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

Minutes of the meeting of the Committee held on 10th March at Manchester Conference Centre, Weston Building, Sackville Street, Manchester, Greater Manchester.

Present

Chairman:	Prof Alan Boobis	
COT Members:	Dr Phil Botham Dr James Coulson Dr Caroline Harris Dr René Crevel Prof Gary Hutchison Dr David Lovell Dr Mac Provan Prof Faith Williams Dr Michael Routledge Dr Cheryl Scudamore Dr Natalie Thatcher Dr John Thompson Prof Matthew Wright Dr Gunter Kuhnle Dr Sarah Judge Prof John Foster Prof Maged Younes	
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland Dr D Gott Dr B Doerr Dr A Cooper Mr B Maycock Ms C Hoppie Dr O Osborne Ms C Potter Dr J Shavila Ms C Thomas Ms S Thomas Ms C Tsoulli Ms F Uy Mr F Lachhman	FSA Scientific Secretary FSA Administrative Secretary
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Officials:	Ms Helen McGarry Mr Alan Dowding	HSE FSA (by Skype)

Assessors	Ms V Swaine	HSE
	Prof T Gant	PHE
	Dr I Martin	EA
	Mr S Fletcher	VMD
Invited Experts and Contractors:	Dr A Povey	University of Manchester
	Dr K Vassaux	WrC
	Dr R Bevan	IEH Consulting
Observers:	E Prochazka	PETA
	Dr A Lorenzoni	FSA

Contents

Announcements

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

2. The Chair announced that this would be the last meeting of Dr John Thompson who had now served 10 years on COT, being Deputy Chair for the last 2 years. The Chair thanked Dr Thompson on behalf of the Committee and the Secretariat for all his hard work over the years.

3. Ms Frances Hill of the Secretariat was leaving the COT Secretariat to take up a 1 year temporary promotion in the Regulated Products team.

Interests

4. 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

5. Apologies have been received from Members Professor Mireille Toledano, Ms Juliet Rix, Dr Stella Cochrane, Ms Jane Case, Ms Daphne Duval from PHE and Dr Douglas Hedley from the Secretariat.

Item 2: Minutes from the meeting held on 3rd of January 2020

6. Mr Liam Johnstone from BEIS had been in attendance and Dr Sarah Bull's affiliation was IEH rather than WRC. There were no other amendments and the minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 3rd December 2019

7. Para 6: Addendum to the Overarching Statement on the potential risks from contaminants in the diet of infants aged 0-12 months and children aged 1- 5 years.

8. The Committee was informed that the addendum was being finalised and would be published shortly.

Para 16: CBD

9. The members were updated on the Food Standards Agency (FSA) announcement on how CBD products currently on the market would be handled. As these products were classified as unauthorised novels foods, they would have 1 year to submit a valid application for authorisation as a novel food or the products would risk being removed from the market. Consumer advice based on the COT discussions was also given in the announcement: This included a maximum recommended intake level of 70 mg CBD/day and that CBD should not be consumed

during pregnancy or with medication. Ms Emily Miles, CEO of the FSA, through the Chair, thanked Members for the work on assessing the safety of CBD.

10. The Committee were also informed that a teleconference took place with US FDA to explain the basis of the FSA advice and approach.

11. Para 76: Horizon scanning

12. Members were informed that the joint COT/COC/COM statement on epigenetics had now been published[1].

Item 4: Safety of turmeric and curcumin: Second draft statement TOX/2020/13

13. No interests were declared.

14. Turmeric has been widely used for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases for centuries.

15. Many of the supposed pharmacological properties of turmeric have been attributed to curcumin, a compound naturally present within turmeric rhizomes. These properties are claimed to include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities.

16. Due to its purported health benefits, the consumption of curcumin/turmeric supplements is increasingly popular. However, a number of reports of hepatotoxicity linked to the consumption of curcumin supplements have been reported in Italy.

17. The FSA has been monitoring incidents related to consumption of raw and powdered turmeric and its supplements. In light of the reported cases and due to the uncertainties surrounding the composition and possible contamination of these products, the COT was asked to comment on the risk to human health from turmeric and curcumin in their various forms.

18. The second draft statement addressed the recommendations made by the Committee on the first draft. These mainly related to separating the different issues of potential lead contamination, the effects of natural constituents and composition, particularly where designed to increase bioavailability.

19. Members made further recommendations on the structure and content of the statement including the need for a comment on current dietary exposure.

20. Members questioned the relevance of comparing exposures from supplement intake to the ADI for dietary curcumin. It was decided that it would not be appropriate

[1] https://www.gov.uk/government/publications/epigenetics-in-chemical-risk-assessment-joint-committee-statement

because synthetic forms or adjuvated curcumin, which may be used in supplements, could have altered toxicokinetic profiles and increased bioavailability thus making the safe levels different from the forms used in food.

21. A number of amendments to the text were suggested by Members and it was agreed that a revised draft statement would be cleared by Chair's action.

Item 5: 2019 COT Annual Report - TOX/2020/14

22. Members were provided with the draft COT section of the Annual Report for 2019 which summarised items considered by the Committee. It contained the lay summaries of COT statements that were published in 2019, provided a summary of each of the EFSA public consultations on which the Committee had given comments/recommendations, work produced or published by COT, detailed the current working groups, and provided a list of ongoing work continuing into 2020. At the end of the section were the declarations of Members' interests for 2019.

23. Members had no substantive comments on the text. Members were then asked to check and update their interests and affiliations and to send in any additional editorial comments on the text to the Secretariat.

24. Members were asked to comment on the extent to which COT evaluations in 2019 had complied with the Good Practice Guidelines in Annex 4 of the report, and if appropriate to make suggestions for future improvements.

25. Members agreed that the problem formulation and approach were clearly defined. With regards to the range of input required, validation of data and information sources, assessment of uncertainty, integration of viewpoints and conclusions, and communication its conclusions and recommendations, the Committee agreed that it adhered to good practice. The Committee were also content with its Terms of Reference.

26. However, a concern was raised regarding paragraph 29 of Annex 4 to the Annual Report, in that Members felt that although feedback on actions was sought and provided by FSA, there was sometimes a lack of detail. In some instances, it was unclear how COT advice had been used in policy.

27. The Glossary to the report had been revised and Members were asked to send any corrections or suggestions for terms that were not currently included to the Secretariat.

Item 6: Potential risks from exposure to microplastics: First draft statement TOX/2020/15

28. Professor Boobis declared a non-personal specific interest as he was a member of a WHO expert group undertaking an assessment of the human health risks to micro- and nano-plastic particles, as a follow-up to their drinking water assessment. He was also involved in an ILSI Europe-convened round table

discussion to identify data gaps in the assessment of the risk to human health of microplastics. No other interests were declared.

29. A number of general comments were provided on the structure and content of the draft statement. These included the lack of discussion regarding dose metrics, issues regarding the expression of exposure and the assessment of study quality. It was noted that microplastics in some foodstuffs (e.g. beer, salt, and honey) were easier to detect and quantify due to the physical state of the food (i.e. liquid or readily dissolved) and therefore were easier to analyse. Overall, the Committee concluded that data were available on an insufficient range of foodstuffs.

30. The Committee agreed that it was important to distinguish between uptake across the GI tract and uptake into internal tissues. Particles <50 µm could be absorbed from the gut via gaps and by phagocytic and endocytic pathways but only those of <1-2 µm in size were able to cross cell membranes of internal organs.

31. Figure 5 of the draft statement, a flow chart which summarised the adverse effects of micro and nanoplastics in animal health, was discussed. It was not clear in which species the reported adverse outcomes had been observed, and it was likely that the figure represented a compilation of all adverse effects seen across diverse species.

32. Information was provided on toxicity to aquatic organisms. The Committee agreed that the focus should be limited to those studies that were of potential relevance to human health.

33. It was agreed that historic data on medical implants, human epidemiology on particles in ambient air and occupational exposure to inhaled plastic fibres should be further reviewed for relevance to potential effects from exposure to microplastics in foods.

34. The Committee considered that the current literature data on the effects of plastic particles on the microbiota could not easily be compared and so it was difficult to draw any meaningful conclusions from these studies.

35. The Committee concluded that the literature data on exposure to particles from tyre wear would need separate consideration from microplastic exposure from food, since the particles were chemically quite different in their polymeric nature. Risk assessment of such material was considered potentially outside the scope of the current exercise.

36. The Committee acknowledged that the available data had been reviewed in some detail, but it was not all relevant to microplastics in food. It was agreed that the problem formulation should be clarified, with the microplastics under consideration being clearly defined. This would allow a more focused statement linking to the discussion papers to be prepared.

Item 7: Discussion paper on the potential risks from almond drink consumption in children aged 6 months to 5 years of age. TOX/2020/16

37. No interests were declared.

38. The Department of Health and Social Care (DHSC), Public Health England (PHE) and the FSA were receiving an increasing number of enquiries regarding the use of plant-based drinks in the diets of infants and young children. The COT were therefore being asked to consider the potential health effects of almond drinks in the diets of children aged 6 months to 5 years of age.

39. Based on a literature search and review, aflatoxin B1 and cyanogenic compounds were identified as the most commonly reported contaminants in almonds, which could be potentially transferred to almond drinks.

40. The Committee discussed the exposure calculations to aflatoxins. Mean and maximal analytical aflatoxin B1 concentrations from the Riba *et al.* paper[2] were used to calculate margins of exposure (MOEs). The calculated MOEs were significantly lower than 10,000, which indicated a potential health concern.

41. Members agreed that aflatoxin exposure from almond drinks was of potential concern but that there were uncertainties in all aspects of the assessment. It was suggested that the aflatoxin exposure assessment should be more refined as it was based on extrapolation from data on almond nuts and not on almond drinks. Members agreed that using this type of data to calculate MOEs was not ideal. Members suggested that additional literature searching should be conducted to identify any papers that indicated what effect processing had on aflatoxin levels in almonds.

42. The Committee then discussed the calculations estimating potential exposure to cyanide. Based on the 97.5th percentile consumption data, the estimated acute exposure to cyanide levels in almond drink made from sweet almonds, based on the assumption that all milk would be replaced by almond drinks, slightly exceeded the acute reference dose (ARfD) of cyanide for children aged 6 to 18 months. Acute exposures of cyanide levels in almond drink if made from bitter almonds would indicate significant cause for concern when compared against the ARfD. However, the Secretariat informed Members that a UK almond drink company had advised that commercial varieties of almonds were used in their almond drink manufacturing, so there was no risk of cross contamination with bitter almonds and no identified risk of cyanogenic glycosides being present in almond drinks, or testing conducted for it. A Member noted that this was consistent with information from an almond drink company located in California that only sweet almonds are used.

43. Data from the 2019 EFSA opinion on the "Evaluation of the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels"[3] indicated that there was no overlap between lower bound and upper bound

[2] Riba A, Matmoura A, Mokrane S, Mathieu F, Sabaou N (2013) Investigations on aflatoxigenic fungi and aflatoxins contamination in some nuts sampled in Algeria. African Journal of Microbiology Research, October 2018, 7(42): 4974–4980

[3] https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2019.5662

concentrations of cyanide. Members stated that if only sweet almonds are used in the preparation of almond drinks, then there would be no health concern. However, Members agreed that more information on the likelihood of bitter almond contamination of almond drinks and what precautions were taken by manufacturers to prevent their entry to the supply chain should be investigated.

44. Members noted that the current government advice regarding consumption of plant-based drinks by infants and young children is based on nutritional considerations and does not include toxicological considerations, so it was not possible for the Committee to comment on whether it was appropriate.

45. Overall, it was agreed that further work needed to be done to refine the aflatoxin exposure assessment and that the likelihood of bitter almond contamination of almond drinks should be further investigated before final conclusions could be drawn.

Item 8: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Second draft statement. TOX/2020/17

46. No additional interests were declared from those declared in December 2018 and December 2019.

47. The Committee was presented with the second draft statement on the potential toxicological risks from E(N)NDS and Members discussed the amendments requested by the Committee at the last meeting in January 2020.

48. Members agreed to refer to recent UK reviews and the NHS website regarding the guidance for people who wish to stop smoking and the potential beneficial effects of e-cigarettes in the process, rather than providing a primary review of the literature, which would be beyond its mandate.

49. The Committee noted that the yellow card adverse drug reaction reporting system does not report adverse effects caused by e-cigarettes *per se*, rather it allows reporting of effects in people who use e-cigarettes. There is not necessarily a causal effect of e-cigarette use and the Members asked for this to be clarified in the document.

50. Members discussed the derivation of the health-based guidance value (HBGV) for nicotine. As it is based on Cmax it can be assumed there is less kinetic variability between individuals. Members noted that this should be kept in mind when assessing the margin of safety, as a margin of less than 3 might be applicable to allow for possible kinetic differences. Members also asked for the statement to reflect the fact that the reversible pharmacological effects used as a basis for the nicotine HBGV are the most sensitive effects and therefore would also protect against long term effects, the LOAEL for long term effects being higher.

51. Clarity was requested around the sensitisation effects of cinnamaldehyde; it was known to cause skin sensitisation and therefore had potential to also cause respiratory sensitisation.

52. The Committee agreed to finalise the draft statement by Chair's action.

Item 9: Draft EFSA opinion on PFAS. TOX/2020/18

53. Professor Alan Boobis had been involved in the SETAC North America workshop on exposure and toxicity of PFASs and in writing the report of the meeting. No other interests were declared

54. Dr Andrew Povey, an epidemiologist from The University of Manchester and a Member of the Committee on Mutagenicity of Chemicals in Foods, Consumer Products and the Environment (COM) was in attendance to provide additional expertise.

55. EFSA had been asked, by the European Commission, to prepare an opinion on the risks to human health related to the presence of perfluoroalkylated substances (PFASs) in food, and to consider existing hazard assessments and available occurrence data. This document had been published for public consultation.

56. In the draft opinion, the EFSA panel assessed 27 PFASs. They decided to use a mixtures approach and have established a Tolerable Weekly Intake (TWI) for the sum of four PFAS (perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS)). These are currently the PFASs which contribute most to the levels observed in human serum, they share toxicokinetic properties in humans and show similar toxicological profiles. Although some other PFASs like perfluorobutanoic acid (PFBA) and perfluorohexanoic acid (PFHxA) also contribute significantly to the exposure, these compounds have much shorter half-lives in humans.

57. EFSA decided to base their PFASs assessment on the effects on the immune system, specifically on a decrease in vaccination response. A TWI had been established from serum levels of the four PFASs in a human study. A no observed adverse effect concentration (NOAEC) of 31.9 ng/mL was taken from the Abraham *et al.* (2020)[4] study for the sum of the four PFASs. Pharmacologically-based pharmacokinetic (PBPK) modelling was then used, taking into account 12 months of breastfeeding by the mother, to calculate an estimated intake by the mother of 1.16 ng/kg bw per day for the sum of the four PFASs. This value was multiplied by 7 to calculate the TWI (1.16 x 7 = 8 ng/kg bw per week).

58. EFSA had summarised EU exposures in the draft opinion. Weekly exposures were calculated for the UK population taken from the data in the EFSA Opinion.

[4] Abraham K, Mielke H, Fromme H, Volkel W, Menzel J, Peiser M, Zepp F, Willich SN and Weikert C. (2020). Internal exposure to perfluoroalkyl substances (PFASs) and biological marker in 101 healthy one-year old children: Associations between levels of perfluorooctanoic acid (PFOA) and vaccine response. Archives of Toxicology, SUBMITTED. Post-meeting note: now in press in Arch Toxicol.

59. UK Lower bound (LB) mean exposures for adolescents and older were below the TWI. Exposures for infants and toddlers exceed the TWI. All LB 95th percentile and upper bound mean and 95th percentile exposures exceed the TWI from < 2-fold to >100-fold.

60. Comments were made on the Grandjean *et al.* (2012[5]) paper on serum vaccine antibody concentrations, in that as a stand-alone paper it was quite convincing, however when the follow-up papers were considered the results in the studies did not appear to be as consistent as reported in the original paper. It was not possible to comment on the Abraham *et al.* (2020) paper as it was unpublished at the time and not available for the Committee to review in full.

61. The Grandjean *et al.* (2012) study was based on data from the Faroe Islands. The data were corrected for polychlorinated biphenyls (PCBs), dioxins etc. It was somewhat surprising that there was no effect suggesting complete randomisation of all other contaminants. Both methylmercury and PCBs have been reported to have independent effects on vaccine response in children.

62. Members were unable to comment on the use of Abrahams et al study as the critical study as they did not have access to it in order to review it.

63. Members did agree with the approach of using the sum of the four PFASs because it better reflected the actual nature of the exposures and the mode of action of the compounds.

64. The Committee were unable to agree the established TWI until they were able to agree that the critical endpoint used was appropriate.

65. There were a large number of left-censored occurrence data, leading to appreciable uncertainty in the exposure estimates. Population immunity in the UK is extremely high If the exposure levels were towards the upper bound, it is likely that there would be a noticeable vaccine failure in the UK. Hazard characterisation has been based on reliable biomarker of vaccine response but no pathological consequence had been observed and this is therefore consistent with the upper bound being an overestimate of the exposure. The critical endpoint would be of concern if it led to a decrease in the effectiveness of vaccination.

66. Members were invited to submit any additional comments on the Opinion to the Secretariat.

Item 10: Draft EFSA opinion on glycoalkaloids. TOX/2020/19

67. No interests were declared.

[5] Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P and Heilmann C. (2012). Serum Vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA. 307: 391-397. doi: 10.1001/jama.2011.2034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22274686

68. In February 2020, EFSA launched a public consultation on their draft opinion on the risks for animal and human health related to the presence of glycoalkaloids in feed and food, particularly in potatoes and potato-derived products. The discussion paper TOX/2020/19 provided a summary of the draft EFSA opinion.

69. Members commented that the half-lives of glycoalkaloids, at < 48 h, was not excessively long relative to that of many other contaminants of concern.

70. Regarding the observed critical effects of glycoalkaloids, Members noted that the EFSA Panel considered that the gastrointestinal effects are likely due to local irritation caused by membrane disruption with a possible contribution from inhibition of acetyl cholinesterase. Members considered the evidence for a role of acetyl cholinesterase inhibition in these effects was very weak. Members discussed the critical effects in humans listed in Table 20 of the EFSA opinion. It was agreed that the effects listed were not toxicologically serious, as although unpleasant, they were mild and reversible.

71. Committee members discussed and agreed that the data indicated that laboratory animals were less sensitive to the effects of glycoalkaloids than humans and that it was preferable to use the human data for risk characterisation.

72. Members agreed that the approach used to estimate exposure was appropriate, as potato types, consumption days and processing factors were incorporated into the exposure assessment.

73. Members discussed the margin of exposures in Table 3 of the discussion paper and agreed with EFSA's indicative margin of exposure of 10 for potato glycoalkaloids as of low concern. The implications of the proposed Margin of Exposure for the UK diet were considered and Members noted that there was a potential concern for high consumers. However, Members concluded that as the greening of potatoes, where glycoalkaloid levels are highest, can be seen and therefore removed, a health risk from potato glycoalkaloid consumption can be minimised. It was noted that the current FSA advice was to remove green, sprouting or damaged areas of potato prior to consumption.

74. Members were invited to submit any additional comments on the draft opinion ahead of EFSA's deadline on Wednesday 15th April 2020.

Item 11: COC- guidance statement on less than lifetime exposure. TOX/2020/20

75. Dr Lovell declared that he is a Member of the Committee on Carcinogenicity (COC). No other interests were declared.

76. The COC had been considering the topic of less than lifetime (LTL) exposure to genotoxic and non-genotoxic carcinogens, and had now produced a set of principles, which would be published soon. The COT had also expressed interest in this topic area at the joint COM, COT and COC meeting in October 2017.

77. The set of principles had been prepared by the COC to enable, where necessary, specific frameworks to be formulated by individual Government departments and agencies. The set of principles was intended to provide guidance to the risk assessor for particular areas of consideration that may apply to the risk assessment of either retrospective or prospective LTL exposures.

78. Although these principles had been developed specifically for evaluating exposures to genotoxic and non-genotoxic carcinogens, there was flexibility to apply the principles for consideration of other types of chemicals, as needed. The COT was therefore asked to comment on the applicability of the current set of principles adopted by COC to the evaluation of LTL exposures for other health outcomes considered by the COT.

79. It was noted that LTL exposures for non-genotoxic carcinogens were compared to the HBGV for long term exposure in the first instance. Where required the establishment of a shorter term HBGV based on a shorter term study could be considered.

80. It was noted that the JECFA residues of veterinary drugs meetings has started to match the exposure profile that best aligns with the toxicological profile of a substance. They consider whether there is life-stage-specific toxicity, e.g. is a point of departure (POD) for developmental toxicity close to the POD from a chronic toxicity study used to establish the ADI (e.g. within 2-fold)? They consider whether the POD for a shorter-term, typically a 90-day, study is close to that for a chronic study. The COC framework also discussed these considerations. The difference is that JECFA uses the same HBGV for all scenarios other than acute.

81. Members discussed the extent to which the COT had addressed LTL exposure to date. It had considered carcinogenic risks to infants exposed for short periods. It had also considered life-stage specific risks such as for caffeine consumption during pregnancy. Members considered it would be useful to test the framework using cases from past COT work.

Item 12: Update on the work of other advisory committees. TOX/2020/21

82. This Item was circulated prior to the meeting and there were no comments from Members on the work of other advisory committees.

Item 13: Any other business

83. There was no other business from the Secretariat or Members.

Date of next meeting

84. The next meeting of the Committee at 10.00am on Tuesday 5th May at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ.