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

Minutes of the meeting held on Tuesday, 2nd of July 2019 in Broadway House Conference Centre, Tothill St, London SW1H 9NQ

Present		
Chairman:	Dr Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr Stella Cochrane Dr James Coulson Dr René Crevel Prof John Foster Dr Caroline Harris Dr Gary Hutchison Dr Gunther Kuhnle Dr David Lovell Dr Mac Provan Dr Michael Routledge Dr Cheryl Scudamore Dr Natalie Thatcher Dr John Thompson Prof Matthew Wright Prof Maged Younes	
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland Dr A Cooper Mr B Maycock Mr Daniel Medlock Ms F Hill Dr D Hedley Dr O Osborne Mr J Shavila Ms Sabrina Thomas Ms C Tsoulli Ms F Uy	FSA Scientific Secretary
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Assessors:	Dr Tim Gant Ms Valerie Swain	PHE HSE

Officials:	Dr Amie Adkin	FSA
	Dr Sarah Bull	WRc
	Dr Kate Vassaux	WRc
	Ms Rachel Elsom	PHE
	Ms Alison Asquith (Item 5)	FSA Novel Foods Policy
	Ms Lisa Nelson (Item 5)	FSA COMMS
	Ms Gillian McEneff	BEIS
Other Invited Experts and Contractors:	Dr Lin Wylie (Item 4)	DSM Nutritional Products (by TC)
	Dr Annette Thiel (Item 4)	DSM Nutritional Products (by TC)
	Dr Chris Jones (Item 5)	MHRA (by TC)
	Dr John Clement (Item 10)	MHRA
Observers:	Ms Julia Heckenast	FSA CSAT
	Mr Freddie Lachmann	FSA

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Announcements

1. The Chair welcomed Members and other attendees.

2. The Chair welcomed in particular the nine new Members that had joined COT and were attending their first meeting, asking them to introduce themselves. The new members are: Dr Stella Cochrane, Dr Gary Hutchison, Dr Gunther Kuhnle, Professor David Lovell, Dr Mac Provan, Dr Michael Routledge, Dr Cheryl Scudamore, Dr Natalie Thatcher and Professor Maged Younes.

3. The Chair welcomed and introduced two new members of the Secretariat, Daniel Medlock and Sabrina Thomas.

4. The Committee were informed that COT Administrative Secretary Hetty Gbormittah has taken up a one-year temporary promotion and would not be working with COT for the moment. The Secretariat hoped to have cover for Hetty in place shortly but for the moment Members were asked to contact the COT mailbox or the Secretariat directly.

5. The Chair also announced that Dr Sarah Judge was not at the COT meeting as she was getting married. The Committee expressed their congratulations

Interests

6. 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

7. Apologies were received from COT Members Dr Sarah Judge, Ms Juliet Rix, Dr Mirielle Toledano, Prof Faith Williams, from Prof Ken Ong and Prof Paul Haggerty from SACN, Mr Ian Martin (Environment Agency), Mr Will Munro (Food Standards Scotland) and Dr David Gott and Ms Claire Potter from the COT Secretariat.

Item 2: Minutes from the meeting held on 7th of May 2019.

8. The draft minutes from the meeting on 7th May were accepted as an accurate record. The reserved minutes were also accepted as an accurate record.

Item 3: Matters arising from the meeting held on 7th May 2019

Item 3: Matters arising from previous meetings:

9. Para 6: The Chair briefed the Members on the recent Scientific Advisory Committee (SAC) Discovery Day, The Members were informed that it had been an interesting day and it had been useful for new and existing Members of the different

FSA SACs and their Secretariats to meet at this kind of event. It was also noted by one of the new Members that it had been useful to hear about the experiences of current SAC Members.

Item 12: COT statement on phosphate-based flame retardants and potential for neurodevelopmental toxicity

10. The requested amendments have been made to the draft statement and it will be sent for approval by Chair's action shortly.

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

11. For the benefits of new Members, it was explained that, at the request of Department of Health and Social Care (DHSC), the Scientific Advisory Committee on Nutrition (SACN) was undertaking a review of scientific evidence that would inform the Government's dietary recommendations for infants and young children from birth to age five years. 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 (0-12 months) and young children (1-5 years). The reviews would identify new evidence that has emerged since the Government's recommendations were formulated and would appraise that evidence to determine whether the advice should be revised. Most of this work has now been completed.

12. Where a full review was not needed, short summaries of the information available on the safety of chemicals of interest have been presented to the Committee. Conclusions and recommendations have been published in 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 years" (COT Overarching Statement 2019/02). The results of the ongoing work will be published in an addendum to the Overarching Statement.

13. As part of the ongoing review, four short papers were presented under Matters Arising. The chemicals discussed in these papers have been previously evaluated by the Committee, but some additional information had been requested.

Para 44: Polycyclic aromatic hydrocarbons (PAHs) - TOX/2019/27

14. No interests were declared.

15. A scoping paper on PAHs (TOX/2019/21) was presented to the COT in May 2019 and the Committee had agreed that a full review paper was not required, and that PAHs could be included in the addendum to the 2019 Overarching Statement. However, while the Committee had agreed in principle that since most of the dietary exposures led to margins of exposure (MOEs) greater than 10,000 and thus were of low concern for health, some MOEs were lower than this. Hence, consideration of the degree to which this might be offset because exposure was for less than lifetime should be included in the overarching statement. Moreover, the Committee had requested that the basis for the health-based guidance values (HBGVs) for BaP and

PAH4 should be included and the data on exposure from soil should be brought into line with earlier assessments. The current paper sought to address these comments

16. The Chairman pointed out that the $BMDL_{10}$ values provided were actually points of departure (PODs), not HBGVs.

17. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the European Medicines Agency (EMA) had concluded that the acceptable dose of genotoxic impurities in medicines given to human volunteers and patients could be modified depending upon the duration of exposure. While the risk-benefit was not the same as that from exposure to toxicants in the diet, Members concluded that the principle was scientifically valid and agreed that a similar approach would be applicable in this case. Therefore, the Committee agreed that while it was reasonable to state that the exposure of children to PAHs should be as low as possible, a MOE of < 10,000 over a short period of life would not necessarily be a major concern for potential effects on health.

18. Members stated that this was not the first time this subject had been brought to their attention and proposed codifying their acceptance of this principle for genotoxic carcinogens.

19. The Chair suggested that an explanation of why toxic equivalency/relative potency factors had not been used in this paper should be included.

February 2019: Exposure estimates from a possible source of exposure for fumonisins via consumption of infant formula - TOX/2019/28

20. No interests were declared.

21. A discussion paper (TOX/2019/02) was presented to the COT in the February 2019 meeting, which reviewed the potential risks from fumonisins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. Following that, the Committee wished to further review the relevant exposure data for infant formulae.

22. The authors of the intake study of fumonisins in Germany (Zimmer *et al.*, 2008)[1] referred to in the previous paper, provided further information to clarify that the infant food was follow-on formulae for children aged from 6 months.

23. Paper TOX/2019/28 presented recalculated fumonisin exposures based on the additional information, utilising UK consumption data.

24. No general comments on the discussion paper were made.

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

25. The Committee discussed the basis of the EFSA tolerable daily intake (TDI) and the JECFA provisional maximum tolerable daily intake (PMTDI), which was for hepatotoxic effects. The potential for immunotoxicity of fumonisins in infants aged > 6 months was noted by a Member, adding that this was a critical time window for vaccination. However, EFSA had considered this endpoint when establishing the TDI, which would therefore be protective of immunotoxic effects.

26. The Committee agreed that the exceedances of the HBGVs were not a major cause of concern since these happened at the maximum concentration of fumonisin and 97.5th percentile consumption levels, which would not be expected to occur on a daily basis, or indeed with any great frequency at all.

27. It was agreed that continued monitoring and representative UK data on fumonisins were required. The Secretariat commented that the FSA had surveillance data for mycotoxins and would review this.

28. The Secretariat was further asked to review the literature to gather data on any differences between the metabolism of fumonisins in adult and infant mice, the species on which the HBGVs were based, and the cumulative risk of mycotoxins.

Para 37: 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/2019/29

29. No interests were declared.

30. Following consideration of paper TOX/2019/29 - 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, COT Members had requested further consideration of the *in vivo* genotoxicity data on 3-MCPD to confirm that it was not genotoxic. Providing this could be confirmed, the Committee agreed with EFSA's evaluation of 3-MCPD and its fatty acid esters.

31. Paper TOX/2019/30 provided additional details on the evaluations of MCPD genotoxicity by the EFSA COMTAM panel and by the Committee on the Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM). The EFSA CONTAM Panel considered that the available studies (i.e. micronucleus, comet and Pig-a mutation assays) indicated that 3-MCPD was not genotoxic *in vivo*. In addition, it was noted that the Committee on Mutagenicity (COM) had concluded in 2000 that 3-MCPD could be regarded as having no significant genotoxic potential *in vivo*.

32. The Committee agreed that 3-MCPD was not genotoxic *in vivo* and thus endorsed EFSA's 2016 evaluation of 3-MCPD and its fatty acid esters.

2017: Review of potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years: Mycotoxins - TOX/2019/30

33. The Chair declared he had been a member of the CONTAM Panel during the time some of the mycotoxins were assessed by EFSA. No other interests were declared.

34. Based on a scoping paper (TOX/2015/32) reviewed by the COT in 2015, a second scoping paper (TOX/2017/30) was presented to the Committee at the July 2017 meeting, providing exposure assessments for all the mycotoxins measured in the UK Total Diet Study (TDS). Members requested a full review of a number of mycotoxins, some of which have been previously presented to the COT or will be presented in due course. The summaries presented in TOX/2019/30 included mycotoxins for which a further detailed review had not been requested.

35. The Committee discussed the mycotoxins presented and noted that the MOE for aflatoxins could be as low as 15. While this was partly due to the concentrations of aflatoxins being below the limit of quantification (LOQ) and therefore exposure calculated at upper bound levels, it raised the question of uncertainties and possible recommendations, especially should more sensitive analytical methods arise in the future. Members requested the range of values (lower bound (LB) and upper bound (UB)) be included in the assessment. They also asked for results of cancer studies on neonatal/prenatal rats be provided, if available, to allow consideration of the differences in sensitivity between infants and adults.

36. The Committee noted that citrinin was classified as a group 3 carcinogen (not classifiable) by IARC and asked for more information on this, given that citrinin induced kidney adenomas in an 80-week rat study. Members further noted that the studies on reproductive/maternal toxicity were single dose studies and asked for the time point of exposure during gestation to be provided and more information on whether the effects might be secondary to maternal toxicity. Members requested the range of values (LB and UB) for exposure to citrinin be included in the assessment and noted that the text needed to reflect more strongly the potential concern regarding the genotoxicity and carcinogenicity of citrinin, although the level of concern was unknown, due to the uncertainties in the database.

37. Members discussed EFSA's conclusion that the reported genotoxicity for zeralenone may be related to oxidative stress and noted that the margin between the $BMDL_{10}$ and the TDI was in the region of 25,000, which was above the margin of 10,000 indicating low concern. The Committee further discussed the estrogenic effect in different species and agreed with EFSA's assessment that an uncertainty factor (UF) for inter-species variability would not be required as humans would not be more sensitive than female pigs.

38. The Committee agreed that ergot alkaloids (EA), sterigmatocystin (STC), zeralenone (ZEN) and nivalenol (NIV) could be included in the Addendum to the Overarching Statement. Members asked to review the additional information requested for aflatoxins and citrinin at the next meeting.

Item 4: Male reproductive toxicity of a novel feed additive, 3-nitro-oxypropanol (3-NOP): benchmark dose modelling report (Reserved Business) - TOX/2019/31

39. No interests were declared.

40. As commercially sensitive information was being considered, this item was discussed as Reserved Business.

Item 5: Scoping paper on the potential adverse effects of CBD products - TOX/2019/32

41. Dr Stella Cochrane and Dr Natalie Thatcher declared that their employers, Unilever and Mondelez International, respectively, have an interest in using cannabidiol (CBD) in their food products. This was considered to be a non-personal specific interest and they were able to contribute to the discussion. No other interests were declared.

42. The potential medical applications of CBD have been investigated and researched for several years, including clinical trials for treatment of epilepsy and seizures. However, non-medicinal CBD-containing products are becoming increasingly popular and have now entered the food sector, including beverages (beer, spirits, wine, coffee and soda style drinks), topicals (tinctures, drops, syrup, olive oils, oils) chewables (gum drops) and chocolate. These products are classified as novel foods which means there is no significant history of consumption in the EU and that they need to be authorised before being placed on the market.

43. Risk assessment advice on CBD has also been increasingly requested from the Food Standards Agency (FSA). It was therefore considered timely for the available toxicological information on CBD to be reviewed.

44. The Committee noted that some CBD products would not only contain CBD but also other cannabinoids such as tetrahydrocannabinol (THC), potentially due to different extraction methods. It was noted that the presence of THC above certain levels would mean that the product would not be authorised as a novel food and would become the responsibility of the Home Office under legislation on the mis-use of drugs.

45. The Committee agreed that there was potential for interactions between the cannabinoids present in CBD products and this in turn, could affect the potential adverse effects of CBD.

46. The Committee agreed that there was a lack of data on the mechanism of action of CBD and whether it was truly non-psychoactive. In particular, there was a lack of understanding of the potential interactions at CB1 and CB2 receptors, as well as the endocannabinoid system, of CBD. A point of departure for CBD could not be identified.

47. Members noted that there was currently a lack of data concerning the absorption of CBD from different food matrices. There was also little information on plasma concentrations and the bioavailability of CBD in different products. The extent of inter-individual variation in disposition of CBD was also uncertain.

48. The Committee noted that CBD could potentially accumulate in adipose tissue (including the brain) as well as other areas of the body due to its lipophilic properties.

49. It was highlighted that based on the currently available *in vitro* and *in vivo* data, CBD appeared to have the following adverse effects: hepatoxicity, immunotoxicity, reproductive toxicity, changes to organ weights and alterations to drug metabolizing enzymes (P450), suggesting adverse effects could occur in consumers. The Committee agreed that there was a lack of toxicological information especially in the areas of reproduction and immunology.

50. The changes to drug metabolizing enzymes following CBD exposure indicated the potential for drug interactions.

51. It was noted that the U.S. Food and Drug Administration (FDA) had approved the first oral solution drug called Epidiolex® - a purified form of CBD oil - comprised of an active ingredient of marijuana to treat epilepsy. Members highlighted that on the Epidiolex® safety data sheet the most common adverse reactions noted were somnolence, decreased appetite, diarrhoea, transaminase elevations (hepatocellular injury), fatigue, malaise, asthenia, rash, insomnia, sleep disorder/poor quality sleep and infections. The supporting data for these observations were not publicly available.

52. It was agreed that the data from the medicinal/pharmaceutical sector on CBD would be very useful if it could be obtained as most of it was currently not publicly available. However, it was important to note that the safety profile of food grade CBD products might be different to medical grade products due to differences in composition.

53. As the genotoxicity data were conflicting but indicated genotoxic potential in some but not all *in vivo* studies, the Committee recommended the genotoxicity data be referred to COM for consideration.

54. The Committee agreed this topic should be reviewed once more data becomes available.

55. Overall, the Committee agreed that it could not reach a conclusion on the safety in use of CBD products based on the information presented.

Item 6: Additional data regarding fusarenon-X (Fus-X) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2019/33

56. No interests were declared.

57. A discussion paper was presented to the COT in the May 2019 meeting, which reviewed the potential risks from fusarenon-X (Fus-X) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. Following that, the Committee asked the Secretariat to obtain additional information on a number of topics; whether it might be appropriate to use mink emesis data, as had been done for type A trichothecenes, the comparative toxicity of Fus-X to other trichothecenes, and combined exposures with other mycotoxins.

58. It was noted that mink emesis data had been used to derive the benchmark doses (BMDs) for other trichothecene families. EFSA had concluded that humans were no more sensitive than mink towards the emesis effect, since the doses of emetine causing emesis were similar in both species. However, this is some residual uncertainty as to whether this would also apply to all of the trichothecenes.

59. Comparative toxicity data for Fus-X in mink suggest that it was more toxic when compared to several other type B trichothecenes, but was of similar potency to deoxynivalenol (DON) when administered orally. It had lower oral emetic relative potency compared to some type A trichothecenes (HT-2 and T2).

60. Acute exposures of Fus-X showed no cause for concern regarding acute toxicological effects when compared against the acute reference dose (ARfD) of DON, since all the MOE values were above 1,000. However, it was noted that there were some uncertainties involved in the extrapolation of the data.

61. Based on the data presented, the Committee agreed that the acute reference dose (ARfD) of nivalenol (NIV) could not be utilised as a comparative HBGV for Fus-X, since it was more acutely toxic for emetic responses.

62. Additive acute exposures of Fus-X, DON and nivalenol (NIV), showed that DON made the highest contribution. Direct comparisons of the summed acute exposures are below the ARfD for DON (8 µg/kg bw/day).

63. For infants and children aged 12-60 months, a MOE of slightly less than 100 was observed for the summed acute exposures of the type B trichothecenes (Fus-X, NIV and DON) for the UB values of the 97.5th percentile acute exposures. However, the Committee noted that the estimates of acute exposure are highly conservative and therefore the calculated MOE values will also be conservative. Furthermore, the likelihood of co-occurrence of Fus-X with DON and NIV at these levels is low.

64. The Committee concluded that acute co-exposure of Fus-X with DON and NIV was unlikely to result in adverse toxicological effects in infants and young children.

65. Members had no general comments on the discussion paper.

66. The Committee agreed that the summary be added to the Addendum of the 0 to 5 years Overarching Statement.

Item 7: Review of physiologically-based pharmacokinetic (PBPK) modelling used for human health risk assessment - TOX/2019/34

67. The Committee had previously recognised the need to ensure appropriate development and application of generic PBPK models in chemical risk assessment. There was growing interest in the use of these models, which have been developed, for example, through the Health and Safety Laboratory (HSL), the U.S. Environmental Protection Agency (EPA), and through projects such as ACROPOLIS (Aggregate and Cumulative Risk Of Pesticides: an On-Line Integrated Strategy), for both forward and reverse dosimetry.

68. In terms of forward dosimetry, it was recognised that PBPK modelling could be used to verify the appropriateness of test concentrations used for *in vitro* assays through their comparison with estimates of human internal exposure. Furthermore, it was considered that the values generated by high-throughput and *in silico* methods for some model parameters (e.g. partition coefficients and transporter activity) can be associated with varying degrees of uncertainty. It was necessary to assess how realistic and reliable these parameter values are. In addition, the Committee considered that further guidance on the use and application of PBPK models developed for nanomaterials would be helpful.

69. The discussion of the Committee focussed on ways to assess the reliability of human PBPK models in the absence of human pharmacokinetic data. A deficiency of human pharmacokinetic data was often noted for those xenobiotics for which PBPK models are developed and assessed by the Committee. This was central to the discussion held in 2003 when PBPK modelling was last brought to the Committee. Approaches that were considered to assess model reliability in this context included use of the read-across approach and conducting interspecies extrapolations to animal species other than humans. Thus, it was noted that in-house expertise in the field of PBPK modelling will be needed increasingly in the future for the interpretation of these models.

70. The Committee agreed it would be useful to have further information in the form of case studies, for example where *in vitro* data have been successfully extrapolated to *in vivo*, or cases where risk assessments considered in retrospect may have benefitted from PBPK modelling. It was also noted a workshop on PBPK would be beneficial since the last one hosted by the COT was in 2003.

Item 8: Scoping paper on the synthesis and integration of epidemiological and toxicological evidence (SETE) in risk assessments - TOX/2019/35

71. Prof Maged Younes declared that he is a member of the EFSA Panel reviewing the integration of epidemiological data. No other interests were declared.

72. The Committees on Toxicity and Carcinogenicity (COT and COC) have recently published a joint report on synthesising epidemiological evidence (SEES). During their meetings the subgroup also discussed the possibility of quantitative synthesis of epidemiological and toxicological evidence and concluded it would be useful for the Committees to have a clear guidance on the subject, for use by the Secretariat and Members. There is also interest in this combined approach from the PHE Air Quality and Public Health team, who oversee the Committee on the Medical Effects of Air Pollution (COMEAP).

73. The paper presented to the Committee provided a proposed outline of a future document to be developed by a SETE working group, whilst also providing some background information and links to guidance documents and frameworks on the proposed topics, available to the Secretariat at the time.

74. The Committee questioned if a Working Group would duplicate ongoing work, as EFSA is currently assessing data integration. However, Members were informed by Prof Younes, who is part of the EFSA Panel assessing data integration, that EFSA is currently assessing the integration of only epidemiological data, as a next step the integration of only toxicological data would be assessed. The Committee therefore decided that it would be useful to establish a joint Working Group with COC to provide guidance on the integration of epidemiological and toxicological data, as this would not be a duplication due to the different scope of work.

75. Members thought it useful to provide a form of guidance document on the integration of epidemiological and toxicological data and to have a clear statement as to how the Committee worked with such data. However, it was proposed by Members that it should include not only theoretical guidance but also case studies, using a number of chemicals such as folic acid, PFOS, dioxins or lead as real examples of data integration. Members also noted it would be useful for the Secretariat to provide the Working Group with publications where data integration has been applied in a formal way.

76. The Committee further noted that it would be difficult to separate the weight of evidence (WoE) approach from data integration and that this, as well as BMD modelling and uncertainty analysis, would need to be included in the guidance, where appropriate. The Chair noted that it would be most appropriate for the WG members to provide and agree on search terms.

77. Members were asked to consider the expertise needed for the Working Group (WG), which could include epidemiologists, toxicologists, PBPK modelling expertise

and biostatisticians and to forward any suggestions to the Secretariat. Members agreed that it would be appropriate for the Chair of the WG to be a member of the COT to link back to the Committee. The Committee asked if the WG would include only COT and COC members or also observers and were informed that this would be considered by the Secretariat as it had been successful for the SEES WG.

78. The Committee requested clarification about the next steps and was informed by the Secretariat that the scoping paper would be presented to COC at their next meeting. Following the COC meeting, an email would be circulated to Members to establish interest in the WG.

Item 9: Discussion paper on potential risks from various sweeteners in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2019/36

79. Prof Matthew Wright and Dr Natalie Thatcher declared that they were part of the EFSA Working Group on the evaluation of the safety of aspartame. Prof Maged Younes also declared that he chaired the Food Additives and Flavourings panel, which would be undertaking the re-evaluation of sweeteners by EFSA.

80. As part of the ongoing review of chemicals in the diet of infants and young children, an overview of the available information of some of the most commonly used sweeteners in food consumed in the UK was presented, namely: acesulfame K, aspartame, saccharin, sorbitol, sucralose, stevia and xylitol. The data for each sweetener were presented in a separate Annex and Members were invited to discuss the information presented and address the questions at the end of each section.

Annex A – Aspartame

81. The Panel agreed that the Acceptable Daily Intake (ADI) of 40 mg/kg bw which was re-confirmed following EFSA's extensive review was still applicable.

82. Member's noted the lack of information on breastmilk data and dietary exposure for infants aged 0 to 1 years old. They agreed that based on the available data presented in the EFSA evaluation for toddlers aged 12 to 35 months and children aged 1 to 9 years, as well as information presented from an evaluation of the dietary intakes of artificial sweeteners in Irish children aged 1 to 4 years old from a paper by Martyn et al. (2016)[2], all exposures were well below the ADI. The Panel concluded that considering sweeteners were not permitted in baby food and given

[2] Martyn DM, Nugent AP, McNulty BA, O'Reily E, Tlustos C, Walton J, Flynn A, Gibney MJ (2016): Dietary intake of four artificial sweeteners by Irish Pre-School Children, *Food Additives & Contaminants: Part A*,333(4), 592-602.

the lower intake of solid foods in infants aged 0 to 1 years it would be unlikely that the ADI would be exceeded in that age group.

83. A summary of the safety of aspartame in the diet of infants and children aged 1 to 5 years would be included in the addendum to the Overarching Statement.

Annex B- Saccharin

84. The Committee noted that saccharin would be re-evaluated by EFSA in due course as part of their ongoing programme of work re-evaluating food additives. Members were in agreement with the JECFA, SCF and IARC conclusions that the bladder tumours seen in rat feeding studies were specific to that species and of no biological relevance to humans. On that basis, the Committee agreed with the current ADI of 0-5 mg/kg bw based on the information currently available.

85. The lack of breastmilk data and dietary exposures for infants aged 0 to 1 years was discussed. Based on the exposure information provided for children aged 1 to 4 years old, dietary exposure to saccharin remained below the ADI for that age group. It was concluded that since the use of sweeteners in baby food was legally prohibited and due to the lower consumption of solid foods in infants aged 0 to 1 years old, it was unlikely that the ADI would be exceeded for that age group. There was no concern regarding the exposure to saccharin in the diet of infants and young children.

86. A summary of the safety of saccharin in the diet of infants and young children aged 0 to 5 years would be included in the addendum to the Overarching Statement.

Annex C- Acesulfame K

87. The Committee noted that Acesulfame K would be re-evaluated by EFSA in due course. Based on the information currently available Members agreed with the ADI of 0-9 mg/kg bw that was confirmed by the SCF in 2000.

88. Exposure information was based on the paper from Martyn et al. (2016) for the dietary intakes of artificial sweeteners in Irish children aged 1 to 4 years old. The slight exceedance of the ADI in the first exposure scenario presented was discussed and it was concluded that the particular scenario was highly conservative as it assumed the presence of acesulfame K in all relevant food categories at the maximum permitted level. When exposure estimates were further refined using analytical data, exposures were below the ADI. It was agreed that there was no safety concern from the exposure to acesulfame K in that age group.

89. The lack of breastmilk data and dietary exposures for infants aged 0 to 1 years was discussed and it was agreed that it would be unlikely that the ADI would be exceeded for this age group as sweeteners were not permitted in baby foods and

solid food consumption for that age group would generally be lower than that of older children.

90. A summary of the safety of acesulfame K in the diet of infants and young children aged 0 to 5 years would be included in the addendum to the Overarching Statement.

Annex D- Sucralose

91. The Committee noted that Sucralose would be re-evaluated by EFSA in due course. The Committee were satisfied that gastrointestinal effects seen in rabbits were attributable to the sensitivity of the species to poorly absorbed substances as concluded by the SCF in 2000.

92. The Committee was aware of reports on the potential formation of chlorinated organic compounds from the heat degradation of sucralose during cooking and baking. It was agreed that the interim position of the COT to be included in the addendum was that: “On the basis of the current data available there was no concern from exposure to sucralose in the diet of infants and young children aged 0 to 5 years old, however this is pending the completion of the EFSA evaluation and further information on the heat degradation of sucralose.”

Annex E- Steviol Glycosides (Stevia)

93. Members agreed with the ADI of 0-4 mg/kg bw. The Committee discussed the data presented and noted that based on the EFSA exposure calculations from 2010, 2011 and 2014 there was a potential for exceedance of the ADI in the age groups of interest. Members acknowledged that the exposures were conservative as they were based on assuming the presence of steviols in food at the maximum permitted levels and not on analytical data, and they requested information on UK-specific exposures using the EFSA approach due to the potential for exceedance of the ADI.

94. The Secretariat would present the data requested at the September meeting.

Annex F- Sorbitol and Xylitol

95. The Panel noted that EFSA would re-evaluate sorbitol and xylitol in due course.

96. It was agreed that the main safety concern associated with polyols were the laxative effects observed following excessive short term consumption of foods containing polyols. These are well documented, and labelling was in place to warn consumers of the potential effects of acute consumption of large quantities of polyols. There was currently no ADI specified for polyols and the Committee agreed that based on the current information there was no concern for the safety of polyols in the diet of infants and children aged 0 to 5 years.

97. A summary would be included in the addendum to the Overarching Statement.

Item 10: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)

98. Dr John Clements from the MHRA attended for this item.

99. No further declarations of interest were presented in addition to those already declared at the meeting in December 2018.

100. For the benefit of new Members it was explained that at the request of DHSC and PHE, the COT has been reviewing the potential human health effects of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS); which overall are referred to as E(N)NDS. So far, a number of aspects have been considered by the Committee. Once the considerations are complete, a draft statement covering all aspects will be prepared for the Committee to review.

Item 10a: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes): Decision tree for risk assessing flavouring compounds in E(N)NDS - TOX/2019/37

101. At their meeting in May 2019, the COT considered the health effects of two flavouring compounds for use in E(N)NDS products, vanillin (TOX/2019/24) and cinnamaldehyde (TOX/2019/25). During this discussion, the Committee agreed that as a number of flavourings were likely to be considered over time, a decision tree would be a useful tool to aid future assessments.

102. The Secretariat produced a draft decision tree for discussion by the Committee at the present meeting, which included a number of end points to be considered including carcinogenicity, mutagenicity, reproductive, acute, and respiratory toxicity, skin sensitisation, respiratory irritation and repeat dose toxicity. Quantitative Structure Activity Relationships (QSAR) and Threshold of Toxicological Concern (TTC) approaches are proposed where data were lacking.

103. The Chair reiterated that the COT role was not to approve flavourings for use in E(N)NDS, but to provide a conclusion on their safety. It was confirmed that only flavours permitted for use in foods were permitted in E(N)NDS in the UK.

104. Members considered that the term “decision tree” was not accurate and it was decided to use a more generic title, such as “Guidance on the risk assessment of flavouring compounds for use in E(N)NDS”. The Committee concluded that steps 1 and 2 should be altered slightly with skin sensitisation moved from step 2 to step 1

and respiratory sensitisation to step 2 in order to keep the routes of exposure consistent across the steps. The type and persistence of irritation should be clarified and incorporated into the final safety assessment. There is no internationally recognised agreement on TTC thresholds for inhalation exposure. Following a discussion on the values that should be used in this case, the Committee concluded that the oral TTC values should be used as a default, with an assumption of 100% bioavailability.

Item 10b: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes): Toxicological review of nicotine - TOX/2019/38

105. Various aspects of nicotine toxicity have been reviewed in previous COT meetings including developmental toxicity, effects in adolescents and young adults and effects of nicotine as an aerosol. The Secretariat was asked by the Committee at their meeting in March 2019 to conduct a full review of the toxicological data available on nicotine with a view to establishing a HBGV for nicotine, which would be relevant when assessing exposure in both users and bystanders. This subsequent review considered all routes of exposure and all toxicological effects; it was noted that addiction was not covered.

106. The reliability of the presented data for establishing a HBGV were discussed, and the Committee concluded that there is a lack of information available to establishing an inhalation HBGV, unless data from oral exposures to nicotine are used, assuming systemic effects are the most sensitive endpoint, and appropriate kinetic adjustments made. The potential for establishing a value based on avoidance of addiction should also be considered.

107. The Committee questioned whether E(N)NDS devices allow a higher absorption of nicotine when compared to traditional cigarettes in users who have switched. Overall, for existing nicotine users, they would continue to have the same risks, to themselves and their offspring, from exposure to a given level of nicotine as they would have had through use of cigarettes. For non-users, who have never been exposed to nicotine and take up vaping, they will be at risk from toxicological effects of nicotine, to which they would not otherwise be exposed. However, a complication in this assessment is whether the extent to which naïve users take up ENDS rather than conventional cigarettes. This is an aspect on which the Committee does not have the expertise to comment. For bystanders, information would be required on how their exposure compared with levels that could be associated with addiction, as well as other effects.

108. Details from the Lindgren *et al.*(1999)[3] study, which was used by EFSA as the basis of their ARfD for nicotine, were requested for more detailed consideration at the next meeting, along with a summary table of all points of departure (POD) from different agencies to aid comparison with user and bystander exposure levels.

[3] Lindgren, M., L. Molander, C. Verbaan, E. Lunell & I. Rosen (1999) Electroencephalographic effects of intravenous nicotine--a dose-response study. *Psychopharmacology (Berl),* 145**,** 342-50.

109. It was agreed that information on atypical situations and health risks resulting from E(N)NDS use should also be included when the COT statement on this topic is prepared. These included; inhaling and direct consumption of the e-liquid, exploding batteries and the possible confusion around packaging; a Member noted that some users have mistaken e-liquid refills for eye drops/ear drops due to the similarity in packaging.

Item 10c: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes): User exposure - TOX/2019/39

110. As part of the ongoing COT review of potential toxicological risks from E(N)NDS, TOX/2019/39 summarises data relating to potential exposures to E(N)NDS users from inhalation of E(N)NDS aerosol. Concentrations of substances present in E(N)NDS aerosols from studies in which aerosol was produced directly via machine puffing are presented, alongside estimates of maximum exposure and these are compared with available HBGVs.

111. Due to the large inter-survey variability, the intake values used in the risk assessment were based on the highest measured concentrations. This resulted in substantial exceedances of health-based guidance values or available reference values for all substances except for propylene glycol, however the Committee could not easily evaluate the overall health risks to users, without further consideration of how to characterise exposure, including the appropriate dose metric.

112. The Committee noted that for local effects, in particular where air concentration rather than dose by bodyweight is the comparator, the approach adopted of deriving a daily dose would not be appropriate. Another aspect that should be considered if data were available, was the potential for ocular effects.

113. The Chair stated that the issue of particles in the vapour had not been fully resolved but that soluble particles might be less of a concern than insoluble ones. Members considered that the combination of metals and other particles in the vapour could exacerbate the inflammatory response and that the possibility of a protein corona around particles could increase cellular uptake and thus toxicity.

114. It was agreed that a table presenting the ranges of possible user exposures would be presented at the next meeting to provide a clearer basis on which to evaluate the potential overall risk.

Item 11: Paper for Information: FSA Scientific Advisory Committees (SACs) update - TOX/2019/40

115. This paper was provided for information.

Item 12: Any other Business

116. The Committee were informed that the FSA was putting together a register of pre-approved specialists to provide *ad hoc* advice. A number of COT Members had expressed an interest to be on the register, and thus the relevant forms would be circulated in due course.

Date of next meeting

117. The next meeting will be held on Tuesday 17th September 2019 at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ.