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

Minutes of the meeting held on Tuesday, 20th of March at 2018 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ

Present

Chairman:	Professor Alan Boobis	
COT Members:	Prof Janet Cade	
	Ms Jane Case	
	Dr Rene Crevel	
	Professor John Foster	
	Dr Mark Graham	
	Dr James Coulson	
	Dr Sarah Judge	
	Prof Brian Lake	
	Ms Juliet Rix	
	Prof Faith Williams	
	Prof Matthew Wright	
Food Standards Agency (FSA) Secretariat:	Mr B Maycock	FSA Scientific Secretary
	Ms C Mulholland	
	Ms F Hill	
	Dr D Hedley	
	Ms C Potter	
	Dr B Dörr	
	Ms C Tsoulli	
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Assessors:	Prof T Gant	PHE
Officials:	Ms Rachel Elsom	PHE
	Ms Daphne Duval	PHE
	Ms Wendy Dixon	FSA
Other Invited Experts and Contractors:	Dr Sarah Bull	WRc
	Dr Kate Vassaux	WRc

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Announcements

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

2. The Chair thanked Prof J Cade for her highly valuable contributions to the committee over the years as this was her last meeting.

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 Prof R Harrison, Dr C Harris, Dr J Thompson, Dr P Botham and from HSE assessor Michaela Benton. Dr Botham and Dr Harris had provided written comments.

Item 2: Minutes from the meeting held on 6th and 7th of February.

5. The minutes were agreed subject to a change in the attendees list to note that Dr Harris was present only on 6th February.

Item 3: Matters arising from the meeting held on 6-7th February 2018

Item 3: Matters arising from previous meetings:

6. Para 8: The statement on the reformulation of 2-chlorobenzylidine malonate (CS) as an irritant spray had been cleared by the Chair and was ready for publication. The Secretariat had been in discussion with the Home Office Centre for Applied Science and Technology (CAST) about the timing of publication and this would be in the near future.

7. Para 9: The draft statement on potential risks from cadmium in the diet of infants aged 0 to 12 months and children aged 1-5 years has been sent to the SACN Subgroup on Maternal and Child Nutrition (SMCN) for comments ahead of being cleared by Chair's action.

8. Paras 10 and 11: The Science and Technology Committee (STC) evidence session on e-cigarettes, attended by Professor David Harrison, COC Chair and former COT member, was held on 27th February. The recording and transcript of the meeting were now available on the STC website: https://www.parliament.uk/business/committees/committees-a-z/commons-

select/science-and-technology-committee/inquiries/parliament-2017/e-cigarettes-17-19/.

9. Para 13: Committee guidance for submission of papers for consideration by the COT regarding irritant sprays, and on the information required, had been approved by the Chair and was ready for publication. The Secretariat had been in discussion with CAST about the timing of this and it would be published shortly.

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

10. Para 19: The statement was in the process of being finalised. It had been sent to the SACN SMCN for comment ahead of being cleared by Chair's action.

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

11. Para 35: The draft statement had been sent to the SACN SMCN for comment ahead of being cleared by Chair's action.

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

12. Para 39: The draft statement had been sent to the SACN SMCN for comment ahead of being cleared by Chair's action.

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

13. The COM had commented on the draft statement at its meeting on 22 February. A revised version would be circulated to members of the COT, COC and COM for comments ahead of clearance by the Chairs.

Item 14: EFSA consultation on nanomaterials

14. Para 66: The compiled comments were cleared by the Chair and submitted to EFSA on Friday 2nd March.

Item 15: Horizon scanning and future work

15. Para 77: Following the last meeting both the Chair and one other Member had suggested microplastics as a potential topic for COT consideration. The EFSA CONTAM Panel had produced a statement on microplastics in the food chain in 2016, with a focus on seafood. Due to the continuing interest in this subject,

discussions between the Secretariat and policy colleagues were taking place with the expectation that a scoping paper will be presented to COT later in the year.

Item 4: Folic acid – scoping paper on setting upper levels of intake – TOX/2018/12

16. No interests were declared.

17. It is well established that folic acid supplementation prior to conception can reduce the risk of having a Neural Tube Defect (NTD) affected pregnancy. Consequently, UK Government advice recommends supplementation with 400 µg/day folic acid from the time contraception is ceased until the 12th week of pregnancy. Women who have already had a NTD-affected pregnancy are advised to take a supplement of 5 mg/day folic acid. However, not all women use folic acid supplements and many pregnancies are unplanned. As a consequence, each year there are a number of avoidable NTD-affected pregnancies.

18. Fortification of flour was first recommended by the Committee on the Medical Aspects of Food and Nutrition Policy (COMA) in 2000 and this was re-iterated by the SACN in 2006, 2009 and 2017. However, the current position is that previous Government ministers had decided not to introduce mandatory fortification but instead to promote the use of folic acid supplements as part of pre- and post-conception care.

19. One of the recommendations made by SACN was that because of the uncertainties around high intakes of folic acid, the number of people exceeding the maximum recommended levels should not increase; this would be achieved by reducing voluntary fortification in other foods and food supplements and regularly monitoring intake levels.

20. Maximum recommended intakes had been set by various expert bodies. These were either Guidance Levels (GLs) as set by the Expert Committee on Vitamins and Minerals (EVM) in 2003 or Tolerable Upper Levels (TULs) as set by the US Institute of Medicine (IOM) and the EU Scientific Committee on Food (SCF) in 1998 and 2000 respectively. These were all at 1 mg/day and were based on either the masking of the neurological symptoms and/or the exacerbation of the neurological symptoms associated with deficiency of vitamin B_{12}, a related vitamin.

21. At the last COT meeting in February, a recent paper by Wald *et al.*[1] (2018) was considered briefly under Any Other Business. The paper argued that the basis

[1] Wald et al. (2018). Public health failure in the prevention of neural tube defects: time to abandon the tolerable upper intake level of folate. Public Health Rev. 39:2

of the TUL was flawed and therefore the concerns about the masking of vitamin B12 deficiency were no longer relevant. It was agreed that, given the age of the EVM GL and related TULs, the evidence underpinning them should be re-examined. The scoping paper TOX/2018/12 provided background information on the relationship between folate and vitamin B_{12}, on the diagnosis of deficiency, and set out how the TULs and GLs were set. The paper by Wald and colleagues focussed on the TUL set by the IOM rather than the EVM or SCF but the data set and endpoints used by the expert bodies were essentially the same, being a series of case reports as well as the known relationship between folate and B_{12} metabolism. No new case reports were identified in a preliminary literature search, but the possibility of other adverse neurological effects resulting from folic acid supplementation had been discussed in the literature.

22. Members considered that there was a strong case for the reduction of NTD affected pregnancies by fortification but noted that the consideration of the benefits was not in the COT remit. It was also important to take the opportunity to remind people of the safety and importance of folic acid supplements. Members were informed that folic acid was used because folate, the natural form, was less stable.

23. It was agreed that the analysis indicated that the TUL might not be sound. However, it might still be necessary to recommend an upper level of intake for folic acid. Hence, Members agreed that they should re-evaluate the original case studies as well as the supporting animal data. The masking of deficiency would need to be distinguished from the acceleration of neuropathy and the development of neuropathy. The neuropathy associated with vitamin B_{12} deficiency could respond to treatment with vitamin B_{12} but damage to the spinal cord might not be reversible. Other neurological and non-neurological endpoints would need to be considered. It would be important to consider effects in the offspring of individuals who were supplemented with folic acid; these would also include individuals given supplements to counteract the effects of anti-epilepsy medication.

24. The association between folate and colon cancer had not been considered in the paper but might need to be revisited at a later date.

Item 5: First draft statement on potential risks from methylmercury in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2018/13

25. No interests were declared.

26. The COT had been asked to review the risks of toxicity from chemicals in the diet of infants and young children age 1-5 years, in support of the review by the 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 methylmercury should be completed.

27. A discussion paper had been presented to the Committee in February (TOX/2018/03), including information on the establishment of the Health-Based Guidance Values from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA), exposure calculations and a risk assessment. This formed the basis for the draft statement.

28. Members agreed that the risk assessment was conservative in assuming that 100% of the mercury in fish was methylmercury.

29. Members requested a number of amendments be made to the text. A revised draft statement would be brought to the May 2018 meeting.

Item 6: Second draft statement on the potential risks from manganese in the diets of infants aged 0-12 months and children aged 1 to 5 years – TOX/2018/14

30. No interests were declared.

31. 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 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.

32. 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 the February and March meetings.

33. Members made a number of suggestions on the second draft statement. The statement would be revised accordingly and finalised via Chair's action.

34. Given the current interest in the potential health effects of dietary manganese and the lack of studies providing a useful comparison of dietary intakes and toxicological effects, the Secretariat considered that a publication in the peer-reviewed literature based on the discussion paper and draft statement may be of value. The discussion paper and draft statement had not yet been placed in the public domain in anticipation of this.

Item 7: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (EN(N)DS – e-cigarettes). Paper 2: Exposure to metals present in the aerosol of EN(N)DS – TOX/2018/15

35. The Chair declared that he was the Chair of the International Organization for Standardization (ISO) Technical Committee (TC) 126 Working Group (WG) 10 on an "Intense smoking regime"; the WG did not address e-cigarettes or ENDS. The Chair also was a member of the World Health Organization Study Group on Tobacco Product Regulation (WHO TobReg), which has discussed ENDS. Professor Williams declared a personal non-specific interest in that her brother-in-law worked for and is now a recipient of a pension from BAT. No further interests were declared.

36. A scoping paper (TOX/2016/25) and first paper (TOX/2017/49) were presented at the COT meetings in July 2016 and December 2017, respectively. The present paper (TOX/2018/15) addressed the potential exposure to metal particles present in the particulate fraction of E(N)NDS aerosols.

37. The Committee noted this was a useful paper summarising a lot of information. It was clarified that the missing values for conventional cigarettes in Table 1 were due to a lack of data.

38. It was agreed that information would be sought on typical daily puff consumption, as this varied widely in the literature. Caution would be required in comparing data on exposures to E(N)NDS aerosol, which was intermittent in nature, with air quality standards for metals, which assume 100% exposure over 24 hours.

39. The Committee noted that one paper reported high levels of silicon. It was agreed that the Secretariat would check for other papers on silicon in E(N)NDS aerosol, whether this was silicon or silica, and the concentration reported.

40. With respect to the biomonitoring papers, it was stressed that there was potential for cross-contamination of saliva samples from the device itself, and it was not always clear to what extent this had been addressed in the research papers.

41. Overall the Committee concluded that there is likely to be some exposure to metals from use of E(N)NDS but there would need to be an appropriate comparison of such exposure with reference values. It would also be helpful to compare with exposure from ambient concentrations as well as from conventional cigarettes and heated tobacco products in the future. Given the rate of development of these devices, it would be important to focus on more recent data, but also details of the methodology used to determine the metal concentrations in the aerosol should be well documented.

Item 8: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (EN(N)DS – e-cigarettes). Summary of data on the constituents of EN(N)DS liquids and aerosols – TOX/2018/15

42. The Chair declared that he was the Chair of the International Organization for Standardization (ISO) Technical Committee (TC) 126 Working Group (WG) 10 on an "Intense smoking regime"; the WG did not address e-cigarettes or ENDS. The Chair also was a member of the World Health Organization Study Group on Tobacco Product Regulation (WHO TobReg), which has worked on ENDS. Professor Williams declared a personal non-specific interest in that her brother in law worked for and is now a recipient of a pension from BAT.

43. A scoping paper (TOX/2016/25) and first paper (TOX/2017/49) were presented at the COT meetings in July 2016 and December 2017, respectively. This paper presented data on constituents in E(N)NDS liquids and aerosol, an outline literature review on genotoxicity and carcinogenicity, and suggestions for further papers.

44. The Committee agreed that the inhalation toxicity of propylene glycol and vegetable glycerine (glycerol) in e-cigarettes should be assessed and in addition, the toxicity of nicotine and user exposure from E(N)NDS should be reviewed.

45. It was noted that due to the great variation in the aerosol as a whole, it would be difficult to extrapolate from experimental studies on these. However, it would be useful to consider epidemiology studies of the health effects of E(N)NDS aerosol. The Committee emphasised that assessments of the effects of user exposure should focus on intended use (including in pregnancy), but bystander assessment should also include potential effects in sensitive groups such as adolescents.

46. Members have discussed the presence of flavourings in E(N)NDS liquids and the Secretariat agreed to check the EU position on these. The potential for allergic or other health effects arising from exposure to E(N)NDS aerosol was noted, and MHRA could be approached for any yellow card reports received. The presence of cannabinoids was highlighted as a concern, as they are illegal in the UK.

47. Regarding genotoxicity and carcinogenicity, the literature searches should be screened and any reporting unanticipated effects should be referred to COM or COC for comment. It was noted that the industry would also likely hold data on genotoxicity.

48. When discussing the comparison of E(N)NDS products with conventional cigarettes and heat-not-burn (HNB) products, Members were unclear on the extent

to which industry had performed comparative studies between these three types of product. It was agreed that comparison of exposures to metals of interest, carbonyls and nicotine, where feasible, would be helpful in the papers on exposure.

Item 9: Energy drinks- report from #notforchildren campaign – TOX/2018/16

49. Sarah Bull (WRC) declared that she had been involved in reviewing evidence on caffeine, consumed alone or in combination with alcohol and/or in energy drinks, for EFSA. No other interests were declared.

50. There are continuing consumer concerns regarding the possible adverse effects of energy drinks in children. In particular, the recent #notforchildren campaign was pressing for the Government to ban the sale of energy drinks to under 16s. The campaign and its subsequent media coverage had resulted in a number of retailers voluntarily restricting the sale of energy drinks to children.

51. The current FSA advice was that children, and those sensitive to caffeine, should only consume caffeine in moderation; this advice was based on the 2015 EFSA opinion. In their voluntary code of practice, the British Soft Drinks Association recommended that energy drinks are not sold to under 16s and the drinks are labelled accordingly.

52. The #notforchildren campaign submitted a report to the Department of Health (DH), which had requested advice from the Food Standards Agency (FSA).

53. In addition to a description of the campaign, the report also cited several studies on caffeine from the literature. The Secretariat had undertaken to consider the most recent literature covering the effects of energy drinks on children and adolescents as well as the studies cited in the #notforchildren report. This discussion paper also contained some additional studies which were published after, or not included in, the 2015 EFSA opinion and were identified in a preliminary literature search.

54. Given the caffeine concentrations involved, the additional effects attributed to energy drinks compared to coffee were most likely to be, at least partly, nutritional and related to sugar or neuropsychological effects. The available evidence suggested that the other components of energy drinks were unlikely to be responsible for any of the reported effects. It was agreed that the most likely interaction was between caffeine and sugar, since the sugar content of energy drinks could be high. It was agreed that it would be helpful to know whether sugar affected caffeine absorption as it delayed gastric emptying. It was considered unlikely that the other components of energy drinks would have any significant effects.

55. Members considered whether there was any evidence that adverse effects could occur at levels lower than the 3 mg/kg bw intake of no concern identified by EFSA. This was unclear, but a Member noted a study by Poole *et al.* (2016)[2] which reported that chronic exposure to low levels of caffeine could have effects on memory in old but not young mice. There was a plausible mechanism for this, since caffeine could affect neurotransmitter levels. It was agreed to review this study.

56. It was suggested that there could be a behavioural or psychological effect involved in the reported adverse effects since they were more marked than might be expected from the known caffeine content of energy drinks. Some studies had shown a placebo or expectation effect for alcohol and this could also be the case for energy drinks. Inter-individual differences and the use of pharmaceutical drugs which affect caffeine metabolism and the effects of consuming caffeine on an empty stomach might also be relevant. There were few data available on caffeine levels in blood since this was usually measured in saliva.

57. It was also pointed out that the design of some of the new studies, which involved self-reporting and questionnaires, might result in biased results.

58. The definition of an energy drink needed to be clear since other soft drinks such as cola contained caffeine, although at lower levels.

59. It was agreed that the Committee should consider some aspects of the database; this would include social, behavioural and psychological effects, and the recent literature on toxicological effects to establish whether there was any evidence that the 3 mg/kg bw level recommended by EFSA was no longer appropriate for under 16s. It was noted that additional expertise would be needed, particularly in psychology.

Item 10: Reports of the COT-COC Synthesising Epidemiological Evidence Subgroup (SEES) – TOX/2018/18

60. The Committee had discussed a proposal, to produce guidance on the COT's approach to assessing the quality of epidemiological research and synthesising the evidence that it generated, at the October meeting in 2014. There had been no written documentation that could potentially be made available on the website for public transparency. Also, development of guidance could provide a timely review on current practice and guidance for Members and the Secretariat. It had been noted at that time, that various bodies were working on similar initiatives. These included a

[2] Poole et al. (2016). Concentration- and age-dependent effects of chronic caffeine on contextual fear conditioning in C57BL/6J mice. Behav. Brain Res. 298(Pt A):69-77.

working group of the FSA's General Advisory Committee on Science (GACS), which was looking at the use of scientific evidence more generally. EFSA was developing guidance on the balance of evidence. An expert workshop on "Implementing systematic review techniques in chemical risk assessments: challenges and opportunities" was to be held in November 2014 at the Royal Society of Chemistry. 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) were pursuing initiatives in this area.

61. At the COT meetings in October and December 2014, Members agreed that it would be useful to set out how the COT reviews evidence, in the light of guidance from other groups, since the COT process, although considered to be robust by the Committee, was not currently explicitly documented. This was also discussed by COC at its meeting in November 2014 and it was agreed that a COT Member would lead a small working group of experts, including epidemiologists from the COC, to undertake this task. The objective would be to produce an overview document explaining the approach of the COT and COC, which would also draw on what other groups were doing, including the Committee on the Medical Effects of Air Pollutants (COMEAP). 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.

62. In February 2015 Dr Hansell introduced a paper on the proposed subgroup, to review approaches that the Committee takes to the synthesis of epidemiological evidence. It was agreed that the subgroup should reflect on whether the output from their work should be guidance for the Committee, or a communication to the public about the approaches currently employed by the Committee.

63. The subgroup met on four occasions (July and October 2015, October 2016 and February 2017). During this time the scope of review was refined and the approaches to epidemiological evidence used by the COT and COC were reviewed, informed by an appraisal of statements and opinions produced by the committees over the period 2008-2015. Scoring systems and systematic reviews of epidemiological evidence were discussed in depth.

64. Two reports were produced by the subgroup. The "Report of the Synthesising Epidemiological Evidence Subgroup (SEES) of the Committee on Toxicity and Committee on Carcinogenicity," intended to form the basis of a guidance document and a "Report on SEES subgroup methods of working and recommendations", providing a summary of the sub-group's activity.

65. These had been discussed by the Committee in March 2017 and the updated reports were discussed at the present meeting.

66. Members requested some minor changes to the main report, which would then be sent to COC for comment before publication. It was also hoped that a publication would be forthcoming in the summer and this work possibly presented at a Congress of the European Societies of Toxicology (EUROTOX).

67. The committee also discussed recommendations in the second report and considered that future reviews should ideally be published but noted that this was labour intensive. Alternatives should be considered, perhaps in collaboration with the British Toxicology Society. Epidemiology training and a workshop were also mentioned but it was felt that the input of the new Committee epidemiologist should be sought before reaching conclusions on these.

68. The integration of epidemiological and toxicological information was discussed and a short scoping paper would be brought to a future meeting. It was noted that the SACN had recently appointed a biostatistician, which would be helpful should such input be required.

Item 11: FSA Scientific Advisory Committees (SACs) update – TOX/2018/09

69. This paper was provided for information.

Item 12: Any other Business

70. The Chair explained that there was a proposal for one FSA Science Council member to act as a champion for each FSA scientific advisory committee. They would act as a conduit between the committee and the Science Council.

71. Members were informed that a new specialist Member, Dr Mireille Toledano, had been appointed to the Committee for three years from 1st April. In addition, Professor Boobis (as Chair), Professor Williams and Dr Coulson had been reappointed as Members for three years with effect from 1st April, and the appointments of Professor Harrison and Professor Lake had been extended for 12 months, also from 1st April.

72. Members were requested to submit expenses claims as soon as possible.

Date of next meeting

73. The next meeting would be held on Tuesday 8th May at the Radisson Blu Edwardian, Hampshire Hotel, 31-36 Leicester Square, London WC2H 7LH.