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

Minutes of the meeting held on Wednesday 13th December 2017 in Aviation House, London.

Present

Chairman:	Professor Alan Boobis	
COT Members:	Dr Phil Botham	
	Ms Jane Case	
	Dr James Coulson	(by teleconference)
	Dr Rene Crevel	
	Professor John Foster	
	Dr Mark Graham	
	Professor Roy Harrison	
	Dr Sarah Judge	
	Professor Brian Lake	
	Ms Juliet Rix	
	Professor Faith Williams	
Food Standards Agency (FSA) Secretariat:	Mr B Maycock	FSA Scientific Secretary
	Ms C Mulholland	
	Dr D Gott	
	Ms F Hill	
	Dr J Shavila	
	Dr D Hedley	
	Ms C Potter	
	Dr B Dörr	
	Ms C Tsoulli	
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Assessors:		
Officials:	Dr C Baskaran	FSA
	Mr I Smith	FSA
	Ms Rachel Elsom	PHE
	Mr L Rockett	WRc

Other Invited Experts and Contractors:	Prof P Aggett	SMCN
	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 welcomed Ms Chara Tsoulli as a new member of the Secretariat and expressed condolences on behalf of the Committee to Ms H Gbormittah (COT Administrative Secretary) for the recent death of her mother.

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 J Cade, Dr J Thompson, Prof M Wright and Dr C Harris. Prof T Gant from PHE and Ms M Benton from HSE also apologised for absence. Dr J Coulson joined the meeting by teleconference.

Item 2: Minutes from the meeting held on 5th September 2017 - TOX/MIN/2017/05

5. The minutes were agreed subject to the date being changed from 4th September to 5th September.

Item 3: Matters arising from the meeting held on 5th September 2017

Item 3: Matters arising from previous meetings:

6. Para 7: The PBDEs statement had been published.

7. Para 8: The report of the joint COT/Scientific Advisory Committee on Nutrition (SACN) working group on potassium-based replacements had been published, along with the statements from the COT and SACN.

8. Para 10: The nickel statement would shortly be sent to the Chairman for clearance by Chairman's action.

9. Para 14: The addendum to the 2014 COT statement on potential risks from vitamin A in the infant diet had been published.

Item 5: Draft statement on reformulation of 2-chlorobenzylidine malonate (CS) as an irritant spray – TOX/2017/36

10. The draft statement had been revised according to Members' comments in September. The Secretariat was discussing with the Home Office Centre for Applied Science and Technology (CAST) what information could be released in the COT statement and, once complete, arrangements would be made to publish the statement.

Item 7: 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

11. The statement was in the process of being finalised and cleared by Chairman's action.

Item 10: Second draft statement on the results of the 2014 survey of metals and other elements in infant foods – TOX/2017/40

12. The statement was in the process of being finalised and cleared by Chairman's action.

Item 12: Heat-not-burn tobacco products – second draft statement

13. The statement and non-technical summary had been amended according to the Committee's comments at the September meeting, and the non-technical summary had been circulated for comment as agreed. The statement and non-technical summary had then been approved by Chairman's action, and published on 12th December, with an associated press release.

Item 4: Review of potential risks from ochratoxin A (OTA) in the diet of infants ages 0 to 12 months and children aged 1 to 5 years – TOX/2017/45

14. The Chairman declared that he was a member of the European Food Safety Authority (EFSA) CONTAM panel that agreed an opinion on recent scientific information on ochratoxin A in 2010.

15. The COT had been asked to consider the toxicity of chemicals in the diets of infants and young children aged 0-5 years, in support of a review by the SACN of government recommendations on complementary and young child feeding. The Food Standards Agency (FSA) had completed a survey of 36 mycotoxins in the 2014 Total Diet Survey (TDS) – mycotoxins analysis. A scoping paper (TOX/2017/30), highlighting details of the concentration data and toxicology of mycotoxins surveyed, had been discussed by the COT in July 2017. Members had concluded that the potential risk from certain mycotoxins, such as OTA, should be reviewed in more detail.

16. This paper summarised the *in vivo* toxicological studies carried out since the opinion by EFSA in 2006. The derivation of the health based guidance values (HBGVs) established by EFSA and the Joint FAO/WHO Expert Committee on Additives (JECFA) were detailed. An exposure assessment for OTA in breast milk, using European data from the literature, had been provided. An exposure assessment had also been carried out using data from a two-year FSA retail survey testing for levels of mycotoxins, including OTA, in a variety of products.

17. The Committee discussed the use of the EFSA TWI and whether any of the newer studies might be more appropriate to establish an HBGV. It was noted that the interpretation of the available studies (two pig studies previously used in the JECFA evaluation in 2001) and the resulting TWI established by EFSA in 2006, were conservative. EFSA had applied an uncertainty factor (UF) of 450, which, while appearing to be justified, added to the overall conservativeness of the TWI. The members discussed EFSA's use of an UF of 6 for kinetic differences in consideration of the plasma half-life in pigs compared to humans, and requested more detail on the half-life of OTA in humans and on the reliability of the data. The Committee agreed that, in the absence of suitable recent toxicological studies, the TWI established by EFSA was the most appropriate value. Members requested that the text reflect that the Committee considered the TWI to be conservative.

18. Members raised concern about the exposure to OTA of infants exclusively fed with breast milk. The Committee noted that the data on concentrations in breastmilk from the literature were skewed, suggesting generally low exposures, although outliers were still a potential cause for concern. The Committee requested that additional text be added to reflect the uncertainties arising from the skewed distribution of the data.

19. The Committee discussed the available studies on reproductive and developmental toxicity and whether they should be considered to provide additional information on the potential health effects for infants. Members requested an additional sentence noting that the margins of exposure for the level of OTA showing reproductive and developmental effects in the two available rat studies were approximately three orders of magnitude greater than the LOAEL in the pig studies used by EFSA to establish the TWI. This provided some assurance regarding these endpoints.

Item 5: Review of potential risks from manganese in the diet of infants ages 0 to 12 months and children aged 1 to 5 years – TOX/2017/46

20. No interests were declared.

21. The COT had been asked to consider the toxicity of chemicals in the diets of infants and young children aged 0-5 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 in the diets of young children was discussed by the Committee in October 2015. Members concluded that a review of the potential risks from manganese in the diet of infants and young children aged 0-5 years should be conducted.

22. The Secretariat carried out a review of the literature published since the review carried out by the Expert Committee on Vitamins and Minerals (EVM) in 2003. The new studies were presented to COT alongside new calculations of current UK exposures. The Committee noted that a large number of epidemiological studies had been carried out on manganese in recent years and that there was a clear relationship between elevated exposure to manganese, primarily from industrial activities, and neurodevelopmental effects in infants and young children. They concluded that there was insufficient evidence showing how such effects related to exposures from the diet. Members noted that the WHO TDI established during drafting of the drinking water quality guidelines was likely to be conservative.

23. The COT was supportive of the proposal from the Secretariat of submitting a paper on manganese to a peer-reviewed journal. The discussion paper would therefore not be published until this had been confirmed.

Item 6: First draft of the potential risks from T2 toxin, HT2 toxin in the diet of infants aged 0 to 12 months and children aged 1 to 5 years – TOX/2017/47

24. The Chairman declared that he was a Member of the EFSA CONTAM panel that agreed the EFSA 2011 Opinion on T2 and HT2.

25. 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).

26. A scoping paper (TOX/2017/30) and discussion paper (TOX/2017/41) were presented to the Committee at the July and September 2017 meetings, respectively. This first draft statement (TOX/2017/47) provided an updated exposure assessment

using data from a 2015 FSA retail survey on oat-based products. Using the available software, it had not been possible to conduct benchmark dose modelling analysis by model averaging with the data used to establish the acute reference dose (ARfD).

27. The Committee discussed the ARfD with respect to the use of the mink as an appropriate model for emesis in humans and expressed concern with the size of the ratio between the BMDU and the BMDL used by EFSA to establish the ARfD. Members agreed that the ARfD could be used with an explanation of the caveats. Further clarification of the exposure assessment was also requested. Some other minor amendments were requested and a revised draft statement would be brought to the February 2018 meeting.

Item 7: Discussion paper on potential risks from copper in the diet of infants ages 0 to 12 months and children aged 1 to 5 years – TOX/2017/48

28. No interests were declared.

29. Copper was 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.

30. The Committee was asked for its opinion on the use of two different health-based guidance values – 100 μg/kg bw from the European Commission's former Scientific Committee on Food (SCF) and 160 μg/kg bw from the EVM. Members considered the EVM value to be robust and that this should be used for the risk characterisation. The SCF value was not inconsistent with the EVM value but was based on a study in human volunteers in which the NOAEL was the highest dose tested, and thus was more conservative.

31. Members agreed that aggregating exposures was unnecessary since non-dietary routes constituted in general < 1% of the total and that there was no concern for the health of infants and young children from the dietary exposures presented.

32. One Member expressed concern that the levels of copper presented by the water agencies and used to make up infant formulae were not for "first draw" water that had sat in plumbing pipes and absorbed copper overnight. If "first draw" water or water from the hot tap were used then levels of copper and hence intake might have been higher than presented. This should be highlighted in the statement.

33. A draft statement would be produced for consideration at a future meeting.

Item 8: Potential toxicological risks from e-cigarettes. Paper 1: Characterisation of the aerosol droplet particle fraction – TOX/2017/49

34. The Chairman declared that he was a member of the World Health Organization Study Group on Tobacco Product Regulation (WHO TobReg) and Convenor (Chair) of the International Organization for Standardization (ISO) Technical Committee (TC) 126 Working Group 10 on an “Intense smoking regime”. Professor Williams declared a personal non-specific interest in that her brother-in-law was a retired senior manager from British American Tobacco (BAT), one manufacturer of e-cigarettes, and in receipt of a pension from BAT. Professor R. Harrison declared that he had contributed to a paper on the volatile compounds in e-cigarette aerosols.

35. During an horizon scanning exercise at the February 2016 COT meeting, the Committee agreed that the subject of the possible human health effects of e-cigarettes (EC) should be evaluated by the COT. It was decided that a full systematic review would not be an efficient way to proceed, and the Committee recommended a more focused review, starting with three key areas: additives, nitrosamines produced by EC use, and secondary exposure to exhaled products.

36. A scoping document (TOX/2016/25) reviewing these three areas was discussed by the Committee in July 2016, with the aim of setting priorities for more in-depth reviews. From these discussions, several areas were agreed for further consideration: the composition of particles; bystander exposure to key analytes; effects of long term inhalation of the main constituents and emissions; the flavourings used (exposure, thermal products, toxicity on inhalation); exposure to metals from the device components. The Committee agreed that further discussion papers should be prepared to address these issues.

37. Paper TOX/2017/49 addressed the first of these topics, the particulate matter found in the mainstream aerosol produced from EC use, focusing on the physical characteristics of the particles. A number of studies had been performed in recent years, using a range of different methodologies and instruments, test materials, test devices and test parameters. This area was still relatively early in development for EC, and because of the current lack of standardisation in protocols and testing equipment, the findings that had been reported were often inconsistent.

38. Evaluations to date suggested that EC aerosol particulate matter comprised submicron particles and nanoparticles. The relative proportion of submicron and nanoparticles was difficult to estimate due to experimental limitations. In addition to aerosol droplets, solid particles (e.g. metal nanoparticles) could also be present, and this area would be reviewed in a future paper.

39. Members noted that the voltage of some devices (third generation) could be manipulated to increase the nicotine dose, but it was unclear whether this would affect the number and size of the particles. Such devices were relatively new so data on them had yet to be published. The EC field was rapidly developing and only information on first and second-generation devices was currently published.

40. In terms of experimental approaches, the Committee pointed out that dilution would affect what was measured. The most relevant studies to humans would be those using low dilution and high humidity, and the next step in the research should move to investigating the deposited doses.

41. Members noted that it would be important to determine the solubility of the particles in the aerosol. It was, moreover, not clear whether the nicotine would be present in the droplets or in the vapour phase. The main solvents were glycerine and propylene glycol, so the nicotine was likely to be very soluble in these and so very bioavailable. The glycol was likely to form micelles in water and would also be absorbed through the skin. Nicotine levels present in the devices were very variable and there were few data available on blood nicotine levels of e-cigarette users.

42. The total number of particles in the nanoparticle to sub-micron range produced by ECs was in the order of 10^9 particles/cm^3, which is comparable to conventional cigarette smoke. The size distribution of the particles has also been reported to be similar to that of normal cigarettes, though the key consideration should be the comparability of the particles. It was noted that particles from e-cigarettes might not occur in a unimodal size range, with some reports suggesting bimodal distribution. The particles could coagulate and any present as nanoparticles would likely agglomerate. Particles smaller than 10 µm would be inhaled and could physically affect the lung epithelium. The condensation rate of droplets was dependent on their concentration in air, so that the higher the concentration, the more rapid the coagulation into larger droplet particles. Because of these effects it was noted that the size distribution might not be key in determining the biological effect.

43. Since most of studies were funded by manufacturers it was pointed out that there might be concerns about their objectivity, but an increasing amount of information was being provided by independent researchers. International standards were also being developed, and groups are also working to develop suitable testing methods for e-cigarettes.

44. The metal particles that could be released from the devices included copper, tin, zinc, cadmium and chromium but the later generations of EC devices were considered likely to release fewer metals from their elements. This would be considered in more detail in a future paper.

45. The study by Pankow (Aerosol Science 107:9-13, 2017), a theoretical discussion of the partitioning of the compounds, suggested that trace levels of various harmful chemicals could occur. However, the same volatile compounds that were substances of concern were also produced by conventional cigarettes and it would be important to consider differences in relative exposure.

46. It was noted that, as well as the statement, there would be a lay summary for this work summarising the various papers that would be discussed. It was noted that the there was little information and a lot of uncertainty so that it was important to describe the difficulties in data interpretation.

Item 9: Risk assessment of regulated products (Reserved Business) – TOX/2017/53

47. Regarding potential conflicts of interest, it was noted that all Members would have a general interest in this topic; however, this discussion was limited to general principles only.

48. This item was discussed as reserved business.

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

49. This paper was for information only. This statement had been finalised by Chairman's action and would be published at the same time as the manuscript in the peer-reviewed literature. A date for this had not yet been agreed.

Item 11: Third draft guidance for submission of papers to COT regarding irritant sprays and information required – TOX/2017/51

50. The Home Office CAST regularly seeks advice from the COT on the safety-in-use of formulations of irritant sprays for use by the police. The COT had agreed to provide guidance to applicants on the types of information that should be provided to enable the Committee to conclude on the safety of the formulations. Drafts of the guidance were considered at the February and September 2017 meeting. Members were asked to consider this revised draft.

51. A number of further amendments were requested, which should also be brought to the attention of CAST. It was agreed that, once the revisions were made, the guidance could be cleared by Chairman's action.

Item 12: Paper for information: FSA Scientific Advisory Committees (SACs) update – TOX/2017/34

52. This paper was provided for information.

Item 13: Any other business

53. The draft Guidance by EFSA and the European Chemicals Agency (ECHA) on identifying endocrine disruptors had been published for public consultation. The Committee agreed to respond to this consultation. Members agreed to send their comments to the Secretariat by the middle of January 2018 for collation and submission.

Date of next meeting

54. Tuesday 6th February 2018 at Jury's Inn, Birmingham, followed on the 7th by a joint workshop on the microbiome with the Interdepartmental Group on Health Risks from Chemicals (IGHRC). It was noted that this was the last time that the COT would meet at Aviation House, as the FSA would be moving to new premises at the beginning of 2018.