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Announcements

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

- Ms Kate Jennings – Head of Division (Aviation Policy Implementation), Department for Transport; Mr Jason Richardson, Department for Transport; Dr Nigel Dowdall - Head of Aviation Health Unit, Civil Aviation Authority; all present for Item 4.
- Dr Tim Marczylo – Public Health England; present for Items 6-8
- Professor Peter Aggett, a member of Scientific Advisory Committee on Nutrition (SACN) and its Subgroup on Maternal and Child Nutrition; present as a co-opted Member for Items 5-7, related to infant feeding.
- Professor Aldert Piersma, National Institute for Public health and the Environment RIVM, The Netherlands; present for Item 8.
- Professor Steve Atkin, Professor Richard Hammersley, Dr Alan Rigby and Dr T Sathyapalan – Hull and York Medical School; Ms Nathalie Golden – Communications Manager, Dr Mark Willis – Food Additives Senior Advisor, and Clifton Gay – Head of Statistics, Food Standards Agency; all present for Item 10.

2. Members were informed that Dr Lesley Hetherington would be leaving Public Health England on 14 November to take up a post at the Department for Environment Food and Rural Affairs (Defra). The Committee wished her well.

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: Dr Caroline Harris, Dr Mark Graham, Prof Brian Houston and Dr John Thompson; and from Rachel White (Public Health England). No written comments had been submitted.

Item 2: Draft minutes of the meeting held on Tuesday, 17th September 2013 – TOX/MIN/2013/05

5. The most recent draft of the minutes, which included substantial revisions, had not been included with the papers sent out in advance of the meeting. It was agreed, therefore, that confirmation of the minutes should be deferred to the next meeting. The reserved minutes from the 2nd July and 17th September 2013 meetings were agreed.

Item 3: Matters arising

Item 3: Matters arising from previous meetings

6. Para 9: (refers to item 4 of 2nd July). Feedback on the draft report had been forwarded to the contractor. A draft manuscript on the aspartame research had been received and was on the current agenda, item 10.

7. Para 10: (refers to item 5 of 2nd July). The draft report on the project on soy phytoestrogens and hypogonadism had still not been received.

8. Para 11: The Waste and Resources Action Programme (WRAP) had been advised of the finalised COT minutes.

9. Para 12: The draft statement on endosulfan isomers, pentachlorobenzene and chlordecone in relation to infant diet was being finalised.

10. Para 14: The draft statement on potential risks from high levels of vitamin A in the infant diet was being finalised.

11. Para 15: A paper on the potential impact of potassium salt replacers on total dietary exposure to potassium was being prepared for the December meeting. Some additional information on potassium handling in infants and young children would also be presented in December.

Item 4: Exposure Monitoring of the Aircraft Cabin Environment

12. Further information on this item, together with draft COT conclusions were to be discussed under item 4 of the current agenda.

Item 5: Discussion paper on the combined use of CS (2-chloro-benzylidene malonitrile) and PAVA (nonivamide) (captor 2) irritant sprays

13. The Home Office was planning to commission the extended study, recommended by COT in para 66. Selected members agreed to advise further on the proposed approach.

Item 6: SACN Review of vitamin D.

14. The views of the COT on the dose-response relationship between serum vitamin D and pancreatic cancer, and between serum vitamin D and all-cause mortality had been fed back to the SACN Working Group on 1st October 2013. Clarification had been received on outstanding issues, with the SACN Working Group asking the COT to advise on whether the tolerable upper level (TUL) would be protective in individuals with conditions that pre-dispose to hypercalcaemia (including sarcoidosis, tuberculosis and hyperparathyroidism). Data on this would be provided to COT at its meeting in December. SACN had also asked for advice on whether it was possible to establish a maximum safe level for a single dose of vitamin D. This would be considered early in 2014, when it was hoped that the first draft of a statement would also be available.

Item 7: Second draft statement on the potential risks from high levels of soya phytoestrogens and soya products in the infant diet

15. A revised draft statement was on the current agenda at item 7.

Item 8: First draft statement of potential risks of α-, β- and γ-hexachlorocyclohexanes in the infant diet

16. A revised draft statement was on the current agenda at item 6.

Item 4: Discussion Paper on Exposure Monitoring of the Aircraft Cabin Environment – TOX/2013/38

17. No interests were declared

18. The Committee had been asked by the Department for Transport (DfT) to provide independent scientific review of the findings from DfT-funded research on the cabin environment of aircraft. This research had been commissioned in response to recommendations made by the COT in 2007. The DfT had funded four studies concerning the assessment of air-monitoring equipment, monitoring of air and surface residues in aircraft, and a statistical analysis of the relationship between fume events and operational data routinely recorded during flights. The PHE COT Secretariat, and through them the PHE Toxicology Unit at Imperial College London, had been commissioned by the DfT to review the reports of these studies and prepare a discussion paper for the COT.

19. A discussion paper (TOX/2013/32) and its accompanying annexes had been considered by Members on 17 September 2013. Before finalising its conclusions and any recommendations for further research, the Committee had agreed to seek the views of a Member with expertise in environmental monitoring who was unable to attend the meeting in September. At the current meeting, Members were provided with additional information to assist in their discussion: a summary of the levels of different chemicals that had been measured in bleed air from the engine of a BAe 146 aircraft, a list of workplace exposure limits for chemicals, and draft COT conclusions on exposure-monitoring of the aircraft cabin environment, ill-health in aircrew, and the possible relationship of such illness to smoke/fume events in aircraft.

20. Members discussed the draft conclusions and requested some minor editorial changes.

21. The Committee agreed that assessment of whether reported illness occurred through a toxic mechanism needed to take into account the pattern and diversity of symptoms, and the levels of exposure to potentially relevant chemicals during fume events. It was noted that the patterns of illness that had been described in relation to fume events were not those which would be expected from inhibition of neuropathy target esterase (NTE) by tricresyl phosphates (TCPs).

22. With regard to possible further lines of research, the Civil Aviation Authority (CAA) commented that it would be challenging to assemble extensive data uniformly on all flights, and difficult to persuade airlines to do so. However, Members pointed out that useful information could be obtained without a large and complex system of data management. Data need only be collated for flights in which a fume event

occurred, and for a representative sample of control flights – a few hundred at the most. The information required would cover items such as: date and time of the flight, aircraft type, engine service record and the age of the aircraft. As long as this information could be retrieved for the flights of interest from data collected routinely by airlines (even if held in a number of different datasets and in different formats by different airlines), a useful analysis could be carried out. In addition, for the small minority of flights in which fume events occurred, it would be useful to record the nature of the incident, the timing during the flight, and the timing and duration of any adverse health effects. The CAA agreed that this approach would be acceptable to them. A proforma could be designed and used to collect such information systematically about flights in which a fume event occurred. Data on flights with fume events and on a sample of control flights should be available from records that are already kept by airlines. Members agreed that the responsibility for implementing such a study would be a matter for discussion with the CAA.

23. One Member stated that the wipe method was difficult to apply usefully without knowledge of the target compounds and was more suitable for non-volatile/semi-volatile chemicals. It would now be possible to provide more quantitative data. A Member noted that one of the research contractors had treated TCP compounds as being volatile and bound to particles without consideration of their partition coefficients. Also, the pumped air-monitoring system had used isopropyl alcohol, and its vapour had interfered with measurements. The particle counter had provided the most useful data. Technology had since advanced, and there were now far better instruments which did not use isopropyl alcohol, could run continuously, and could be used to trigger an active sampling system. It would be possible to design a relatively small package of instruments for this purpose, but the target chemicals would first need to be identified.

24. The CAA confirmed that under the Mandatory Occurrence Reporting (MOR) system, fume events were reported in about 1 in 2000 flights, and that serious incidents occurred at a much lower rate. The types of incident of most concern were those involving bleed air contamination, and they constituted a minor proportion of all incidents. The CAA said that it might be possible to induce bleed air contamination on the ground, and at take-off under 'hot and fast' conditions, but that the latter would be against flight regulations. Members concluded that while the monitoring of 5 to 10 aircraft over a year would give data on a large number of flights, if the risk of fume events differed importantly from one plane to another, then it was still possible that no serious fume events would be characterised.

25. Members considered the data on chemicals detected in bleed air alongside workplace exposure limits. The chemicals identified included a wide range of volatile organic compounds (VOCs). Where workplace exposure limits had been set for such chemicals, they were generally 1 part per million (ppm) or higher for a 15 minute exposure. This was three orders of magnitude greater than the levels measured in aircraft bleed air in test rig studies, and also much higher than the concentrations that had been measured in the cabin air-monitoring study.

26. Members considered whether any of the chemicals which had been identified in bleed air might have caused acute toxicity in aircrew. The levels of these chemicals which had been measured in the studies to date were a few parts per

billion (ppb), and at these concentrations no significant toxicity would be expected. However it was uncertain which chemicals would be present during fume events, and at what concentrations. Members agreed, therefore, that it would be helpful to explore whether any of a representative range of chemicals could occur during fume events at levels at least two to three orders of magnitude above baseline. Compact, automated equipment could now be designed to trigger the collection of suitable air samples during fume events, although even with such automation, it would be expensive to monitor sufficient numbers of planes and flights to be confident of including serious fume events. An alternative approach might be to make measurements during a simulated fume event on the ground, or in experimental flights under conditions that were likely to induce fume events.

27. The CAA informed the Committee that the temperature of the bleed air into which engine oil sometimes leaked would be approximately 200-500°C. This could be simulated in the laboratory and the vaporisation and pyrolysis products characterised. This would not provide information on levels of exposure but would help to identify target chemicals.

28. The Committee agreed that in view of the low background levels of the pollutants that had been measured, and the extent to which they would need to increase during an incident to produce toxic effects, it seemed unlikely that such toxicity was responsible for the acute symptoms that had been reported in relation to fume incidents. Furthermore, the symptoms that had been documented were diverse, and could not readily be attributed to any specific chemical.

29. Nor were there indications of a toxic explanation for the chronic illness in some aircrew that had been attributed to pollution of cabin air. Inhibition of NTE was a well-established mechanism of toxicity but typically caused a peripheral neuropathy. Moreover, the low levels of exposure to organophosphates in cabin air were insufficient to cause overt cholinergic effects, and when last reviewed by the Committee, the balance of evidence had not suggested that long-term neurological illness could occur as a consequence of exposure to cholinesterase-inhibiting organophosphates that was insufficient to produce overt acute poisoning. A COT working group was currently re-examining this question, and a draft statement on the topic would be discussed at the COT meeting in February 2014.

30. Members considered that it would also be useful to collect urine and blood samples from the crew on flights in which fume events had recently occurred, to look for biomarkers of potentially relevant exposures. Metabolites of TCPs could be measured in urine, and there was evidence that TCPs formed a specific adduct with butyryl cholinesterase, which again could be measured.

31. The Committee agreed that their conclusions and recommendations should be revised, finalised by correspondence and then published as soon as possible. In the meantime continuing efforts should be made to prevent fume events. Even if reported symptoms occurred through nocebo effects, this still had safety implications.

32. The Chair thanked the DfT and the CAA representatives for assisting the discussion.

Item 5: Scoping paper on potential risks from perfluorooctane sulfonate (PFOS) in the infant diet – TOX/2013/40

33. No interests were declared.

34. 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, was discussed by the COT in February, 2012. Members had agreed that a more detailed review on perfluorooctane sulfonate (PFOS) was needed as the chemical had not been evaluated with regard to exposures through the infant diet. None of the existing Government dietary advice for infants and young children related specifically to PFOS.

35. Members were provided with a scoping paper, TOX/2013/40, on potential risks from PFOS in the infant diet. Since the most recent evaluation of PFOS by EFSA in 2008, substantial new information had been published, which might indicate a need to lower the Tolerable Daily Intake (TDI) value. These new data were being reviewed by EFSA, but the process was likely to take some time. It was proposed that for this evaluation the current TDI should be used with the caveat that the Committee's conclusions might need to be reconsidered following publication of EFSA's conclusions on the new research findings.

36. The Committee asked that further information be provided on PFOS precursors, their importance, whether there could be dietary exposures to these compounds, and whether they can be metabolised to PFOS once in the body.

37. Members noted that a previous COT statement in 2006 reported the possibility that high level consumers aged 1.5-6 years might exceed the TDI, but that there was a lack of information on PFOS in the infant diet specifically.

38. Based on the limited information available, Members concluded that the contribution to total PFOS exposure from non-food sources (food contact materials, water, air and dust) was likely to be low.

39. The Committee concluded that from the information presented to them, there was no basis for dietary recommendations to limit exposures to PFOS. However once the new toxicity data have been reviewed by EFSA, this conclusion might need to be revisited.

40. A draft statement on PFOS would be prepared for discussion at a future meeting. This should highlight the assessments of exposure, the derivation of the TDI, and the caveat concerning the new data that were being reviewed by EFSA.

Item 6: Second draft statement of potential risks of α-, β- and γ-hexachlorocyclohexanes in the infant diet – TOX/2013/41

65. No interests were declared.

66. Within the context of toxicity of chemicals in the infant diet, Members had agreed at the COT meeting in February 2012 there was a need for evaluation of persistent organic pollutants that had been included in the Stockholm convention since 2009. An initial paper on α-, β- and γ-hexachlorocyclohexane (HCH) (TOX/2013/04) had been discussed at the COT meeting in February 2013, followed by a first draft statement (TOX/2013/37) in September 2013. This second draft of the statement (TOX/2013/41) reflected the discussion at the meeting in September.

67. Members requested further information on the metabolism of the three isomers, and particularly on γ-HCH. Key points on metabolism should be incorporated in the overall conclusion. Likewise, a number of epidemiological studies would be reviewed in order to provide a more comprehensive summary in the next draft.

68. It was agreed that the section on exposure would require further consideration to address particular points such as the use of arithmetic rather than geometric means when estimating exposures to β-HCH via breast milk. It was noted that infant formula consumed in the UK is mostly imported from Ireland, and therefore data on levels in cows' milk from Ireland needed to be taken into account if available. In addition, Members requested minor editorial amendments throughout the paper.

69. A third draft statement would be provided to members for discussion at the next meeting.

Item 7: Third draft statement on the potential risks from high levels of soya phytoestrogens and soya products in the infant diet – TOX/2013/43

70. No interests were declared.

71. At its meeting in February 2012, the Committee had identified a need for more detailed consideration of possible health risks from soya phytoestrogens in the infant diet. Subsequently, a discussion paper (TOX/2012/39) had been presented to members in December 2012 and draft statements in March 2013 (TOX/2013/11) and September 2013 (TOX/2013/36).

72. A third draft of the statement (TOX/2013/43) was now presented to the Committee. As requested, tables had been included as appendices. Further information and clarification had been provided in relation to metabolic pathways, sources of isoflavone other than soya, and the methodology of relevant animal and epidemiological studies. Additional editorial changes had also been made.

73. Members were content with the overall structure of the statement. It was agreed that epigenetic modifications resulting from dietary exposure to isoflavones should be mentioned. Additionally, in Table 1, values for Relative Binding Affinity (RBA) in comparison with 17β-oestradiol, if not reported by authors, should be calculated. It was noted that soya-based infant formula was the source of highest exposures to isoflavone in infants, and that epidemiological research had suggested that it might be associated with subtle long-term health effects of uncertain clinical significance. It was not possible to set a health-based guidance value for soya

isoflavones in infants. Members concluded that there was no basis for revising the current government advice that soya formula should only be used in exceptional medical circumstances to ensure adequate nutrition.

74. Minor editorial changes were requested and the statement would be sent to the SACN Subgroup on Maternal and Child Nutrition) for comments and subsequently finalised by Chair's action. A lay summary would be drafted and circulated for comment.

Item 8: Presentation on the adequacy of testing methods for juveniles by Professor Aldert Piersma, National Institute for Public Health and the Environment RIVM, The Netherlands

75. In the 2012 and 2013 COT discussions on horizon scanning, recent research on the assessment of developmental immunotoxicity had been noted, and it had been agreed to look at this topic in more detail. No new guidance on immunotoxicity testing per se had been issued. However, Members had been interested in recent review articles about juvenile animal testing, which included assessment of immunotoxicity, and had suggested that the review should be broadened to encompass the concept of juveniles as a sensitive group more generally. Professor Aldert Piersma had been invited to give a presentation on the topic.

76. The presentation provided an overview of current knowledge in the area, and included description of relevant tests available in the current Organisation for Economic Cooperation and Development (OECD) test guideline 443 (extended one-generation reproductive toxicity study). It then focussed on explanations for findings on developmental immunotoxicity that had been obtained by Professor Piersma and his colleagues, using various exposure designs, and the observation that effects occurred at lower doses when exposure commenced in the pups post-natally than when the dams were exposed pre-mating.

77. The Chairman invited a discussion on the presentation. The Committee noted that the inclusion of immune end points in current tests was particularly important for assessment of immune status in juvenile animals, as it is not possible to extrapolate from end points for adult animals in 28- or 90-day toxicity studies. The significance of changes in some immune markers for hazard assessment needed further consideration.

78. A Member questioned whether new technologies such as toxicogenomics and investigation of adverse outcome pathways could be incorporated into study design. This was under consideration by OECD and was at a more advanced stage with respect to the assessment of sensitisation than for other endpoints.

79. The Committee agreed that it was currently not possible to know if the observed changes in immune markers under different exposure scenarios were specific to certain chemicals or occurred as a generalised response. Testing with a wider spectrum of compounds was needed to gain further insight into the specificity of the observed response in the test species and its relevance to adult animals.

80. The Committee concluded that in absence of a dose-response relationship and a mechanism, the reported experimental findings on immune parameters following chemical challenge should be regarded as preliminary, particularly as the link to human disease was not obvious. The implications of the experimental findings in juveniles when dosing commenced post-natally would require further consideration when developing drugs specifically targeted to children.

81. The Chairman thanked Professor Piersma for his valuable presentation and discussion.

Item 9: Assessment of the adequacy of the 10-fold uncertainty factor to allow for interspecies variation in developmental toxicity – TOX/2013/42

82. Due to a lack of time this item was not discussed but would be presented at the next meeting.

Item 10: FSA funded research: T01054 Determination of the symptoms of aspartame in subjects who have reported symptoms in the past compared to controls: a pilot double blind placebo crossover study (RESERVED BUSINESS) – TOX/2013/39

83. No interests were declared

84. This item was discussed as reserved business pending publication of the research.

Item 11: Any other business

92. No other business was raised

Item 12: Date of next meeting

93. The next meeting was scheduled to take place on Tuesday 10th December 2013 in Conference Rooms 4 & 5, Aviation House, 125 Kingsway, London WC2 6NH.