TOX/MIN/2014/05

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

Minutes of the meeting held on Tuesday, 28th October 2014 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 R Harrison Prof B Houston Prof B Lake Prof I Morris Dr N Plant Prof R Smith 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 Hedley Dr L Kent Dr M Kurzawa-Zegota Mr B Maycock 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 David Basketter	DABMEB Consultancy Ltd	Item 4
Officials:	Dr Sharon Broby Mr Robin Clifford Dr Halina Garavini Dr Lesley Hetherington	PHE FSA – Senior Statistical Officer Imperial College Department for	 Item 8

	Professor Guy Poppy	Environment, Food and Rural Affairs (DEFRA) FSA Chief Scientific Adviser	Items 5-12
Assessors:	Professor Tim Gant Sally Thomas	PHE Health and Safety Executive (HSE)	
External Observers:	Dr Meera Cush	Delphic HSE solutions Ltd	

Contents

Announcements

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

2. The Chairman announced that Professor Guy Poppy, the FSA Chief Scientific Adviser, was expected to attend for part of the meeting.

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 members Professor David Harrison and Dr Caroline Harris. No written comments were received. Apologies were also received from assessors Sam Fletcher (Veterinary Medicines Directorate) and Michaela Benton (HSE), who was represented by Sally Thomas at the meeting.

Item 2: Draft minutes of the meeting held on 2nd September 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. Para 8: The Hansard record of the statement by Baroness Kramer (Minister of State for Transport) from a House of Lords debate in March 2014 on aircraft cabin air was read. Members agreed that the record did not adequately reflect the COT's views and therefore the Chair would write to the Permanent Secretary at the Department for Transport, copied to Sir Mark Walport (Chief Scientific Adviser to HM Government), expressing the Committee's concerns, and asking that where possible, future briefings for Ministers be checked with the Committee's Secretariat.

7. Para 9: The Chair reported that he had presented the COT's consideration of cabin air and its findings at an Aviation Health Conference on 23rd September in Paris. He said that there had been a misunderstanding of the COT's views amongst some external stakeholders. His presentation on the COT's position was therefore very useful, and conference attendees had appreciated the COT's contribution.

8. Para 11: The paper on aspartame research was expected to be published in the journal PLOS ONE soon. The final report of the study would then be published on the FSA website.

9. Para 12: Members discussed the proposal to produce guidance on the COT's approach to assessing the quality of epidemiological research and synthesising the evidence that it generated. It was noted that various bodies were working on similar initiatives. These included: a working group of the FSA's General Advisory Committee on Science (GACS), which was looking at the use of scientific evidence more generally, and the European Food Safety Authority (EFSA), which was developing guidance on balance of evidence. An expert workshop on "Implementing systematic review techniques in chemical risk assessments: challenges and opportunities" would be held on 18th November 2014 at the Royal Society of Chemistry, and would be attended by the COT chair and Scientific Secretary. DEFRA's Hazardous Substances Advisory Committee had produced a document on evaluation of risks from chemicals. In addition, the Chartered Institute of Environmental Health, the United States Environmental Protection Agency, and the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) had pursued initiatives in this area. Members agreed that it would be useful to set out how the COT looks at evidence, in the light of guidance from other groups, since the COT process currently, although robust, was not documented. It was agreed that a COT Member would lead a small working group of experts, including epidemiologists from the COC, to undertake this task. Administrative support would be provided by the FSA Secretariat. The objective would be to produce a simple document explaining the COT's approach, which would draw on what other groups were doing, including the COC. It was agreed that the guidance would focus on epidemiology to start with, and a decision would then be made on whether to extend it to include the assessment of toxicological evidence.

10. Para 13: An update on the evaluation of the risks and benefits associated with consumption of Lactobacillus rhamnosus GG as a component of fully hydrolysed formula was expected at the December COT meeting.

11. Para 14: A draft paper on interspecies variation in developmental toxicity was being prepared and was expected to be ready for the December meeting.

12. Para 16: The draft statement on soy phytoestrogens and thyroid status was expected to be on the agenda of the December COT meeting.

Item 4: Consultation of the European Food Safety Authority on a Draft Scientific Opinion on Acrylamide in Food

13. There would be an EFSA stakeholder meeting on 10th December. It was likely that a COT member would be invited to attend the meeting.

Item 4: Recommendations of the Bystander Risk Assessment Working Group report concerning skin sensitisation from exposure to pesticides – TOX/2014/30

14. No Members declared interests. Dr David Basketter (DABMEB Consultancy Ltd) was in attendance as an invited expert to advise the Committee. In addition, written comments had been received from Professor Ian Kimber (Manchester University) and circulated to Members.

15. In 2012 the COT and the Advisory Committee on Pesticides (ACP) had published the report of a joint Bystander Risk Assessment Working Group (BRAWG) on the methods used in regulatory assessment of potential health risks to bystanders and residents from the application of pesticides. The BRAWG had reviewed current approaches to modelling exposures of bystanders and residents, and noted a concern that some individuals might become sensitised to pesticides. The working group had been concerned that risk factors for dermal sensitisation were not well understood, and that further work was needed to characterise and quantify the potential of pesticide formulations to induce skin sensitisation in humans.

16. The BRAWG report had made several recommendations regarding skin sensitisation. These included: conducting research on the extent to which current or new formulations may change the ability of chemicals to act as sensitisers; further work on characterising the potency of formulations using the Local Lymph Node Assay (LLNA), and on clarifying the relationship between potency estimates and human risk; and work on the influence of co-formulants on sensitisation. The Government had accepted the recommendations of the BRAWG report and had asked for the COT's views on how they might be taken forward.

17. The mouse LLNA was now the main test used to determine whether a chemical might be a skin sensitiser. Recent EU regulations required that data to support approvals for plant protection products must include information on the potential of active substances and formulations to cause sensitisation, and that the LLNA was the test to be used. A key advantage of the LLNA was that it gave a quantitative estimate of the relative potency of sensitisers: Estimated Concentration 3 (EC3) values, often expressed as a percentage, gave an indication of the amount of sensitiser needed to induce a sensitisation response, and made it possible to discriminate between strong and weak sensitisers.

18. The Committee understood that if a pesticide active substance was classed as a sensitiser, but was diluted to less than 1% in a product, then the product was not considered to be a sensitiser. On the other hand, if the concentration was more than 1%, the product would also be classified as a sensitiser. [Post meeting note: BRAWG had concluded that this approach needed to be supported by empirical data, to counter concerns that had been expressed in a report by the Royal Commission on Environmental Pollution on bystanders and pesticide exposure]. A product that was classed as a sensitiser could not be approved for non-professional use, but it might be approved for use by professional operators, with a specification that appropriate

personal protective equipment must be used. Some pesticides, for example captan, were known to cause skin sensitisation in humans.

19. The Committee asked whether there had been any documented cases of skin sensitisation in operators caused by pesticide products that had not been labelled as sensitisers, and whether there had been any documented cases at all of skin sensitisation in re-entry workers, bystanders, residents or non-professional pesticide users. The Health and Safety Executive (HSE) Chemicals Regulation Directorate (CRD) would be asked to check. Dr Basketter advised that occupational allergic contact dermatitis caused by pesticides was extremely rare and that he was not aware of any cases in bystanders, residents or non-professional users.

20. Members noted wider public concerns about bystander and residential exposure to pesticides, and queried the focus on skin sensitisation. It was explained that skin sensitisation was a particular area of uncertainty identified in the BRAWG report, and on which the COT had been asked for advice. One Member, who had been part of the Bystander and Resident Working Group, explained that the level of uncertainty around skin sensitisation had been the greatest concern of the Group. The ACP would be providing advice on some other matters raised in the BRAWG report.

21. Although as part of the regulatory risk assessment for pesticides, models were used to estimate the potential exposure of bystanders and residents, there had been a lack of empirical data on such exposures. However, results would shortly be available from a biomonitoring study of residents.

22. A member queried the emphasis on the LLNA rather than in vitro methods, noting that while the latter were not fully quantitative, they might perhaps be used to rank potency. However, they could not be used to test formulations, and there would be a need to take into account factors such as skin penetration. Dr Basketter advised that draft OECD guidelines had been prepared on two alternative methods of assessment, and that a third was in preparation. These were likely to be combined to give a dichotomous hazard classification, and there were ideas on how the methods might be developed further to assess potency. However, he did not foresee their practical application in assessment of potency in the near future.

23. Dose per unit area of skin was the metric most relevant to dermal sensitisation, although Dr Basketter advised that the relationship to this measure weakened when only very small areas of skin, less than a few mm in diameter (e.g. from minor splashes), were exposed. Exposure of such small areas was insufficient to induce sensitisation. The duration of exposure and repetition of exposures also influenced responses. If a chemical was immediately washed off the skin, risk would be determined by the remaining residue.

24. Regarding validation of estimates of potency using the LLNA, Dr Basketter advised that a study had classified 131 chemicals into six grades of potency, based on human experimentation, and compared the rankings with results from the LLNA. The study had found that the LLNA could be benchmarked against human potency. The chemicals considered were mostly ingredients of cosmetics rather than pesticides, but provided the relevant chemistry was represented, it would be reasonable to extrapolate the findings to other chemicals. The paper would be provided to the group.

25. Dr Basketter advised that the LLNA had been validated a number of years ago, and found to have good sensitivity and specificity; he would provide a reference to the paper.

26. Members agreed that it might be useful to conduct a study using the LLNA to compare the sensitising potency of active substances with that of different formulations containing them. However, the information obtained would need to be of sufficient value to justify the use of laboratory animals that the research would entail.

27. Dr Basketter advised that use of different vehicles appeared to have a relatively limited effect on the potency of a substance: at most one order of magnitude, and more commonly, 3-4 fold. However, he was unsure how well the vehicles that had been tested would represent the chemicals in pesticide formulations. He also advised that available data did not indicate a way by which the effect of co-formulants on the sensitising potency of a substance could be predicted from their chemical properties. While a substance which enhanced skin penetration might often be expected to increase sensitising potency, it might sometimes reduce it by causing the exposure of the skin to be more transient. Dr Basketter advised that studies could be performed using the same active substance and varying the vehicle. The Committee considered that such research would be worth conducting, although not necessarily for pesticides. Whether it was worth focusing on pesticides would depend on the frequency of any pesticide-related skin sensitisation in relation to products that were not currently classed as sensitisers.

28. The Committee concluded that further work to characterise the relative sensitising potency of active substances was not necessary if using the LLNA.

29. The Committee concluded that there was no need to develop a more detailed classification of preparations based on the concentrations and sensitising potency of their ingredients, unless there was evidence of sensitisation in re-entry workers, bystanders, residents or non-professional pesticide users. If there was no evidence that such sensitisation occurred then it could be concluded that the current approach to risk assessment was adequate to protect bystanders and residents. It was noted that Professor Kimber considered the 1% trigger for classification of formulations as

sensitisers to be reasonable. If cases of skin sensitisation were shown to have occurred in re-entry workers, bystanders, residents or non-professional pesticide users then the Committee would need to reconsider this.

30. Members considered research that had been done on modelling of skin sensitisation, and noted that modelling approaches were not yet sufficiently developed for application in regulatory risk assessment. They concluded that unless there was evidence of skin sensitisation in bystanders or residents, further work to develop such methods was not a priority for pesticides, although they might be useful for other categories of chemical. Dr Basketter noted that there were a large number of ongoing projects related to cosmetics.

31. The Chairman thanked Dr Basketter for his advice.

Item 5: Scoping paper on the potential risks from polybrominated biphenyls (PBBs) in the infant diet – TOX/2014/31

32. No interests were declared.

33. In support of a review by the Scientific Advisory Committee on Nutrition (SACN) of the 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 polybrominated biphenyls (PBBs), should be considered as part of that body of work.

34. The Committee had previously produced statements in 2006, concerning PBBs in fish and shellfish, and in 2010, in relation to risk assessment for mixed halogenated dioxins and biphenyls. In addition, there had been a review of PBBs by the International Program on Chemical Safety (IPCS) of the World Health Organization (WHO) in 1994, and an evaluation of PBBs in food published by the EFSA in 2012, while the International Agency for Research on Cancer (IARC) was due to publish a monograph in the near future up-grading PBBs to Class 2A, "probably carcinogenic for humans". The Committee considered a scoping paper, TOX/2014/31, which provided information from the previous reviews, summarised findings from relevant toxicokinetic, toxicological and epidemiological studies that had been published since the 2012 EFSA evaluation, and presented estimates of the exposures of infants to PBBs from breast milk, food and non-dietary sources.

35. With regard to the toxicity and mode of action (MOA) of PBBs, the Committee agreed that planar PBBs were likely to be of higher concern than the non-planar congeners. PBBs would be expected to have a MOA similar to polychlorinated biphenyls (PCBs), whereby the effects of planar molecules were mediated via the Ah

receptor and occurred at exposure levels lower than those of non-planar molecules, which were likely to be ligands for the pregnane X receptor (PXR) and constitutive androstane receptor (CAR), the latter being of questionable relevance to human toxicity. Moreover, the potency of effects mediated by the Ah receptor was likely to be less than that of the corresponding PCB congeners. Thus, the Committee concluded that the WHO toxicity equivalency factors (WHO-TEFs) allocated to the planar PCBs could conservatively be applied to the planar PBBs. For the non-planar molecules, the tumour incidence in a National Toxicology Programme (NTP) carcinogenicity study, although possibly CAR-related, could be used to provide a reference point for the purposes of risk characterisation.

36. Epidemiological data from a cohort of people who had been exposed to unusually high levels of PBBs in an incident in Michigan, USA, were considered to be more robust than those for some of the other BFRs, but were not adequate to provide a reference point for use in risk characterisation. It was noted that the epidemiological studies indicated possible effects on the thyroid gland and on lymphocytes. However, from their toxicology, immunotoxicity would not be expected to be a main effect of PBBs.

37. For the limited range of PBBs that had been investigated, levels measured in food and the environment had frequently been below the limit of detection (LOD). The Committee agreed that it would be difficult to perform a meaningful risk assessment when only a small proportion of the total number of congeners had been analysed and the vast majority of results were below the LOD, and that it would not be realistic to add multiple LODs in an upper bound approach. Further information was needed on the rationale for selection of the congeners that had been analysed. For example, did the choice depend on their prevalence in the technical mixtures of PBBs that had been used commercially, the profile of PCBs that was expected to occur in the environment, or the technical feasibility of analytical methods?

38. The Committee noted that further research on the toxicity of PBBs was not likely to be a high priority since their use is now restricted, and it was expected that exposures would decrease over time. However, it would be useful to obtain more data on levels of the planar congeners in foods, and taking into account their relative potency (as estimated from those of the corresponding PCBs), to establish whether any important congeners had been omitted from earlier surveys. A Member informed the Committee that on-going biomonitoring studies included analysis of PBBs.

39. The Committee concluded that the available data were not sufficient to support a meaningful risk assessment, and asked that a position paper be drafted, highlighting the key gaps in information. This would be tabled for discussion at a future COT meeting.

Item 6: Second draft statement on the potential risks from polybrominated diphenyl ethers (PBDEs) in the infant diet – TOX/2014/32

40. No interests were declared.

41. Within the context of toxicity of chemicals in the infant diet, Members had agreed at the COT meeting in February 2012 that there was a need for evaluation of brominated flame retardants (BFRs). A scoping paper on polybrominated diphenyl ethers (PBDEs) in the infant diet (TOX/2014/19) had been discussed at the COT meeting in May 2014, followed by a first draft statement (TOX/2014/27) in September 2014. The Committee now considered a second draft of the statement (TOX/2014/32), which reflected the discussion at the meeting in September.

42. Additional information had been included on extrapolation from a single experimental administration in rats to a repeated daily dose in humans which would be expected to produce a similar body burden at steady state. Reservations were again expressed about this approach to derivation of reference points. The elimination half-life of BDE-209 in rodents and humans was reported in the statement as not significantly different. Therefore the benchmark dose lower confidence 10% ($BMDL_{10}$) value had been applied without adjustment for body burden. The lack of adjustment for accumulation with repeated exposure and its effect on margin of exposure (MOE) calculations were questioned.

43. A Member confirmed that the toxicokinetic model used in the EFSA opinion on PBDEs was appropriate for estimating the levels of chronic dietary intake in humans that would result in the body burdens associated with the $BMDL_{10}$s for neurodevelopmental effects in mice for BDE-47, BDE-99 and BDE-153.

44. The Committee suggested some editorial changes and clarifications to the draft statement. Inclusion of information on exposures from air was also suggested.

45. The draft statement would be revised in line with the comments made and a tracked version would be sent to COT Members. It was expected then to be cleared by Chairman's action.

Item 7: Second draft statement on adverse effects of high levels of vitamin D – TOX/2014/33

46. No interests were declared.

47. 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 second draft of a COT statement was now presented to the Committee in paper TOX/2014/33.

48. Members made a number of suggestions and comments on the overall structure and content of the draft statement. A Member noted that the low vitamin D intakes indicated in the National Diet and Nutrition Survey (NDNS) were potentially an artefact of missing data on the vitamin D content of some foods. This needed to be checked, and if appropriate, mentioned in the statement.

49. SACN had asked for a brief document to attach to their report, and it was envisaged that this would be based on the final summary section of the draft statement (paragraph 134 onwards), although the full statement would also be provided to SACN and published on the COT website in the usual way.

50. The draft statement would be revised in line with the Committee's comments. Any changes would be agreed by correspondence and the statement would only return for discussion at a future COT meeting if specific concerns were raised by the Committee.

51. The recommended changes to the summary section would be finalised urgently by Chairman's action as it was to be included in a draft SACN report ahead of their meeting on 5th November.

Item 8: Second draft statement on domoic acid in King Scallops (pecten maximus) – TOX/2014/34

52. No interests were declared.

53. At its March and May meetings, the COT had considered the evidence that was available to support shucking (removal of the non-edible parts) as a scientifically robust and effective method for managing the health risks associated with Amnesic Shellfish Poison (ASP) toxins in King Scallops. This required analysis of data on the distribution of domoic acid (DA) in different tissues from whole King Scallops to identify of an upper level for DA in whole scallops at which consumption of a large portion of the shucked product (i.e. the edible parts) would not result in intakes that exceeded the acute reference dose of 30 µg/kg bodyweight established by the EFSA in 2009. It was anticipated that such a level would provide a basis for future risk management decisions. A first draft statement incorporating the analyses that had been performed had been considered in September 2014. Subsequently, further independent statistical advice had been sought about ways of addressing the uncertainties associated with the data, and a new section on this, with two additional annexes (Annex 3 and 4), had been added to the second draft statement.

54. Members discussed the second draft statement and suggested some minor editorial changes. It was agreed that the statement should be finalised by Chairman's action. A lay summary would be drafted and circulated for comment.

Item 9: First draft statement on the potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet – TOX/2014/35

55. Due to lack of time, this item was carried over to the next meeting on 9th December 2014.

Item 10: Paper for information: COT response to the EFSA Consultation on a draft scientific opinion on the risks to public health related to the presence of acrylamide in food – TOX/2014/36

56. This paper was provided for information only.

Item 11: Paper for information: FSA Scientific Advisory Committees (SACs) update – TOX/2014/37

57. This paper was provided for information only.

Item 12: Any other business

58. A COT symposium was to be held on 18th March 2015 discussing the effects of obesity on toxicokinetics. The aim would be to provide a basis for interpreting FSA-funded research on biomonitoring of persistent organic pollutants in obese subjects, and to consider more generic implications for the risk assessment process. Members were provided with a list of possible topics for presentations and speakers, and were asked for their opinions on the proposals. They noted that such a symposium was timely, and suggested a number of modifications to the planned programme. The draft programme would be developed further with Members' help and would be tabled at the next COT meeting on 9th December 2014.

59. There was no other business.

Item 13: Date of next meeting

60. Date of next meeting – Tuesday 9th December 2014, Conference Rooms 4 & 5, Aviation House, 125 Kingsway, London. WC2B 6NH.