TOX/MIN/2015/05

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

Minutes of the meeting held on Tuesday, 27th October 2015 in Aviation House, London.

Present

Chairman:	Professor A Boobis		
Members:	Mr D Bodey		
	Prof J Cade		
	Dr J Coulson		
	Dr R Crevel		
	Dr M Graham		
	Dr A Hansell		
	Prof D Harrison		
	Prof B Lake		
	Prof I Morris		
	Dr N Plant		
	Prof R Smith		
	Dr J Thompson		
Food Standards Agency (FSA) Secretariat:	Ms R Acheampong		
	Ms L Buckley		
	Ms H Gbormittah		
	Dr D Hedley		
	Dr L Kent		
	Ms F Hill		
	Mr B Maycock		
	Ms C Potter		
	Mr A Sbaiti		
	Dr J Shavila		
Public Health England (PHE) Secretariat:	Ms F Pollitt	Scientific Secretary	
	Dr H Garavini	Imperial College London	
Invited Experts and Contractors:	Prof Peter Aggett	Sub-group on Maternal and Child Nutrition of the Scientific Advisory Committee on Nutrition	
	Dr Robert Boyle	Imperial College London	Item 6
	Prof Ian Kimber	University of Manchester	Item 6
	Dr Paul Turner	Imperial College London	Item 6

Officials:	Ms Elaine Boylan	PHE	Item 6
	Ms Elizabeth Kendall	FSA, Food Allergy Branch	Item 6
Assessors:	Prof Tim Gant	PHE	
	Mr Scott Samuels	Health & Safety Executive (HSE)	
Observers:			

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Announcements

1. The Chairman, Professor Boobis, welcomed Members and Assessors to the meeting.

2. The Chairman particularly welcomed Professor Peter Aggett, a Member of the Scientific Advisory Committee on Nutrition's (SACN) Sub-group on Maternal and Child Nutrition (SMCN).

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 Professors Roy Harrison, Brian Houston and Faith Williams and Drs Roger Brimblecombe and Caroline Harris. Written comments had been submitted by one Member. Apologies were also received from Dr Diane Benford (FSA Scientific Secretary).

Item 2: Draft minutes of the meeting held on 8th September 2015 – TOX/MIN/2015/04

5. The minutes were agreed subject to a minor amendment in the apologies for absence.

Item 3: Matters arising

Item 3: Matters arising from previous meetings

6. Para 7: The second meeting of the joint COT/Committee on Carcinogenicity (COC) subgroup would be held on 29th October and would review the approaches to epidemiological evidence used by the COT and COC. Members were provided with an update explaining that the subgroup were aiming to produce a high level guidance document by the end of the 3rd meeting. This document would be discussed in more detail at the upcoming meeting on the 29th October along with scoring systems and systematic reviews of epidemiological evidence. This was an area of interest internationally, particularly the development of guidance on observational studies.

7. Para 8: The COT Chair had met with the Chair and Deputy Chair of the SACN as well as members of each of the two Secretariats to discuss how to take forward the work on potassium-based replacements for sodium chloride and sodium-based

additives. The two Committees had separately considered the risks and the benefits of potassium-based replacements. It had been agreed that a joint subgroup would be set up in order to take a risk–benefit approach to the two strands of work so that a joint outcome could be agreed and presented to risk managers. The two Secretariats would be discussing draft terms of reference to be considered by the committees in the near future (for the COT this would be at the December COT meeting).

8. Para 9: The finalised statement on the effects of soya consumption on thyroid status would be published once the unpublished data were in the public domain.

9. Para 10: Some of the information that had been requested from the Specialist Cheesemakers' Association (SCA) and the Provision Trade Federation (PTF) had been received, and some more was expected soon. It was anticipated that all of this information would be brought to the December COT meeting.

Item 4: EFSA consultation on draft guidance document on uncertainty in scientific assessment

10. The Committee's response to the European Food Safety Authority's (EFSA) consultation on a draft guidance document on uncertainty in scientific assessment had been submitted. The response was tabled at the meeting and was on the agenda under Item 8: Papers for information.

Item 6: Review of risks arising from the infant diet and the development of atopic and autoimmune disease: Systematic review C Part I

11. A draft Statement had been prepared for consideration and would be discussed at agenda item 4.

12. As an additional matter arising, the consultation on the SACN's report on vitamin D, which incorporated the COT's advice on the toxicity of high intakes, had closed on 23rd September. A total of 44 responses had been received and these would be discussed at the next SACN Vitamin D Working Group meeting on 12th November. The responses had been examined by the COT Secretariat; the vast majority related to the nutritional recommendations. There had been a number of points that may be of interest to the COT, these would be discussed at the December COT meeting, once the SACN Vitamin D Working Group had met.

13. Members were reminded that the six scientific advisory committees for which the FSA was the sole or lead sponsor, including the COT, were being reviewed together. In addition, the Committee on Mutagenicity (COM) was undergoing a triennial review by the Department of Health, which was its lead sponsor. The review of the COM had produced a provisional report which had been seen by the COM and was waiting to be accepted by the Department of Health. The review of the COT was

ongoing. The Chair had already been interviewed, and stated that it had involved more a general discussion about the role of such committees overall rather than the specifics of how they operate. The current aim was to complete the review of the COT by the end of the year, for discussion and early adoption next year. The reviewers intended to interview other COT Members in the near future.

14. No other matters were raised.

Item 4: Follow-up paper on the recommendations of the Bystander Risk Assessment Working Group (BRAWG) report concerning skin sensitisation from exposure to pesticides – TOX/2015/30

15. In 2012 the COT and the Advisory Committee on Pesticides (ACP) published the report of a joint Bystander Risk Assessment Working Group (BRAWG) on methods used in regulatory assessments of potential health risks to residents and bystanders from the application of pesticides. The BRAWG report noted a concern that some individuals might become sensitised to pesticides and recommended that, as risk factors for dermal sensitisation were not well understood, further consideration was needed to justify the default assumptions used when characterising and quantifying the potential of pesticide formulations to induce skin sensitisation in humans. This matter was considered by the COT in October 2014.

16. The COT had discussed the current methods used to determine whether a chemical was a skin sensitiser, and particularly considered the local lymph node assay (LLNA), which was now the test required by European Union regulations to assess the skin sensitisation potential of pesticide active substances and formulations. An invited expert had been present at the October 2014 meeting who had agreed to provide the COT with a number of relevant papers. These papers were now provided to the Committee and covered the validation of the LLNA, comparison of potency in the LLNA with human data, the collection of a database of human skin sensitisers, and the impact of vehicle on the results of the LLNA. The COT had also asked for information from the Health and Safety Executive's (HSE) Chemicals Regulation Directorate (CRD) on whether there had been any documented cases of skin sensitisation in operators caused by pesticide products that were not labelled as sensitisers, or skin sensitisation in bystanders, residents or non-professional pesticide users. The CRD response was now provided to the COT, including information from two reporting schemes on pesticide exposure monitoring in the UK.

17. The Committee agreed that the key factors to consider were whether there was evidence that following dilution of a skin sensitiser by 1/100 in would no longer cause skin sensitisation and/or whether there was sufficient evidence from surveillance programmes that the risk was low or minimal.

18. Members noted that the submitted papers reported work funded by cosmetics and personal care product industries, although that in itself did not invalidate the scientific soundness of the findings; indeed, the LLNA was an Organisation for Economic Co-operation and Development (OECD) validated and accepted test, the expertise of one of the authors in skin sensititation was world-renowned, and Members could identify no significant flaws in the papers.

19. Members observed that Basketter *et al*. (Contact Dermatitis 53, 260-7; 2005) had observed a linear relationship between results in the LLNA and human skin sensitisation data, albeit with some variability. However, while this was adequate for the chemicals considered, these did not include any pesticides. Members noted from the results of Jowsey *et al*. (Cutaneous and Ocular Toxicology 27, 67-75; 2008) that estimation of the EC3 (Effective Concentration 3, the amount of a chemical needed to induce a stimulation index of 3-fold) from the LLNA may vary more than 10-fold depending on the vehicle. This would potentially erode the 100-fold margin allowed by the 1/100 dilution. However, the HSE Assessor confirmed that not only were pesticide active ingredients tested in the LLNA but so were the formulated pesticide products.

20. The Committee noted that there was no specific evidence to support a dilution factor of 100 as being adequate to ensure that a skin sensitiser would no longer have a sensitising effect.

21. The Committee discussed whether it should distinguish between chemicals that were also irritants and those which were primarily sensitisers. However, irritation was often a major component of sensitisation. Residents and bystanders should not be exposed to irritant concentrations of pesticides.

22. The data provided by the CRD on the results of pesticide exposure monitoring schemes provided very little evidence of sensitisation in people exposed to pesticides. The Committee was relatively reassured by this, although mild cases would be expected to be more common than severe cases and these would be less likely to be picked up by the schemes. One Member offered to provide the Committee with a paper reporting on 10 years of data from the National Poisons Information Service (NPIS) on pesticide exposures. This reported on all pesticide-related incidents. Because there was no direct contact with patients there was no long term follow-up and thus skin reactions may be reported but there would not be information on whether these were skin sensitisation.

23. The data from the CRD included reports of effects on skin in workers following exposure to the relatively new active substance pinoxaden, which was a potent sensitiser in the LLNA and a skin irritant, though it was not clear whether these effects were due to sensitisation or irritation. There was also a report from the NPIS programme of wheeze, facial swelling and swelling of the throat, though no skin

reactions, in a group of cadets who had crawled through a field that had been treated with pinoxaden. It was queried whether this was consistent with the regulatory processes being adequate as, if pinoxaden had been flagged up as a skin irritant and sensitiser, risk management options such as warning signs around sprayed fields might have been indicated. On the other hand, the level of exposure from crawling through a recently sprayed field would have been high relative to that in most bystanders and residents. Members considered that the possibility of more intensive, targeted monitoring of pinoxaden should be considered.

24. Summarising, the Committee agreed that there was no specific evidence demonstrating that following dilution of a skin sensitiser by 1/100 it would no longer cause skin sensitisation, but it was reassured by the absence of reports from available pesticide exposure monitoring schemes. The Committee recommended further and expanded monitoring for skin sensitisation, particularly of new pesticide active substances suspected of causing sensitisation.

Item 5: Presentation on the microbiome by Prof. Tim Gant (Public Health England)

25. No interests were declared.

26. Prof. Tim Gant of PHE gave a presentation about the microbiome. Members had requested this presentation during the discussion of horizon scanning at the February 2015 meeting. Prof. Gant had been exploring the emerging toxicity issue of the effect of an individual's microbiome on chemical toxicity on behalf of the Health and Environmental Sciences Institute (ILSI HESI), and the presentation was based on work presented at the International Human Microbiome Consortium meeting that took place in March 2015.

27. The presentation provided some background information about the microbiome using the gut microbiome as an exemplar and how a variety of genetic and environmental factors (e.g. age, diet, ethnicity and disease state) can alter it. The presentation also gave some examples of how the microbiome might impact toxicological responses, and discussed how the aforementioned genetic and environmental factors could result in altered susceptibility to chemicals via the microbiome. Members were asked to comment on the subject and discuss whether the microbiome was a topic that the Committee should consider further.

28. Member recognised that while there was a plethora of observational data available regarding the impact of certain genetic and environmental factors on the microbiome, there was currently a paucity of data on the functional consequences of these effects. Members noted that there were significant differences between human

and animal microbiomes, and that these differences could impact on the way *in vivo* toxicology studies were interpreted during future risk assessments.

29. Members discussed the overall stability of the microbiome, and considered the potential impact that various changes to an individual's environment (e.g. treatment with antibiotics or cohabitation with a partner) could have on the microbiome and thus their response to future chemical exposures. Members also discussed the rate at which such environmental changes could begin to impact the microbiome (e.g. how soon after cohabitation began would the microbiome adapt), and the length of time for which they might impact it (e.g. how long does it take for the microbiome to recover after dietary-induced change).

30. Members also noted that a key point when considering changes to the microbiome, and the impact of these changes on toxicological responses, was not the change in the diversity of the microbiome but rather the change in its overall function. It was possible that while one microbe may replace another, they may have the same biological capabilities and output, and therefore the change may have no impact on toxicological response.

31. Overall, Members considered the microbiome to be of potential toxicological relevance and would like to consider further information on the microbiome and the impact of genetic and environmental factors such as ethnicity, diet and disease state in the future, once the functional consequences of these factors were better understood.

Item 6: Review of risks arising from the infant diet and the development of atopic and autoimmune disease: Systemic review C part I – the role of hydrolysed cows' milk formulae in influencing the development of atopic and autoimmune disease: First draft statement – TOX/2015/31

32. The Chair had previously declared a non-personal, non-specific interest in this item as he was employed at the same institution as the contractors who had performed the review. This had not been considered a conflict and Members were content for him to chair this item.

33. Professor Ian Kimber and Dr Paul Turner were present to provide the Committee with additional expertise on allergic and atopic disease. The lead contractor who prepared the review, Dr Robert Boyle from Imperial College London, was also present. Prior to the meeting, Dr Turner had provided details of his potential conflicts of interest.

34. Dr Turner's declarations of interest included that he worked within the same group as the contractors at Imperial, but had had no involvement in the work on the

review, and that he had an academic “sponsor” who had conducted work that had been funded by infant formula manufacturers, but had made no contributions to this work. In addition to this, Dr Turner had academic links with researchers at the University of Utrecht who were part-funded by Nutricia Research, but had not received any funding, gifts or products as a result of this collaboration, and he had declared that Nutricia Research were the industry partner for the fellowship held by a post-doctorate student that he supervised, but that he had had no contact with Nutricia through this work.

35. Finally, Dr Turner had declared that he was a co-investigator on a possible National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) submission on formula in cow’s milk allergy. The study would be a multi-centre study and the researchers would possibly accept a supply of formula from milk companies. Dr Turner would not be the co-investigator on the study, which would be conducted as per NIHR guidelines (i.e. the milk companies would have no influence on the study), and would be overseen by an Independent Data/Monitoring Committee to ensure its independence. The Committee considered that Dr Turner’s interests should not exclude him from advising them on clinical aspects of allergic and atopic disease.

36. Imperial Consultants had been commissioned by the FSA to conduct a systematic review of the published scientific literature on infant formulae containing hydrolysed cows’ milk protein, and their ability to influence the risk of infants and young children developing atopic and autoimmune disease. This review had been commissioned in support of the SMCN’s review of UK government recommendations on breastfeeding and the introduction of solid foods in the diet.

37. The Committee had considered this review at their meeting in September 2015. A Statement had been drafted and was considered at the current meeting. Members made a number of requests for changes to the draft Statement. A revised version would be produced for consideration at a future meeting.

Item 7: COT contribution to SACN review of complementary and young child feeding; proposed scope of work for 1-5 year old children – TOX/2015/32

38. No interests were declared.

39. The SACN was undertaking a review of the scientific evidence that underlied the Government’s dietary recommendations for infants and young children. The review would identify new evidence that had emerged since the Government’s current recommendations had been formulated, and would appraise that evidence to determine whether the advice should be revised. The recommendations covered the diet from birth to age five years, but were being considered in two stages, focusing

first on infants aged 0 to 12 months, most of which had been completed, and now on advice for children aged 1 to 5 years. The COT had been asked to review the risks of toxicity from chemicals in the diet as part of the review of the dietary recommendations for these age groups.

40. Paper TOX/2015/32 proposed the scope of the COT evaluations for the 1-5 years age group, and listed a number of chemicals for the Committee's consideration. The Committee was asked to consider whether the various chemicals should be reviewed and, if so, to provide feedback on the depth of review required. The Committee based its recommendations on the level of toxicological concern for the substance in question, how recently the substance had been reviewed by other organisations (such as EFSA or the Joint FAO/WHO Expert Committee on Food Additives (JECFA)), how recently it had been reviewed by the COT and exposure considerations (e.g. availability of new information).

41. Members wished to carry out full reviews of the following chemicals: caffeine, vitamin A, arsenic, cadmium, copper, iodine, nickel, manganese, zinc, perchlorate and chlorate.

42. The Committee requested that exposure assessments be carried out for methylmercury, aluminium, lead, hexaxchlorocyclohexanes (HCHs), endosulfan, pentachlorobenzene and chlordecone, and appended to the 0-12 month infant feeding overarching Statement or individual chemical Statements, depending on the chemical.

43. Exposure assessments should also be carried out, and literature reviews undertaken to capture any new toxicology data since the most recent COT Statements, for bisphenol A, phthalates, soya phytoestrogens, polybrominated diphenyl ethers (PBDEs), perfluorooctane sulfonate (PFOS), polybrominated biphenyls (PBBs), hexabromocyclododecanes (HBCDDs), chromium, acrylamide, furan, polycyclic aromatic hydrocarbons (PAHs), perfluorooctanoic acid (PFOA) and tetrabromobisphenol A (TBBPA).

44. Exposure assessments and toxic equivalency (TEQ) calculations should be undertaken for dioxins and dioxin-like compounds. Members requested that for mycotoxins, an exposure assessment should be undertaken for all those mycotoxins measured in the UK Total Diet Study – Mycotoxin Analysis (samples had been analysed and the data were currently being processed), and from this a decision should be made as to what depth of review was required for each mycotoxin. The data available for tropane alkaloids should be considered and then the depth of review decided.

45. Members noted that pesticides, veterinary medicines and food additives were subject to regulatory risk assessments and risk management. In particular it was

noted that previous evaluations of food additives by the COT and other committees had considered all age groups of the population. However, Members requested that exposure assessments be carried out for commonly used low-calorie sweeteners to ensure that current intakes were within health based guidance values.

46. No further reviews would be required for alcohol, as risks would not be greater for this age group than for infants, or for legacy pesticides, as exposures were declining.

47. An exposure assessment for 0-12 month olds should be carried out for any chemicals for which exposure data had been produced since the COT carried out the 0-12 month infant feeding review of chemicals.

48. The Committee requested that the following additional substances be considered for inclusion: selenium, monochloropropanediols, and trans-fatty acids.

49. Papers would be presented to the Committee for discussion at future meetings.

Item 8: Paper for information: Response to EFSA Draft Guidance Document on Uncertainty in Scientific Assessment – TOX/2015/33

50. This paper was provided for information only.

Item 9: Paper for information: FSA Scientific Advisory Committees (SACs) update – TOX/2015/34

51. This paper was provided for information only.

Item 10: Any other business

52. The Chair explained that he would not be available for the next meeting as he would be travelling to attend a World Health Organization (WHO) meeting. The Deputy Chair would chair the next meeting. No other business was raised.

Item 11: Date of next meeting

53. Date of next meeting – Tuesday 8th December 2015, Conference Rooms 4&5, Aviation House, 125 Kingsway, London, WC2B 6NH.