COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Minutes to the meeting held on Tuesday, 23rd October 2018 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ

Present

Chairman:	Professor Alan Boobis	
COT Members:	Dr Phil Botham Dr René Crevel Prof John Foster Dr Mark Graham Dr Caroline Harris Dr Sarah Judge Prof Brian Lake Dr Mireille Toledano Ms Juliet Rix Prof Matthew Wright	
Food Standards Agency (FSA) Secretariat:	Mr B Maycock Ms H Gbormittah Ms C Mulholland Ms C Potter Mr A Cooper Dr B Doerr Ms C Tsoulli Dr D Hedley Ms R Acheampong Dr J Shavila Ms F Hill Dr O Osborne	FSA Scientific Secretary
Public Health England (PHE) Secretariat:	Ms B Gadeberg	PHE Scientific Secretary
Assessors:	Prof T Gant	PHE

Officials:	Ms Daphne Duval	PHE
	Ms Anne Milne	FSS
	Mr Patrick Miller	FSA
	Ms Wendy Dixon	FSA
Other Invited Experts and Contractors:	Prof P Aggett	SMCN
	Dr S Bull	WRc
	Ms S Lloyd	WRc
	Dr R Bevan	IEH Consulting
	Dr S O'Rourke	Dstl
	Mr N Sutcliffe	Police
Observers:	Mr M Hartwig	Energy Drinks Europe
	Dr M Cush	Ramboll Environment and Health UK
	Ms U Arens	Writer, nutrition and dietetic topics

Contents

Announcements

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

2. The Chair welcomed Dr Olivia Osborne and Mr Alexander Cooper as new members of the Secretariat.

3. 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

4. Apologies were received from COT Members Professor Roy Harrison, Professor Faith Williams, Dr James Coulson, Dr John Thompson and Ms Jane Case, from Dr David Gott from the FSA Secretariat, and from Michaela Benton from HSE and Ian Martin from the Environment Agency.

Item 2: Minutes from the meeting held on 11th September 2018.

5. The minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 11th September 2018

Item 3: Matters arising from previous meetings:

6. Para 5: The Statement on copper had been cleared by Chair's action. It would be published shortly once the lay summary had been finalised.

7. Para 6: The report of the COT-COC Synthesising Epidemiological Evidence Subgroup (SEES) had now been published.

8. Para 7: The Statement on methylmercury was in the process of being finalised and would be published shortly.

Item 4: First draft interim position paper on potential risks from "energy drinks" in the diet of children and adolescents

9. Para 17: The interim position paper had now been published.

Item 8: EFSA public consultation on the MIXTOX guidance

10. Para 51: The COT comments were submitted to EFSA ahead of the deadline.

Other matters arising

11. At the July meeting, under AOB, the Chair had commented on the possible implications of a new EFSA PPR panel opinion on pesticides in foods for infants and young children. This had been referred to the Expert Committee on Pesticides (ECP), which had discussed this opinion, the related guidance of the EFSA Scientific Committee on the risk assessment of substances present in food intended for infants below 16 weeks of age, and EFSA's approach to the risk assessment of mixtures of pesticides at its meetings in July and September.

Review of potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2018/36

Additional information on other tropane alkaloids (TAs)

12. A short overview of the contribution and concentrations of all 20 TAs reported in the FSA's survey was presented to the Committee, following a request by Members at the July meeting of this year.

13. The Committee discussed the pharmacological effects of (-)-hyoscyamine and (-) scopolamine and enquired if information regarding the pharmacological effects of the other TAs was available and could be provided to the members. Members noted that information on the pharmacophore of (-)-hyoscyamine and (-) scopolamine would be helpful in assessing the possible pharmacological effects of the other TAs.

14. The Committee asked for the above information, if available, to be presented to the Members to assist in the final assessment of tropane alkaloids for the overarching Statement.

Item 4: First draft statement on the EFSA Opinion on "Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food" – Reserved Business **-TOX/2018/37**

15. EFSA were shortly to publish an Opinion, "Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food". New health-based guidance values had been established for both perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA).

16. This item was discussed as reserved business.

Item 5: Submission of data on PSI PRO irritant spray- Reserved Business - TOX/2018/38

17. This item was discussed as reserved business.

Item 6: Phosphate-based flame retardants and the potential for developmental toxicity: a scoping paper -TOX/2018/39

18. No interests were declared.

19. Brominated flame retardants such as polybrominated diphenyl ethers (PBDEs) had been the most common chemical flame retardants used for furnishing and textiles. However, recent bans and restrictions on their use have led to an increase in the use of alternatives such as phosphate-based flame retardants (PFRs).

20. PFRs share some structural similarity with organophosphate (OP) pesticides, which have been shown to interfere with neurodevelopment by inhibition of cholinergic and noncholinergic esterases. Infants and young children have been identified as having a greater potential for exposure to PFRs. Therefore, this scoping paper aims to investigate the potential for developmental toxicity following exposure to PFRs, with a focus on children and the developing fetus, and provides background information on proposed mechanism of action, exposure, biomonitoring and toxicity of PFRs.

21. The Committee discussed the structural similarity of PFRs with OP pesticides and the available data. It was decided that it would be useful to look at the structures of the PFRs and determine whether they have structural characteristics necessary to interact with the active site of acetylcholinesterase (AChE). While there were no IC50 data identified, based on the paper by Eldefrawi et al. (1977)[1], Members considered that the PFRs appear to be at most only weak inhibitors of AChE.

22. It was noted that little information was available on levels of exposure, but that the concern was for potential exposures e.g. to infants sleeping on new mattresses.

23. Some clarity was sought on papers describing tricresyl phosphate (TCP) exposure, as the identity of the isomer is not always mentioned, but it is known that the ortho- and para- isomers have different toxicities. It was noted that the TCP poisoning incident in Bombay was unlikely to be relevant for exposures such as those being considered.

24. The available epidemiological studies in children suggested some potential effects; however, there is some inconsistency in the findings between studies. The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study[2] is considered to be a well-designed cohort study. While different outcomes

[1] Eldefrawi, A.T., Mansour, N.A., Brattsten, L.B., Ahrens, V.D. and Lisk, D.J. (1977) Further toxicologic studies with commercial and candidate flame retardant chemicals. Part II. *Bull Environ Contam Toxicol,* 17, 720-6

[2] Castorina, R., Bradman, A., Stapleton, H.M., Butt, C., Avery, D., Harley, K.G., Gunier, R.B., Holland, N. and Eskenazi, B. (2017) Current-use flame retardants: Maternal exposure and neurodevelopment in children of the CHAMACOS cohort. Chemosphere, 189, 574-580

were identified as significant across the epidemiological evidence, these all generally related to cognitive function or performance of children. It was noted that it was not clear whether these studies had adjusted sufficiently for potential exposure to other chemicals or factors affecting cognitive performance. The Committee noted that the mode of action for any potential neurotoxic effect is unlikely to be the same as for OP pesticides.

25. Overall, the Committee determined that the experimental evidence suggested that PFRs were not similar to OPs in terms of activity and therefore there was a lack of biological plausibility of the potential for PFRs to exhibit similar effects to OPs. There was no evidence of a direct developmental effect of PFRs. However the epidemiological evidence had suggested a potential neurodevelopmental effect, though there were limitations to this evidence.

26. It was noted that overall human exposure would be to a mixture of newer and older, banned or restricted, flame retardants.

27. The Committee agreed that, given the limited information available on the topic of PFRs and developmental toxicity, this paper should be summarised as a short Committee view, including discussion of the other potential neurotoxic mechanisms.

Item 7: Discussion paper on the basis for the Upper Level for folic acid - TOX/2018/40

28. It is well established that supplementation with folic acid can reduce the risk of having a neural tube defect (NTD) affected pregnancy. UK Government advice is that women should take a folic acid supplement prior to conception and up to the third month of pregnancy. However, as many women do not take supplements and many pregnancies are unplanned, the rate of NTD-affected pregnancies has not significantly changed.

29. Consequently, SACN have recommended that wheat flour should be fortified with folic acid. This recommendation came with the proviso that fortification should not increase the number of people who were currently exceeding the Upper Level (UL) for folic acid, meaning that levels in supplements or other fortified products would need to be reduced.

30. Members were informed that the possibility of fortification of wheat flour with folic acid was discussed in recent press articles and that the Government had announced that a consultation exercise on the topic would be launched in the new year.

31. ULs or equivalents of 1 mg/day have been established by a number of scientific bodies, including the UK Expert Group on Vitamins and Minerals (EVM), based on the observation that folic acid may mask the diagnosis of pernicious anaemia by improving haematological status while allowing neurological damage to progress. Both the US Institute of Medicine (IOM), and the EU Scientific Committee on Food (SCF) also considered that it was not possible to rule out the possibility that folic acid could exacerbate the neurotoxicity associated with pernicious anaemia, although both noted that there was no clear evidence for this in humans.

32. The COT had considered folic acid at three meetings since the publication of a paper by Wald *et al*. (2018) which argued that the basis of the UL was flawed. The criticisms made in the paper applied to the IOM TUL but some were also relevant to maximum intakes recommended by the EVM and SCF since some of the same endpoints were used to establish the UL. Wald's main criticism of the IOM related to them using the possibility of folic acid having a direct neurotoxic effect in those with B_{12} deficiency in the establishment of the UL.

33. The Committee discussed the basis of the UL at their meeting in July 2018 and agreed that the data on which the UL is based should be reanalysed to see if any dose-response relationship could be determined. Paper TOX/2018/40 contained data that has been discussed by COT previously, but it had been expanded and presented in a revised way. Other endpoints that could be used to determine a UL were included in the paper.

34. The limitations of the original case reports were discussed. The adverse effects had originally occurred when folic acid had been first isolated in the 1940s and patients had been treated with folic acid rather that the meat or liver extract which had been used as treatment previously and some of these patients had gone on to have new neurological effects or to relapse. The way the data were presented and reported made it difficult to determine a dose-response relationship. An attempt had been made to see if the duration of dosing was important, but it had not been possible to identify any such relationship.

35. As the Committee had noted previously, there was no evidence that folic acid had a direct neurotoxic effect but it appeared able to mask diagnosis by treating the anaemia also associated with B_{12} deficiency. The Committee concluded that this was the most relevant end-point on which to set an Upper Level or Guidance Level.

36. It was possible that any dose-response relationship among the dose levels of folic acid that had been used would be flat, i.e., that once the folic acid was sufficient to treat B_{12} deficiency further increases did not have any additional effect. Members asked whether it was possible to identify the minimum amount of folic acid required to treat B_{12} deficiency.

37. Members did not agree with the comment in the Wald paper that diagnosis was sufficiently improved that the possibility of masking was no longer relevant. Although serum B_{12} levels could be measured, this did not indicate whether the B_{12} was functional; the test for the latter was not widely available. However, once diagnosed, pernicious anaemia could be readily treated.

38. When establishing their guidance level, the UK EVM had considered 5 mg/day folic acid as a LOAEL, where there was some evidence of masking, and 1 mg/day, where there was little evidence, as a NOAEL. Members agreed that there was little more that could be done with the data set and that the EVM had taken an appropriate approach, setting a guidance level rather than a TUL as this indicated the supporting data were less secure.

39. Members considered other endpoints but agreed that none of these would be appropriate to use as a basis for a TUL or GL.

Item 8: Scoping paper on the potential risks from "energy drinks" in the diet of children and adolescents – TOX2018/41.

40. Professor Alan Boobis declared that he had consulted for Coca Cola until 2014, and in 2014 he had signed a consultancy contract with Red Bull but had not taken up the post and received no payment. The Committee agreed that he should not be excluded from the discussion; however, Dr Phil Botham chaired this item.

41. No other interests were declared.

42. Recent media interest had led to a voluntary restriction on the sale of so-called "energy drinks" to adolescents under 16 years of age by the major retailers. The Committee had considered it appropriate, after the subject was introduced at the March meeting (TOX/2018/17), to consider in more detail whether a problem exists with the consumption of these products in young people. Following discussion of a scoping paper at the July meeting, amendments have been made to the text and this scoping paper was now presented to the Committee for further comment.

43. The Committee asked that a précis be made of the information on the reported cardiovascular effects of "energy drinks".

44. Members stated that the table of caffeine and sugar content of various beverages was useful but unclear in places as to the product being referred to, especially in terms of the branded coffee. Moreover, it should not appear to emphasise one brand over another.

45. The table of drivers for consumption of “energy drinks” was difficult to use for comparison purposes because of the different ways the questionnaires in the studies had been analysed. The Committee asked for the table to be amended.

46. The Committee found no evidence that “energy drink” constituents other than caffeine and sugar had any significant influence on the reported effects of these beverages.

47. The conclusions reached by the authors in some of the cited papers amounted to no more than speculation on their part and should not for part of Committee’s weight-of-evidence.

48. Members asked for information on confounding factors such as mobile phone and other device use, particularly prior to sleeping, the possibility of co-consumption of “energy drinks” with other sources of caffeine, such as coffee.

49. Overall, little evidence was available to conclude that “energy drinks” posed a specific risk to the health of children and adolescents, as compared to other sources of caffeine or sugar, when considered in the context of confounding factors. Most studies were cross-sectional and so the direction of causation could not be determined. The risk of regular caffeine consumption in adolescents remains to be clarified. A risk possibly exists in individuals of all ages with certain underlying health problems, such as ECG long Q-T interval.

Item 9: Discussion paper on the EFSA opinion on “Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food” - Reserved Business -TOX/2018/42

50. The European Food Safety Authority’s Panel on Contaminants in the Food Chain (CONTAM) were asked for a scientific opinion on the risks for animal and human health from to the presence of dioxins and dioxin-like PCBs (DL-PCBs) in feed and food, respectively.

51. This item was discussed as reserved business.

Item 10: FSA Scientific Advisory Committees (SACs) update

52. This paper was provided for information.

Item 11: Any other Business

53. Members were updated on planned changes to the structure of the FSA Scientific Advisory Committees. This item was discussed as reserved business.

Date of next meeting

54. The next meeting will be held on Tuesday 4 December 2018 at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ.