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

Minutes of the meeting held on Wednesday, 6th February 2019 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ

Present

Chairman:	Professor Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr James Coulson Dr Rene Crevel Dr Caroline Harris Prof Brian Lake Dr John Thompson Dr Mireille Toledano Ms Juliet Rix Prof Faith Williams Prof Matthew Wright	
Food Standards Agency (FSA) Secretariat:	Mr B Maycock Ms H Gbormittah Ms C Mulholland Ms F Hill Dr D Hedley 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:	Ms B Gadeberg	PHE Scientific Secretary
Assessors:	Dr T Marczylo	PHE
Officials:	Mr M Birkenshaw (by teleconference) Dr S Runacres	DHSC FSA

Other Invited Experts and Contractors:	Dr S Bull Dr K Vassaux	WRc WRc

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 had been received from COT Members Prof John Foster, Prof Roy Harrison, Dr Sarah Judge and Dr Mark Graham, from Dr David Gott and Ms C Potter from the FSA Secretariat, and Prof Tim Gant from PHE.

Item 2: Minutes from the meeting held on 4th of December 2018.

4. The minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 4th December 2018

Item 3: Matters arising from previous meetings:

5. Para 14: The FSA had been awaiting the publication of the EFSA report on the information session it held with Member States in November on the new EFSA opinion on dioxins and dioxin-like PCBs. The FSA had seen the report and remained concerned that the criticisms and concerns raised had not been fully addressed. Internal discussions on the way forward were on-going but it was possible that this would be brought back to the Committee.

6. Para 15: Members were provided a verbal update on the recruitment for the scientific advisory committees and expert working groups. A large number of applications had been received, which were currently being sifted. The interviews would most likely be held in early March. The FSA was today also launching a recruitment campaign to expand its Register of Specialists. Specialists on the register could be commissioned to undertake individual pieces or work for the FSA or the scientific advisory committees on an ad hoc basis. The idea was to capture individuals who have particular niche specialisms, or who might not want to undertake a full committee role. It may also interest present and former members of committees.

Item 6: Draft overarching statement on the potential risk from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

7. Para 51: The overarching Statement had been cleared by Chair's action and was in the process of being published.

Item 7: Folic acid – Statement on the tolerable upper level (TUL)

8. Para 58: Following the last meeting and after the COT previously reviewed the statement on the Upper level for Folic acid, Wald at al. had submitted comments to the Chair and Secretariat. These were circulated to Members in December and a

teleconference was held on 1st February. Those present at the teleconference concluded that the majority of the questions posed by Wald et al. had been sufficiently addressed by the revised Statement. There were a couple of areas where attendees considered the Statement could be strengthened. A slightly revised statement had been circulated to Members on 1st February with amendments from the Chair and the two extra sentences as tracked-changes. Members were asked to comment on the revised Statement. The Chair had also agreed to telephone Professor Colin Blakemore, (a co-author of Wald) to discuss the COT actions and clarify the situation.

9. Members agreed that the concerns had been addressed and that the Statement could be finalised.

Item 8: First statement on the potential risks from energy drinks in the diet of children and adolescents

10. Para 66: The Statement had been finalised by Chair's action and published, together with a lay summary.

Item 11: Any other business

11. Para 81: Members were thanked for providing comments on the EFSA consultation on the draft "Scientific Opinion on evaluation of the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels." These had been submitted to EFSA ahead of the deadline.

Item 4: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Paper 8: Additional information on toxicity in adolescent and young adult users -TOX/2019/01

12. No further interests were declared in addition to those previous declared at the COT meeting in December 2018.

13. At the December 2018 COT meeting, a review on the available evidence on the potential toxicity of E(N)NDS aerosol on adolescents and young adults was requested, and the present paper collated information from previous COT discussion papers and an update on recent literature on the topic.

14. It was noted that studies show that some E(N)NDS products may deliver the same nicotine amounts as cigarettes. In addition, the plasma nicotine concentration profile following E(N)NDS use indicates that a rapid peak of nicotine occurs, which is more similar to smoking, compared to nicotine replacement patches which give a continuous, but lower plasma concentration profile.

15. No human studies existed where nicotine alone had been tested, so the evidence in the literature was drawn from data on conventional cigarettes, which also expose the user to a range of substances, such as particulates, carbon monoxide and other vasoactive substances, which may not be present in E(N)NDS aerosol, or are present at lower levels. Some of the reviewed literature appeared to cite evidence from human in utero exposures to extrapolate to effects in the adolescent brain, which the

COT considered inappropriate, other than for effects on the offspring of pregnant adolescents. It was noted that brain development continues until 25 years of age in humans. This is important as cognitive development is still occurring during adolescence and nicotine is neuroactive. Hence, adverse neurodevelopmental effects might occur, though more information on the quantification of these potential effects is required.

16. It was noted that animal studies on the effects of nicotine appeared to mirror effects seen in human studies following conventional cigarette exposure. However, Members had some reservations about quantifying the effects of nicotine from animal studies as the comparability of the dosing to human exposures was not clear.

17. Members considered that it was unlikely that the public are generally aware that nicotine itself is harmful. The risk reduction with E(N)NDS products occurs if people who are already smoking switch to them, or if E(N)NDS are taken up instead of conventional cigarettes. Information on the profile of user uptake and behaviour, e.g. whether E(N)NDS prevents or is a gateway to cigarette use would be informative.

18. There was concern about the possible relationship between nicotine use and anxiety, depression and other neuro-psychiatric and neuro-functional effects, and whether E(N)NDS could have a similar effect, as there are discussions around use of E(N)NDS in the mental health care system.

19. Members were informed of an ongoing study that had not yet been published, which should elucidate some of the questions above.

20. The presented data on non-neurological effects, for example asthma exacerbation, suggested no such effects would occur just in adolescents as compared to adults.

21. Members suggested that information on how the nicotine doses administered to rats compared with human exposure would be useful. Overall it was expected that any effect of nicotine from cigarettes would also occur following E(N)NDS exposure. While other components of cigarettes might also have an effect, this had not been studied.

22. The Committee agreed that the evidence presented supported that E(N)NDS products containing nicotine pose a risk to young people.

23. It was queried whether in addition to the information on plasma nicotine concentrations and levels of nicotine metabolites in urine, any data were available on nicotine concentrations in the brain following cigarette or E(N)NDS use. There was potential for the other chemicals in E(N)NDS and conventional cigarettes to affect nicotine delivery to the brain and any animal or human data on this would be of interest.

24. The Committee agreed that one aspect to cover in the statement is the difficulty of distinguishing behavioural trends and whether E(N)NDS availability is a gateway to smoking conventional cigarettes.

Item 5 - Review of potential risks from fumonisins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years – TOX/2019/02

25. No interests were declared.

26. The Scientific Advisory Committee on Nutrition (SACN) was undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. The 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 had been completed, and young children. The reviews would identify new evidence that had 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. 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" had been reviewed by the COT in 2015. A further scoping paper for mycotoxins was presented to the COT in 2017.

27. In respect to the text in paragraph 8 of TOX/2019/02, the Committee commented that ester metabolites are hydrolysed, not formed by hydrolysis, and only a few percent of the parent compound are excreted in the bile.

28. Regarding the neural tube defects observed, Members commented that these were thought to be due to interference with folic acid at high dose levels; however, the European Food Standards Agency (EFSA) Opinion[1] should be further consulted.

29. The Committee commented that the fumonisins subtypes that EFSA has reviewed were only 1-4 and not 1-6 as stated in paragraph 20.

30. Members discussed JECFA's comments on the analytical method utilised to quantify fumonisins in breast milk by Mahoga et al (2014)[2] as being inadequate and/or inappropriate. A Member would review this paper. Members further commented on the likely ethnic influences of specific food group intake on the levels of fumonisins in breast milk.

31. Members agreed that a further review of the Zimmer et al. (2008)[3] paper which reported concentrations of fumonisins in infant and follow-on formulae products within the German population should be carried out to identify and determine a cohesive exposure distribution to compare with the UK Total Diet Study data.

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[1] EFSA CONTAM (2018) Appropriateness to set a group health-based guidance value for fumonisins and their modified forms.

[2] Mahoga, H., De Meulenaer, B., Kimanya, M., Hipolite, D., Lachat, C., Kolsteren, P. (2014) Fumonisin B1 contamination in breast milk and its exposure in infants under 6 months of age in Rombo, Northern Tanzania. Food and Chemical Toxicology 74, pp. 112-116.

[3] Zimmer, I., Usleber, E., Klaffke, H., Weber, R., Majerus, P., Ottender, H., Gareis, M., Dietrich R., Märtlbauer, E. (2008) Fumonisin intake of the German consumer. Mycotoxin Research 24 (1), pp. 40-52.

32. The Committee agreed that details should be provided on the limits of quantification and limits of detection of fumonisins in the 4-year surveillance study for mycotoxins carried out by the FSA, as well as the samples tested (size and types).

33. The Committee deliberated whether it would be necessary to further discuss and/or review the health risk(s) from co-exposure to mycotoxins. No conclusion could be reached and further consideration would be necessary.

34. Members discussed using the maximum concentration for infant formula, which was 200 times higher than the median. They concluded that the distribution was highly skewed and estimated exposures based on the maximum concentration could be a large overestimate. However, if the estimated exposures were below the tolerable daily intake (TDI) there would be no toxicological health concern and hence no refinement of the exposure estimate would be necessary.

35. The Committee noted that acute dietary exposure assessments were not required as the fumonisins were of low acute toxicity.

36. The Committee discussed the differences in the conclusions between paragraph 44, which concluded that the (PM)TDI may be exceeded in infants and children, and paragraph 47, which concluded that intakes were within the (PM)TDI. The latter was based on the UK Total Diet Study (TDS). However, infant formula was not included in the TDS. The conclusion in paragraph 44 was based on the intakes estimated for consumption of infant formula in infants younger than 6 months using data from the Zimmer et al. study. This will be clarified in the statement.

37. The Committee agreed to include the fumonisins in an addendum to the overarching Statement on potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years.

Item 6: Review of potential risks from moniliformin (MON) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years – TOX/2019/03

38. No interests were declared.

39. As part of the review by SACN of Government recommendations on complementary and young child feeding, the COT had been asked to review the toxicities of chemicals in the diets of infants and young children aged 1-5 years. This review included mycotoxins including moniliformin (MON).

40. Members questioned the suitability of a 90-day repeat-dose study (Jonsson et al. 2015) for an acute risk assessment, and whether cardiotoxicity (heart failure) in rats would be observed after a single dose. The NOAEL of 6 mg/kg bw identified from this study was considered to be conservative for acute risk assessment.

41. It was noted that acute toxicity studies in other animal species were referenced in the EFSA opinion with points of departure below the NOAEL of 6 mg/kg bw for cardiotoxicity. These included a NOAEL of 0.92 mg/kg bw/day from a developmental

and reproductive toxicity study in mink. It was not clear why EFSA did not use a lower point of departure.

42. Members questioned whether a 28-day toxicology study in pigs was of sufficient duration to be used for chronic risk assessment. Furthermore, it was questioned why the measured endpoint of haematotoxicity in this study was not used for the acute risk assessment. No evidence was identified as to whether haematotoxicity was not also an acute effect because no intermediate timepoint data were apparent from the EFSA opinion. The original study should be checked. However, even if the point of departure for acute risk assessment was decreased by about 10-fold, the MOE's would still appear to be acceptable. One Member questioned whether the haematotoxicity was caused by a genotoxic mechanism, but this was considered to be unlikely.

43. It was noted that for the LC-MS/MS analysis of MON, only one concentration was used to spike the food group samples. This was considered to be a limitation of the analytical method, and confidence in the analytical results would be greater if several concentrations were used to spike samples.

44. Overall, all of the calculated UK MOEs were considered to be acceptable. Members agreed with the MOE approach taken for MON for assessing human health risk and noted that for the acute risk assessment of a non-genotoxic endpoint, an MOE > 100 would be considered protective if based on the study of haematological effects.

45. For chronic risk assessment, the estimated MOEs of ≥ 650 were considered acceptable. Normally, an MOE of >100 would be considered of low concern, but taking into account the absence of long-term toxicology studies and that the exposure estimates were based on non-detects, the Committee felt that there would be potential concern if the MOE was below 500.

46. The Committee agreed that moniliformin could be included in an addendum to the overarching Statement.

Item 7: Review of potential risks from tetrabromobisphenol A (TBBPA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2019/04

47. Professor A. Boobis declared that he was a member of the EFSA CONTAM panel in 2011 and of the working group that evaluated TBBPA.

48. As part of the review by SACN of Government recommendations on complementary and young child feeding, the COT was asked to review the toxicities of chemicals in the diets of infants and young children aged 1-5 years. This review included tetrabromobisphenol A (TBBPA).

49. Members agreed that hydrolysis of conjugates of TBBPA in breast milk was a possible explanation for the high concentrations of TBBPA measured therein. However, Members questioned whether conjugates of TBBPA would appear in breast milk due to their relatively high hydrophilicity.

50. Members concluded that the available scientific data indicate that the carcinogenicity of TBBPA is not mediated through a genotoxic mechanism. Given the

absence of genotoxicity, that there were plausible non-genotoxic modes of action, and that tumours were only observed at high doses, the estimated MOEs to the LOAEL for carcinogenicity of approximately 10 million were considered to not be of concern.

51. The calculated MOEs were approximately 1 million or greater when using the critical point of departure derived by EFSA, a $BMDL_{10}$ based on decreased circulating T4 in a study in rats, and were considered not to be cause for concern.

52. Members discussed the previous TDI established by the COT in comparison to the MOE approach used by EFSA. The $BMDL_{10}$ used by EFSA was lower than the NOAEL used previously by the COT to establish its TDI and was based on more recent information.

53. The Committee agreed that TBBPA could be included in an addendum to the overarching Statement.

Item 8: Risks to human health from the use of antimicrobials in chicken and other poultry (Reserved Business) -TOX/2019/05

54. The FSA was preparing for a future outside the European Union (EU). In anticipation of the UK Government engaging in trade negotiations with various countries, the FSA had identified a number of food production practices and uses of chemicals in the food chain in countries outside the EU, which were currently prohibited in the EU and on which the FSA would need to form a position on the risks to health.

55. This item was discussed as reserved business.

Item 9: Risks from residues of a class of veterinary product used in beef cattle (Reserved Business) - TOX/2019/06

56. Professor Boobis declared that he had been a member of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) when it evaluated some of these veterinary products in 2000-2008. Dr Thompson declared that he had been a member of the Veterinary Products Committee (VPC) when it adopted the report these veterinary products. No other interests were declared.

57. This item was discussed as reserved business.

Item 10: Update paper for information: FSA Scientific Advisory Committees (SACs) – TOX/2019/08

58. This paper was tabled for information.

Item 11: Any other Business

59. No other business was discussed.

Date of Next Meeting

60. The next meeting would be held on Tuesday 19th March at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ