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

Minutes of the meeting held on Wednesday, 7th May 2019 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ

Present

Chair:	Professor Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr James Coulson Dr Rene Crevel Dr Caroline Harris Dr Sarah Judge Ms Juliet Rix Prof. Faith Williams	
Food Standards Agency (FSA) Secretariat:	Dr D Gott Ms H Gbormittah Mr B Maycock Ms C Mulholland Ms F Hill Dr D Hedley Ms C Potter Dr B Dörr Ms C Tsoulli Dr A Cooper Dr O Osborne Ms F Uy Dr J Shavilla Ms R Acheampong	FSA Scientific Secretary
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Assessors:	Prof. Tim Gant Valerie Swaine	PHE HSE

Officials:	Daphne Duval	PHE
Invited Experts and Contractors:	Prof. Peter Aggett	SMCN
	Dr Sarah Bull	WRc
	Dr Kate Vassaux (Items 13 and 14 by teleconference)	WRc
	Dr Lin Wylie (Item 4)	DSM Nutritional Products
	Dr Anette Thiel (Item 4)	DSM Nutritional Products
	Jon Elliott	OPSS
	Christopher Green	Defra
	Helena Bird	MHRA

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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.

3. This was Professor Peter Aggett's last COT meeting, providing a liaison with the Scientific Advisory Committee on Nutrition (SACN) and its subgroup on Maternal and Child Nutrition (SMCN). The Chair outlined Professor Aggett's contributions to the COT over the years, starting with his being a member of the COT from 1993 and later Vice Chair, Chair of two Working Groups and Vice Chair of a third, and most recently attending COT meetings to provide liaison with SACN and its SMCN. The Chair thanked him for his contributions to the COT over the years and wished him well for the future. From the July meeting onwards, the role of SACN liaison would be shared between two SACN members, Professor Ken Ong (who also chairs the SMCN) and Professor Paul Haggerty. Officials from PHE would also continue to attend as observers.

Item 1: Apologies for absence

4. Apologies were received from COT Members Prof. Wright, Dr Mireille Toledano, Dr Thomson and Prof John Foster. Prof. Foster had submitted written comments.

Item 2: Minutes from the meeting held on 19th March 2019.

5. The minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 19th March 2019

Item 3: Matters arising from previous meetings:

6. Para 8: The proposed discovery day for committee members and members of the Joint Expert Groups that was proposed for 16th May had been postponed and would now be on 13th June.

7. The Committee was updated on the recruitment of new members. Letters of appointment been send out to the new members and they would be joining the COT from the July meeting.

Item 4: Male reproductive toxicity of a novel feed additive, 3-nitro-oxypropanol (3-NOP) (Reserved Business) - TOX/2019/16

8. No interests were declared.

9. 3-Nitro-oxypropanol (3-NOP) is a novel feed additive. As commercially sensitive information was being considered, this item was discussed as Reserved Business.

Item 5: Update on work being undertaken on risk analysis on preparation for EU exit (Reserved Business) -TOX/2019/27

10. No interests were declared.

11. A paper outlining the proposed risk analysis process that has been agreed by the FSA board had been circulated prior to the meeting. This was discussed in further detail and the Members were given the opportunity to comment on it and address questions.

12. This item was discussed as Reserved Business.

Item 6: Review of potential risks from mycotoxins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. Fusarenon-X -TOX/2019/17

13. No interests were declared.

14. SACN was undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. SACN was examining the nutritional basis of the advice. The COT had been asked to review the risks of toxicity from chemicals in the diet of infants, which has been completed, and young children. The reviews would identify new evidence that has emerged since the Government's recommendations were formulated and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years.

15. A scoping paper (TOX/2015/32) "COT contribution to SACN review of complementary and young child feeding; proposed scope of work for 1-5 year old children" was reviewed by the COT in 2015. A further scoping paper for mycotoxins was presented to the COT in 2017. This discussion paper provided a review of the evaluation performed by The Netherlands National Institute for Public Health and the Environment (RIVM) in 2002 for the toxicity of fusarenon-X (Fus-X), and the description of available literature. Currently there was no evaluation available by the European Food Safety Authority (EFSA) or the Joint FAO/WHO Expert Committee

on Food Additives (JECFA). Margins of Exposure (MOE's) for Fus-X had been calculated by dividing the $BMDL_{05}$ for nivalenol (NIV) used to establish the TDI for NIV by the estimated UK dietary exposures for Fus-X. NIV is the major metabolite of Fus-X.

16. The Committee agreed that the ribotoxic mode of action of Fus-X was an important factor in considering the possibility of dose-addition with other mycotoxins.

17. The Committee questioned why a dopamine-deficient dopamine transporter knockout (DDD) mouse model had been used to study the carcinogenicity of Fus-X since this is not considered to be a standard model for this endpoint.

18. The exposure assessment section of the paper was short on detail and a Member commented that it was difficult to ascertain the main sources of exposure. Exposure assessments from breast milk and infant formula should also have been included. However, Members also noted that the MOEs were large, although a possible cumulative risk assessment would need to be considered further.

19. The Committee discussed whether it would be appropriate to make use of the emesis data in mink for Fus-X in the risk assessment, since this animal model was sensitive to mycotoxin effects and had been used to determine points of departure for other tricothecenes.

20. The Committee requested that the Secretariat review further information on the relative potency of Fus-X in relation to other trichothecenes prior to performing read-across analyses and to consider combined exposure assessments and cumulative risk assessment.

Item 7: Review of potential risks from cyclopiazonic acid (CPA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years- TOX/2019/18

21. No interests were declared

22. This was a further paper in the risk assessment of mycotoxins as part of the SACN review of scientific evidence that would inform Government's dietary recommendations for infants aged 0-12 months and young children aged 1-5 years.

23. Due to the limited availability of relevant toxicity data for CPA, currently no evaluations had been performed by European or International agencies or committees such as EFSA, JECFA and IARC. Summaries of ADME and toxicity studies had been provided along with exposure assessments. There was currently no HBGV against which to compare exposures and therefore a risk characterisation had not been conducted.

24. Members advised that the toxicity data on broiler chickens contributed little, and the other available mammalian studies were of more relevance. It was suggested the studies in chickens be summarised in one paragraph.

25. The Committee requested that more detailed exposure data be provided.

26. Members agreed that the NOAEL of 0.1 mg/kg bw/day from the 90 day dog study by Nuehring et al. (1985) be used to determine MOEs for CPA, once the paper had been reviewed to confirm that the NOAEL of that study was 0.1 mg/kg bw/day.

Item 8: Review of potential risks from patulin in the diet of infants aged 0-12 months and children aged 1-5 years- TOX/2019/19

27. No interests were declared.

28. This was a further paper in the risk assessment of mycotoxins as part of the SACN review of scientific evidence that would inform Government's dietary recommendations for infants aged 0-12 months and young children aged 1-5 years.

29. This discussion paper forms part of the work on the infants and young child feeding review. A scoping paper (TOX/2015/32) "COT contribution to Scientific Advisory Committee on Nutrition (SACN) review of complementary and young child feeding; proposed scope of work for 1-5 year old children" was reviewed by the COT in 2015. A further scoping paper for mycotoxins was presented to the COT in 2017.

30. Patulin has been evaluated twice by JECFA and its conclusions endorsed by the former EU Scientific Committee on Food (SCF). The most recent evaluation by JECFA was in 1995, when it established a PMTDI. No further evaluation of patulin had since been carried out. The COT had requested a review of the recent toxicological data available in order to evaluate whether the PMTDI was still appropriate.

31. This paper summarised and reviewed the toxicological data in the published scientific literature from 1995 to 2018. Dietary exposure assessments and a risk characterisation were included, which used the current PMTDI.

32. The Committee noted that investigation of patulin as a possible chemopreventative agent was interesting and may provide information on effects in humans in due course.

33. The Committee noted that there were a large number of genotoxicity studies with variable results. There may be a genotoxic effect via a threshold-based reactive

oxygen species mechanism. However, Members concluded that the genotoxicity dataset was complex and requested that the advice of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) be sought.

34. Members agreed that the other data would probably not require a change to the PMTDI. However, they requested more detailed summaries be provided of a series of single dose studies.

35. Members recalled action in the 1990s in the USA in relation to patulin in apple juice. It was suggested that the data for patulin in apple juice from a previous (FSA-funded) UK total diet study be considered in the exposure assessment.

36. A Member requested that the exposure assessment provide more detail. It was also clarified that there were no data available on patulin in breastmilk.

Item 9: Review of potential risks from 2-MCPD, 3-MCPD and glycidol and their fatty acid esters in the diet of infants aged 0 to 12 months and children aged 1 to 5 years -TOX/2019/20

37. This was a further paper as part of the COTs risk assessment of chemicals in the diets of infants aged 0-12 months and young children aged 1-5 years in order to contribute to SACN's review of scientific evidence that would inform Government's dietary recommendations.

38. In 2016, the EFSA Panel on Contaminants in the Food Chain (CONTAM) had published an opinion on the human health risks related to the presence of 2-MCPD, 3-MCPD and glycidol and their fatty acid esters in food. An overview of the EFSA opinion was provided.

39. Given the limited UK occurrence data, Members agreed that the European dietary exposure estimates could be considered to be reasonably representative of UK exposures.

40. The Committee concluded that it is not currently possible to characterise risks for 2-MCPD due to a lack of toxicological information and insufficient data for dose-response assessments.

41. For 3-MCPD, EFSA and JECFA had derived different values for the $BMDL_{10}$, based on renal hyperplasia in male rats. The basis for this was discussed in terms of different modelling assumptions and constraints, and it was noted that a COT consideration of best practice for benchmark dose modelling may be required in the future.

42. Members requested further consideration of the *in vivo* genotoxicity data on 3-MCPD to confirm that it is not genotoxic *in vivo*. Providing this was confirmed, the Committee agreed with EFSA's evaluation of 3-MCPD and its fatty acid esters and its evaluation of glycidol.

43. The Committee agreed that some of EFSA's MOE values for infants, toddlers and 'other children' with respect to glycidol and 3-MPCD exposure are of potential concern.

Item 10: Scoping paper on the potential risks from polycyclic aromatic hydrocarbons (PAHs) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2019/21

44. No interests were declared.

45. This was a further paper as part of the COTs risk assessment of chemicals in the diets of infants aged 0-12 months and young children aged 1-5 years in order to contribute to SACN's review of scientific evidence that would inform Government's dietary recommendations.

46. The Committee requested a number of changes and clarifications to the text of the paper. It was noted that infant formula, rather than breast milk, appeared to represent the major source of PAH intake for infants.

47. The case-control study on household dust and carcinogenesis summarised in the paper was noted to be of limited value as it did not provide quantitative data useful for risk assessment and there are many other such studies, as well as authoritative reviews, on the carcinogenicity of environmental PAHs, which had not been included.

48. The biological basis for the $BMDL_{10}$s for BaP and PAH4 derived by EFSA should be stated.

49. It was suggested that reference be made to the approach of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) of scaling the TTC for genotoxic substances for less than lifetime exposures in support of the statement that short-term exposure to PAHs giving MOEs of less than 10,000 for infants exposed via infant formula and food were of low concern.

50. It was noted that the concentrations of PAHs, especially BaP, in soil referred to differed from a reference source that had been used in earlier reports by PHE.

51. A comment should be added about urban soils since exposure from this source may contribute significantly to total intake.

52. Members agreed that the use of PAH4 to represent the presence of PAHs in food was appropriate.

53. The Committee agreed that this paper could be abridged for inclusion in the addendum to the overarching Statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5.

Item 11: Review of the potential risk from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years – Additional information on tropane alkaloids – TOX/2019/22

54. No interests were declared.

55. As part of the review of chemicals in the diets of infants aged 0 to 12 months and children aged 1-5 years the Committee had considered a review of tropane alkaloids (TAs) in July 2018. Members had requested additional information on other TAs reported in an FSA survey, which was considered by the Committee in October 2018. At the October 2018 meeting Members had discussed the pharmacological effects of (-)-hyoscyamine and (-)-scopolamine and had enquired if a) information on the pharmacological effects of other TAs and b) information regarding the structural motifs of (-)-hyoscyamine and (-)-scopolamine which are responsible for their pharmacological effects was available and could be provided. TOX/2019/22 provided the additional information requested.

56. Members noted that a number of TAs were present at higher concentration than (-)-hyoscyamine and (-)-scopolamine and raised concern about the contribution of the other TAs to the overall exposure, should these TAs have similar or greater potency to (-)-hyoscyamine and (-)-scopolamine.

57. The Committee agreed that a search of the literature to identify whether the pharmacophore for muscarinic effects of TAs was known would be desirable. One Member volunteered to contact an expert and forward information received to the Secretariat and Committee.

Item 12: Committee Statement on phosphate-based flame retardants and the potential for neurodevelopmental toxicity – second draft -TOX/2019/23

58. No interests were declared.

59. At the October 2018 COT meeting a scoping paper on phosphate-based flame retardants (PFRs) and the potential for developmental toxicity (TOX/2018/39) had been presented. Subsequently a follow up paper (TOX/2019/09) and the first draft of a Statement (TOX/2019/10) was presented in March 2019. In the current meeting, the second draft Statement, incorporating several amendments following discussion in March was presented to the Committee. Notably, the COT conclusion had been amended to reflect that although limited epidemiological evidence is available that suggests potential neurodevelopmental effects, there is lack of biological plausibility for PFRs to exhibit similar effects to organophosphates.

60. Members considered the second draft and provided suggestions for a number of minor amendments to the text of the Statement. In particular, it was suggested that a clarification should be made in the Conclusions to reflect that there was no experimental evidence in mammals to support a Mode of Action for neurodevelopmental toxicity.

61. It was agreed that once the comments had been addressed, the Statement would be cleared by Chair's action.

Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes): Toxicity assessment of flavourings used in E(N)NDS: Vanillin - TOX/2019/24

62. No further interests were declared in addition to those previously declared at the meeting in December 2018.

63. The Chair reported that he had been invited to join an ad-hoc working group of the Commission on Human Medicines on e-cigarettes.

64. The Committee requested information, if available on the market share of vanillin as a flavouring in E(N)NDS in the UK.

65. While vanillin was approved for use in food, which could lead people to assume that it is a safe product in E(N)NDS, it was important to highlight in the COT Statement that food flavourings have not been specifically assessed for inhalation use.

66. Members noted that sensory irritation is not the same as local irritation. It does not progress to any pathological outcome, including local irritation. The Committee agreed that sensory irritation would be explained in the lay summary of the Statement when this was prepared. Members queried whether people would

carry on using a product if they experienced sensory irritation, and noted that someone with behavioural expertise might be required to investigate this further.

67. The Committee discussed the two aspects of concern with respect to the potential toxicity of E(N)NDS flavouring compounds. These are, firstly, the potential for systemic toxicity, which would likely be covered through information on oral toxicity, although the effects of heating the flavouring in the E(N)NDS device would need to be addressed; and secondly, route-specific toxicity including local effects. For vanillin, the oral gavage study for mutagenicity could provide information on systemic effects.

68. There was potential concern over acetal formation with propylene glycol or glycerol and vanillin in E(N)NDS, and it was understood this would occur at room temperature. However, these chemicals were present in food and thus acetal formation might also occur in food. If this was found to be the case, no specific assessment of systemic toxicity of acetal would be required.

69. It was also noted that as some foods are heated, the potential thermal effects of E(N)NDS on the flavouring compound might also occur in food. It was noted that the temperature of 350°C reported in one study was not a realistic in use temperature for E(N)NDS devices. The evidence base suggests much lower heating temperatures and that pyrolysis does not occur. Therefore, extrapolation from food where flavourings could be cooked might be appropriate, although consideration would need to be given to systemic exposure levels of the degradation products by the different routes.

70. For vanillin itself, read across from 4-methoxy-benzaldehyde was considered reasonable, though with respect to acute toxicity, it was considered that vanillin in any case was unlikely to be of concern.

71. It was suggested that an approach could be adopted considering: the toxicity assessment conducted for use of flavouring compounds as food additives; whether there would be any potential specific effect associated with inhalation exposure or as a result of heating in an E(N)NDS device. This would be preferable to requiring a full toxicity data package and the potential for unnecessary toxicity studies to be carried out. It was agreed that a decision tree would be developed to facilitate this.

Item 14 – Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Paper 10b: Toxicity assessment of flavourings used in E(ND)NDS: Cinnamaldehyde - TOX/2019/25

72. No further interests were declared in addition to those previously declared at the meeting in December 2018.

73. As for the previous paper on vanillin, this paper presented the available information on toxicity of cinnamaldehyde relevant to the inhalation route of exposure.

74. The Committee agreed that there was concern over the potential for sensitisation to cinnamaldehyde present in e-liquids. There was both concern for people becoming sensitised, and whether consumers who were allergic to cinnamon (and its related compounds) would know to avoid cinnamon flavoured e-liquids. It was suggested that the Yellow Card data from the Medicines and Healthcare Products Regulatory Agency could be reviewed to assess if any dermatological effects had been reported following use of cinnamon flavoured e-cigarettes.

75. A number of data gaps with respect to E(N)NDS flavourings were discussed. Firstly, with respect to information on the flavourings used most commonly in E(N)NDS devices, to enable prioritisation of compounds for assessment and to indicate how widely was the use of individual compounds. The Secretariat commented that these data were not readily available for the UK.

76. Other gaps included the potential for co-exposure to flavouring compounds both within a single e-liquid but also since the mixing of e-liquids is considered common practice. The consequence of the addition of the flavouring compound on the pH of the e-liquid, altering the protonation of nicotine would also be important to consider as this could affect self-titration of nicotine. Finally, it was acknowledged that further technological advances of E(N)NDS were occurring that could affect use patterns.

Update paper for information: FSA Scientific Advisory Committees (SACs) – TOX/2019/26

77. This paper was tabled for information.

Any other Business

78. No other business was discussed.

Date of Next Meeting

79. The next meeting would be held on 2nd July 2019 at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ.