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

Minutes of the meeting held on Tuesday 6th and 7th February at the Jurys Inn, Birmingham.

Present

Chairman:	Professor Alan Boobis	
COT Members:	Dr Phil Botham (by teleconference on the 7th February only) Ms Jane Case Dr James Coulson Dr Caroline Harris (6th February only) Professor Roy Harrison Professor Brian Lake Ms Juliet Rix Dr John Thompson Professor Faith Williams	
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland Mr B Maycock Dr D Gott Ms F Hill Dr J Shavila Ms R Acheampong Dr D Hedley Ms C Potter Dr B Dörr Ms C Tsoulli Ms H Gbormittah	FSA Scientific Secretary
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Assessors:	Dr Ovnair Sepai	PHE (7th February only)

Other Invited Experts and Contractors:	Prof P Aggett	SMCN
	Sarah Bull	PHE (6th February only)

Contents

Announcements

1. The Chair welcomed Members and other attendees to the meeting.

2. The Chair reminded those attending the meeting to declare any commercial or other interests they might have in any of the agenda items.

Item 1: Apologies for absence

3. Apologies were received from Members Prof. J Cade, Dr R Crevel, Dr J Foster, Dr M Graham, Dr S Judge and Prof. M Wright, and from assessors Michaela Benton (HSE), Tim Gant (PHE) and Ian Martin (Environment Agency).

Item 2: Draft minutes from the meeting held on 13th December 2017 - TOX/MIN/2017/06

4. The Chair stated that his membership of the EFSA CONTAM Panel that agreed the EFSA 2010 Opinion on OTA had not been recorded.

5. No other amendments were noted.

Item 3: Matters arising from the meeting held on 4th July 2017

Item 3: Matters arising from previous meetings

6. Para 8: The statement on potential risks from nickel in the diet of infants aged 0 to 12 months and children aged 1 to 5 years would be published in February 2018.

7. Para 12: The second draft statement on the results of the 2014 survey of metals and other elements in infant foods – TOX/2017/40 would be published in February 2018.

8. Para 10: Draft statement on reformulation of 2-chlorobenzylidine malonate (CS) as an irritant spray. This statement had been further discussed with CAST and the manufacturer, and it had been agreed that the statement could be published as is, with the formulation information. This was also the case for the statement on a reformulation of PAVA discussed earlier in 2017. Both statements were in preparation for publication.

9. Para 11. The second draft statement on potential risks from cadmium in the diet of infants ages 0 to 12 months and children aged 1 to 5 years – TOX/2017/*37* was in the process of being finalised and cleared by Chair's action.

10. Para 13. Heat-not-burn tobacco products – second draft statement. Written evidence from the COT, supported by COC and COM, was submitted to the House of Commons Science and Technology Committee inquiry on e-cigarettes, describing the planned work by COT and also outlining the conclusions on heat-not-burn tobacco products which were also being considered by the inquiry.

11. The COT Chair had been invited to participate in a future oral evidence session focusing on the toxicology of these products. Unfortunately, he was unable to attend the session but Professor David Harrison, COC Chair and former COT member, would be attending instead.

Item 10: Statement on maternal and infant dietary exposures and risk of development of atopic outcomes and autoimmune disease – TOX/2017/50

12. Para 49. The statement had been published and the manuscript by Imperial College London would be published in PLOS Medicine on the 2nd March.

Item 11: Third draft guidance for submission of papers to COT regarding irritant sprays and information required

13. Para 50. This guidance had been amended following the discussions at the December meeting, and had been sent on to CAST. It was expected that this would be sent on for approval by Chair's action soon.

Item 4: First draft statement on ochratoxin A (OTA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2018/01

14. The Chair declared that he was a member of the EFSA CONTAM Panel that agreed the EFSA 2010 Opinion on OTA. No further interests were declared.

15. The Food Standards Agency (FSA) had completed a survey of 36 mycotoxins in the 2014 Total Diet Survey (TDS) – mycotoxins analysis (FSA, to be published). Estimates of dietary exposure had been calculated for each toxin for UK infants and young children aged 4 to 60 months using food consumption data taken from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) and the National Diet and Nutrition Survey (NDNS).

16. A scoping paper (TOX/2017/30) and discussion paper (TOX/2017/45) were presented to the Committee at the July and December 2017 meetings, respectively. This first draft statement (TOX/2018/01) provided additional information on the skewness of the distribution of breastmilk data and updated calculations and risk characterisation for non-exclusively breastfed infants and young children.

17. The Committee discussed the *in vivo* studies used by JECFA and subsequently by EFSA for the establishment of the health based guidance values (HBGVs). The members asked for clarification on the dosing/concentrations of OTA described in the original studies used for the derivation of the HBGVs, as there appeared to be some inconsistency in the way in which these had been reported in the different opinions. The members noted that JECFA used a lowest observed effect level (LOEL), while EFSA used a lowest observed adverse effect (LOAEL), based on the same original studies and asked for clarification in this regard.

18. Members discussed using the highest concentration of OTA in breastmilk in the exposure assessment. The members enquired about including the distribution of the raw data to validate using a concentration which might not be representative.

19. The Committee asked for a final concluding paragraph on other dietary sources of OTA to be included. Members requested some further minor amendments and for a revised version to be circulated to the Committee. Following their agreement, the paper should to be cleared by Chair's action.

Item 5: First draft statement of potential risks from manganese in the diets of infants aged 0-12 months and children aged 1 to 5 years - TOX/2018/02

20. No interests were declared.

21. The COT had been asked to consider the toxicity of chemicals in the infant diet and the diet of young children aged 1-5 years, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. A scoping paper (TOX/2015/32), highlighting some of the chemicals for possible consideration for the diet of young children aged 1-5 years was discussed by the COT in October 2015. Members concluded that a review on the potential risks from manganese in the diet of infants and young children aged 1-5 years should be completed.

22. At their meeting in December 2017, the COT discussed a review of the literature on manganese. Members' comments were used to draft a statement which was the subject of discussion at this meeting.

23. Given the current interest in manganese in the literature and the lack of studies that give a useful comparison of dietary intakes and toxicological effects, the secretariat consider that a publication in the peer-reviewed literature based on the discussion paper and draft statement may be of interest. The discussion paper and draft statement have not yet been placed in the public domain in anticipation of this.

24. Members made a number of suggestions on the statement and a revised draft with track changes will be taken to the next meeting.

Item 6: Review of potential risks from methylmercury in the diets of infants aged 0-12 months and children aged 1 to 5 years - TOX/2018/03

25. No interests were declared.

26. The COT was asked to review the risks of toxicity from chemicals in the diet of infants and young children aged 1-5 years, in support of the review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. Methylmercury was being considered as part of the review. For dietary exposure, total mercury had been included in the FSA's 2014 Total Diet Study (TDS) (FSA, to be published). The COT had commented on total mercury exposure as part of the Infant Metals Survey (FSA, to be published).

27. Details on the derivation of the health based guidance values established by JECFA (2004) and EFSA (2012) were presented in the paper. A literature search on toxicology data following the 2012 review was carried out. This identfiied results from Nutrition Cohort 2 of the Seychelles Child development study, at age 20 months; and updates from the Main Cohort of the Seychelles Child Development Study at age 22 and 24 years as well as the Faroe Island follow up evaluations at age 22 years. Exposure assessment to methylmercury from breast milk had been provided, based on literature data from European populations. Combined with the information on total mercury from the TDS and the Infant Metals Survey, a risk assessment and conclusions were presented.

28. The Committee noted that due to heightened public interest regarding the presence of mercuric compounds in vaccines, a comment should be made in the statement regarding the presence of ethylmercury, which has similar effects to methylmercury, in vaccines for this age group. These should include the latest conclusions of the Royal Colleges and other sources, such as the World Health Organisation (WHO).

29. The Committee discussed the updates on the various neurodevelopmental studies available. They highlighted the complexity of these studies that made them difficult to interpret without the relevant expertise and agreed that, for the scope of this paper, these should be summarised in a simpler manner.

30. A number of amendments to the text were suggested by Members and a revised draft statement would be brought to the March 2018 meeting.

Item 7: First draft statement on the potential risks from copper in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2018/04

31. No interests were declared.

32. The COT had been asked to consider the toxicity of chemicals in the infant diet and the diet of young children aged 1-5 years, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. A scoping paper (TOX/2017/), highlighting the risks of copper in the diet of infants aged 0 – 12 months and young children aged 1-5 years was discussed by the COT in December 2017 and a first draft statement was requested.

33. Members noted that although the first draft stated that domestic hot water contained more dissolved and dispersed copper than the cold supply, no data were given on the amounts present.

34. A number of amendments to the text and tables were suggested by Members.

35. It was agreed that the final paragraph should reflect the advice already given by the Department of Health on the best practice use of domestic water supplies to reduce infants' exposure to copper and other potentially hazardous substances present in water. This paragraph would be reworded and emailed to Members for comment; once agreed, the statement would be finalised by Chair's action.

Item 8: First draft statement of T2-toxin (T2) and HT2-toxin (HT-2) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2018/05

36. The Chairman had been a Member of the EFSA CONTAM panel when the 2011 Opinion was adopted.

37. Mycotoxins were being reviewed as part of the COT's consideration of the risks from chemicals in the diets of infants and young children aged 0-5 years. The FSA had completed a survey of 36 mycotoxins in the 2014 TDS – mycotoxins analysis. The results of the survey included information on the concentrations of HT2 toxin, neosolaniol and T2 toxin in relevant foods. Estimates of dietary exposures had been calculated for each toxin for UK infants and young children aged 4 to 60 months using food consumption data taken from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) and the National Diet and Nutrition Survey (NDNS).

38. A scoping paper (TOX/2017/30), discussion paper (TOX/2017/41) and first draft statement (TOX/2017/47) had been presented to the Committee at the July, September and December 2017 meetings, respectively. This second draft statement (TOX/2018/05) had addressed requests for changes made by the Committee at the December meeting. A model-averaged BMDL analysis of the Acute Reference Dose (ARfD) had also been performed and was presented to Members. This had been possibly due to a recent update in the PROAST software. However, as it was unclear whether this functionality of the PROAST software, had yet been fully validated by EFSA, it was decided that the ARfD established by EFSA in 2017 would be used in the risk assessment but a paragraph included to highlight the ARfD calculated using model averaging.

39. The Committee requested a small number of further modifications and the statement would then be cleared by Chair's action and published shortly.

Item 9: First draft statement from a joint Committee workshop on the use of epigenetics in chemical risk assessment - TOX/2018/06

40. No interests were declared.

41. The field of epigenetics research and the potential role of epigenetic changes in toxicology have been considered previously by COC, COM and COT, and all have recently recommended maintaining a watching brief on developments in their respective Horizon Scanning exercises. To fulfil this brief, a workshop for Members of all three Committees was organised in October 2017 with the aim of considering the overarching question; '*Whether epigenetics should be used in chemical risk assessment'*. The COC had already commented on the draft statement.

42. A small number of changes to the text were suggested by the Committee.

43. The revised statement would be presented to the COM before being finalised.

Item 10: Draft Annual Report – TOX/2018/07

44. Members were asked to comment on the draft COT Annual report. Members were then reminded that they could provide comments to the Secretariat in writing.

45. The Chair reminded Members to update their Declarations of Interest.

Item 11: Update on actions taken subsequent to COT advice. - TOX/2018/08

46. This paper provided an update on actions taken by the FSA or other Government departments, subsequent to COT advice published in 2017.

47. Members had no comments on this paper.

Item 12: Update paper for information: FSA Scientific Advisory Committees (SACs) update- TOX/2018/09

48. Due to time constraints, this paper was not presented at the meeting but would be circulated to Members in due course.

Item 13: Any other business

Folic acid supplementation.

49. A paper had been newly published by Wald *et al*, (2018)[1] disputing the current Upper Level for the maximum recommended intake of folic acid. The paper argued that the basis for the upper level (masking of vitamin B12 deficiency) was flawed and unnecessarily prevented the use of fortification. As there had also been previous concerns that folic acid could promote colon cancer in individuals with pre-neoplastic lesions, COC and SACN had considered the issue jointly in 2013, with the advice being updated in 2017. The current advice was that fortification was recommended but measures should be in place to ensure that there was no increase in the number

[1] Public health failure in the prevention of neural tube defects: time to abandon the tolerable upper intake level of folate. Wald, N.J., Morris, J.K., Blakemore, C. (2018). Public Health Reviews, 39:2.

of individuals exceeding the maximum recommended intake. Members were asked whether the current guidance level of a maximum of 1 mg/day recommended for folic acid should be reconsidered.

50. The Committee agreed that the information in the newly published paper should be evaluated. Since it was some years since maximum intakes were discussed, Members agreed that any additional information identified following the 2003 evaluation should also be reviewed.

Caffeine in energy drinks

51. Members were informed of a current campaign headed by Jamie Oliver requesting a ban on the sale of energy drinks to under 16s due to adverse health and behavioural effects; this had been followed by a number of retailers banning the sale of energy drinks to under 16s. A report had been submitted to FSA/DH by the campaign and it had been agreed that this would be considered and a review of the most recent literature conducted to see whether the current FSA advice (based on the 2015 EFSA opinion) should be reconsidered.

52. The Members noted that the ban by the retailers was voluntary, following the campaign, rather than being based on any new data on the effects of energy drinks on children. The lack of studies regarding the combination effects of the ingredients in the energy drinks was also noted. The Committee agreed that this issue should be considered.

Day 2

Item 14: EFSA consultation on nanomaterials - TOX/2018/10

53. EFSA had released for public consultation updated draft guidance on the risk assessment of nanomaterials. This draft was the third version of EFSA guidance on nanomaterials and took into account developments that had occurred in other pieces of EFSA guidance, for example, it followed a tiered approach. The guidance applied only to oral exposure.

54. The approach was to first characterise the material; to consider if the material remains in the nano form in the gastrointestinal tract, and to assume that it does if this possibility could not be excluded; to consider if there was oral exposure; the guidance then contained a framework to consider what toxicity data were required. The Committee was asked to comment on the guidance and, in particular, if it made sense to risk assessors who were not nanomaterial specialists. PHE had provided

some written comments to the Committee from the Group Leader of their Nanoparticle Inhalation Research Group.

55. The Committee discussed which materials were in the scope of the guidance. It was indicated that these would be materials which met a recommended definition by the European Commission of containing 50% or more of particles in the number size distribution with one or more external dimensions in the size range 1 nm – 100 nm, plus materials with less than 50% of particles in the number size distribution having one or more external dimensions in the size range 1 nm – 100 nm, plus materials which contained particles with a size above 100 nm which could retain properties that are characteristic of nanoparticles.

56. Any powdered material would contain some particles in the nanoscale and the Committee wondered what percentage should be a cut-off if this was set at less than 50%. This could depend on whether the toxicity of the nanomaterial was increased compared to the non-nano form. A material could have a particle size a little greater than 100 nm and still have the properties of a nanomaterial but the guidance was not clear what characteristics a particle larger than 100 nm would need to possess to be considered within scope. Page 16 of the draft guidance listed 11 characteristics but most of these were not specific to nanomaterials, e.g. bioaccumulation. Quantum effects were specific to nanoparticles but would only occur for very small nanoparticles.

57. The guidance implied that nanomaterials may have greater toxicological potency for any toxicological effect than non-nano forms of the same material, and the Committee questioned what the available evidence for this was. It recognised that there was evidence of local reactions in the wall of the gastrointestinal tract for some nanomaterials.

58. One Member asked why conventional toxicological testing was not considered sufficient for nanomaterials, as it would test the consequences of such materials in the diet.

59. Members noted that the gastrointestinal tract removes insoluble materials. Molecules with molecular weights more than 1500 Da were not absorbed and few nanomaterials would be smaller than that. In addition, the likelihood that material would remain in the nano form once it had reached the gastrointestinal tract was very low, due to processes such as dissolution and aggregation/agglomeration.

60. The Committee continued to work through the guidance, following the general outline in Figure 1 and considering the text in the guidance for each step. After characterising the material as being a nanomaterial or having properties characteristic of the nanoscale, the guidance asked whether the material quickly and fully degrades in in vitro digestive tract conditions. PHE had questioned the security

of the degradation rate cut-off of “12% or less of the material is present as particles after 30 minutes of intestinal absorption.” The Committee considered that this cut-off would work for homogenous materials but not heterogenous materials as only the larger particles would have been degraded.

61. The next step was to assess the stability in lysosomal fluid and *in vitro* testing. The assumption was that nanoparticles were taken up by lysosomes and only if they persist and were not degraded were they a concern. However, this did not indicate what might be happening elsewhere in the cell. The authors of the draft guidance had perhaps considered that this would be identified by the other *in vitro* tests.

62. A Member questioned how the data from a suite of *in vitro* cytotoxicity tests should be interpreted. It was difficult to see how it would be possible to conclude that there was no effect. It was presumed that the intention was that experience would be built up over time. However, there was no guidance provided on which test methods to use or on establishing *in vitro* methods that were fit for purpose.

63. Regarding *in vivo* testing it was noted that the design of the 90-day study should be guided by the toxicokinetic studies, showing where the nanoparticles were distributed.

64. Regarding exposure, the Committee observed that the worst-case scenario assumed in the absence of evidence to the contrary, was that 100% of nanomaterial added to a food or feed product would be ingested and absorbed.

65. Chapter 7 on nano-specific risk characterisation was not considered specific to nanomaterials. Section 6.9, on considerations when testing nanomaterial, contained the aspects which were specific to nanomaterials. Similarly, chapter 8 on uncertainty was largely not specific to nanomaterials. It was suggested that section 8.2 could be replaced with links to existing guidance on uncertainty.

66. Comments would be compiled by the Secretariat for submitting to EFSA. All Members, including those absent from this meeting, would be asked to email further comments by 28th February.

Item 15: Horizon scanning and future work - TOX/2018/11

67. Members noted a list of agenda items for 2018 that were planned or underway, and discussed several other suggested topics that might also be considered. The Committee’s input into the Scientific Advisory Committee on Nutrition (SACN) review of complementary and young child feeding focussing on children age 1 to 5 was highlighted as an area that could be prioritised further for

freeing up resources. It was agreed that the COT and SACN Secretariats should discuss and agree a way forward for this area of work.

68. The Committee noted that it may be asked to respond to European Food Safety Authority (EFSA) consultations on the mixtures work by the first half of 2018, and agreed to consider its approach further when responding to the consultation on endocrine disrupters in the light of the UK exit from the EU.

69. Members noted that the Secretariat was currently reviewing various options for considering the microbiome area.

70. Members agreed to receive a presentation by the Chair on the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) Risk Assessment in the 21st Century (RISK21) project

71. It was noted that it would be useful to keep abreast of developments in the area of physiologically-based toxicokinetic (PBTK) modelling. Members noted that as a follow-up to SEES, it was important to understand how epidemiological and toxicity data can be integrated for informing risk assessment. The importance of global data generated by other regulatory agencies was highlighted, in view of the anticipated exit of the UK from EU.

72. A Joint Committee Horizon Scanning session took place in October 2017 and a number of items were discussed which would be of interest to COT. Topics included uncertainty in risk assessment, extrapolation from lifetime animal studies to early human less than lifetime exposure, and the balance between environmental exposure and food exposure.

73. Members were informed that work on uncertainty in risk assessment and risk communication was also under consideration by the FSA Science Council. It was noted that a draft joint JECFA/JMPR paper on extrapolation from lifetime animal studies to early human less than lifetime exposure was in preparation. The COT had been taking a case-by-case approach on considering the balance between environmental exposure and food exposure. A member suggested that approaches which could predict possible interactions between environmental and food exposures could prove useful in highlighting potential issues. The value of read across from chemical structures, consideration of long-term-trends, seasonal variations in exposure to food chemicals, and setting thresholds for toxicological concern were highlighted as important areas in this respect.

74. A potential concern over natural products and “new” natural products was raised at the joint Committee horizon scanning meeting. The Secretariat informed members that it had applied to EFSA for securing a research fellowship via the EUFORA program. If successful, it would be anticipated that the research fellow

would be assigned a project on investigating the effects of natural foods and supplements.

75. In terms of priorities for joint Committee consideration, one important area that was suggested was how to evaluate the biological or toxicological relevance of a reported response or perturbation, especially where this may be an atypical endpoint and how statistics can, and should, be used to help determine this. It was agreed to raise this suggestion with COC and COM before it is taken further.

76. Members agreed that the Committee would reconsider the balance of expertise of the Committee at a future meeting in order to take account of developments with the UK exit from the EU.

77. Members were invited to suggest new topics for consideration at future meetings and reminded that they could raise new topics at any time. A member noted that a new class of energy drinks that were designed to induce ketosis had appeared in the market, which could be discussed in future; the Secretariat noted that it was possible that these products would be captured by Novel Food legislation. Members agreed to write to the Secretariat if there were other suggestions for future topics.

Date of next meeting

78. The next COT meeting will be on 20th March 2018 (location to be confirmed).