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

Minutes of the meeting held on Tuesday, 28th of January 2020 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ

Present

Chairman:	Prof Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr Stella Cochrane Dr James Coulson Dr Caroline Harris Dr René Crevel Prof Gary Hutchison Dr David Lovell Dr Mac Provan Ms Juliet Rix Prof Faith Williams Dr Michael Routledge Dr Cheryl Scudamore Dr Natalie Thatcher Dr John Thompson Prof Matthew Wright Prof Paul Haggerty Dr Gunter Kuhnle (skype) Dr Natalie Thatcher (skype)	
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland Dr A Cooper Dr B Doerr Mr B Maycock Dr D Hedley Ms C Hoppie Dr O Osborne Ms C Potter Dr J Shavila Ms C Thomas Ms S Thomas Ms C Tsoulli Ms F Uy Ms F Hill Ms B Davies	FSA Scientific Secretary

Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Officials:	Dr Daphne Duval	PHE
	Mr Freddie Lachmann	FSA
	Rachel Hodgson	FSA
	Dr Paul Tossell (skype)	FSA
	Ms Karen O'Connor (skype)	FSA
	Karen Sturgeon	MHRA
	Ms Helena Bird	MHRA
	Gillian McEneff	BEIS
Other Invited Experts and Observers:	Prof John O'Brien	Science Council
	Erik Prochazka	PETA
	Dr Sarah Bull	WRc
	Dr Kate Vassaux	WRc

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Announcements

1. The Chair welcomed Members and other attendees.

Interests

2. The Chair reminded those attending the meeting to declare any commercial or other interests they might have in any of the agenda items.

Item 1: Apologies for absence

3. Apologies have been received from Members Professor Maged Younes and Dr Sarah Judge, Assessors Dr Tim Gant (PHE) and Ms Valerie Swain (HSE). Dr Gunter Kuhnle, Dr Natalie Thatcher and Will Munro (Food Standards Scotland) wold be attending the meeting via Skype.

Item 2: Minutes from the meeting held on 3rd of December 2019

4. The minutes were accepted as an accurate record, subject to minor editorial changes.

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

Para 31: COT Workshop on 11th March

5. Members were updated on the planned agenda and were asked to send any comments regarding the workshop to the COT inbox. Details on practicalities such as timing and accommodation would be circulated shortly.

Para 72: Addendum to the Overarching Statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years.

6. The Addendum was currently being finalised and would be sent to the Chair for clearance shortly.

Para 17: EFSA consultation on ochratoxin A

7. Comments on Ochratoxin A were submitted to EFSA and the Chair thanked Members who contributed.

8. Members noted that the US had recently applied a new program for modelling and that while the output from the different approaches (US, EU) were similar, the interpretation of the data fit were different.

9. Members were informed that the publication of EFSA consultations on glycosides and PFAS had been postponed and these were now expected to be published on the 17th February. Depending on the timelines these would be discussed at the March meeting or circulated for comment.

10. There were no other Matters Arising.

Item 4: WHO public consultation on the JECFA/JMPR update of Chapter 5 (EHC 240) (Deadline: 31 Jan 2020) - TOX/2020/01

11. This paper provides a summary of chapter 5 (dose-response assessment and derivation of health-based guidance values) of the "principles and methods for the risk assessment of chemicals in food, Environmental Health Criteria 240" (EHC 240) guidance document that was released by the World Health Organisation for public consultation. Members of the Committee were invited to comment on the draft update.

12. No interests were declared.

13. Potential discrepancies between the descriptions of the benchmark dose approach in paragraph 25 and by the Environmental Protection Agency were addressed.

14. Comparisons were made between the flow chart presented in figure 1 of TOX/2020/01 and that used by EFSA; preference for the flow chart used by EFSA was expressed.

15. The Committee concluded that the methodologies of the updated draft chapter and the previous version were the same, and the main differences were in the structure of the chapter.

Item 5: Update on Cannabidiol (CBD)- Additional data - TOX/2020/02

16. Dr Stella Cochrane and Dr Natalie Thatcher declared indirect personal interests as their employers were interested in CBD as a potential food ingredient.

17. Two representatives from GW Pharmaceuticals were present as observers.

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

19. As risk assessment advice on CBD has been increasingly requested from the FSA it was considered timely for the available toxicological information on CBD to be reviewed. In July 2019, a scoping paper on the potential adverse effects of CBD products (TOX/2019/32) was presented to the Committee.

20. Members were reminded that, at the July meeting, they could not reach a conclusion on the safety in use of CBD products based on the scoping paper. The Committee had agreed that this topic should be reviewed once more data became available but that the data from the medicinal/pharmaceutical sector would be very useful if it could be obtained as most of it was not then publicly available.

21. Members asked how the products had entered the market if they were unauthorised. It was explained that the status of CBD had been uncertain and that the products entered the market before the novel food status was determined. Foods made from hemp or hemp oil had a history of use and were not considered to be novel.

22. It was noted that as the Committee had concluded that the genotoxicity data were conflicting, indicating genotoxic potential in some but not all of the available *in vivo* studies, the Committee recommended the genotoxicity data be referred to Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) for consideration. The COM had discussed it at their October meeting and had concluded that the *in vitro* and *in vivo* genotoxicity studies were inadequate and therefore a conclusion on the genotoxic potential could not be reached.

23. It was explained that with the cooperation of GW Pharmaceuticals (the manufacturers of Epidiolex®), the Secretariat had been able to examine and discuss some of the recent clinical and non-clinical data on the medicinal form of CBD, reviews and assessment reports of which were now publicly available online.

24. Members discussed the overview of data (studies in laboratory animal species, patients and healthy human volunteers) that was submitted to the US Food and Drug Administration (FDA) for the approval of Epidiolex®, and to the European Medical Agency (EMA) Assessment Report) as well as the scientific submission of GW Pharmaceuticals highlighting some of the key adverse reactions.

25. Members noted that the data available was in summary form and some of it was redacted. It was further noted that pharmaceutical grade of CBD in its purest form was >98% CBD and that other commercially available CBD products were likely to contain other cannabinoids which would have effects in their own right as well as having the potential for interactions with CBD and might affect the possible adverse effects of CBD. Few data was available on these compounds. Members agreed that when considering the data on medicinal products, it should be noted that there will be a trade-off between risks and benefits that did not apply to food.

26. The Committee noted that most of the data from clinical trials were from human patients, but they were made aware of healthy volunteer data which was not currently available in the public domain. Members requested the Secretariat to ask if this data could be made available along with further data in areas such as

pharmacokinetics (especially at the lower doses tested) which would aid with determining a point of departure as well as LOAEL and NOAEL.

27. The Committee agreed that there were no indications that pharmaceutical grade CBD was genotoxic based on the summary genotoxicity data from range of tests available, which would be considered adequate to assess CBD. It was suggested that these data be reviewed by the COM.

28. The Committee discussed the pharmacokinetic parameters of CBD and noted that although CBD has low bioavailability, consumption with food could increase CBD uptake by, for example, up to 5-fold if taken with a high fat meal. Furthermore, Members were made aware that CBD products were currently being formulated to increase uptake. Therefore, the information on CBD potency assessed by the Committee may be underestimated when assessing the risk of CBD in food.

29. Members concluded that there were observable adverse effects from CBD exposure in the following: hepatic impairment (liver injury) at a CBD dose of 5 mg/kg bw/day, inhibitory interactions with some medications at a CBD dose of 1 mg/kg bw/day, somnolence effects were noted at 10 mg/kg bw/ day. Furthermore, reproductive toxicity was observed in laboratory animals treated with CBD as well developmental effects in the offspring, however, the mechanism was unclear. Due to CBD's physiochemical properties CBD was likely to transfer into milk and should be avoided by breast feeding as well as pregnant women. Members agreed that the British National Formulary warning regarding driving and operating machinery should also be noted. CBD also had the potential to cause interactions when taking other medicines.

30. Members noted that humans may be more sensitive than laboratory animals to the adverse effects of CBD but there was insufficient data to draw definitive conclusions on this.

31. Members agreed that there were insufficient data to undertake a provisional risk assessment as it was not possible to determine a reliable point of departure. However, some general conclusions could be drawn that applied to CBD alone.

Item 6: Discussion paper on the health risk of mycotoxin contamination in oat drinks for children aged 6 months to 5 years of age - TOX/2020/03

32. No interests were declared.

33. 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. Therefore, the COT was being asked to consider the potential health effects of oat milk drinks in the diets of this age group.

34. Under cool and moist conditions, *Avena sativa* (the common oat) could be

colonised by various species of fungus in the Fusarium genus such as *F. langsethiae*. This colonisation was often accompanied by the production of the T-2 mycotoxin. This mycotoxin commonly entered the food chain through contaminated food, mainly cereals. In animals, the T-2 toxin was rapidly metabolised with the HT-2 toxin being a major metabolite. Based on the rapid metabolism of T-2 to HT-2 and structural similarities, EFSA established a TDI of 0.02 µg/kg bw per day for both T-2 and HT-2 based on a 90-day subchronic toxicity study in rats which showed that immune- and haematotoxicity are the critical effects of T-2. In addition, the Panel established an ARfD of 0.3 µg for T-2 and HT-2/kg bw, based on acute emetic events in mink.

35. The “sum of T-2 and HT-2” was used for estimating exposure assessments which is consistent with what has been done previously for other contaminants.

36. Two approaches were taken for estimating UK infant and toddler exposures to T-2 and HT-2 from oat milk consumption. These were using the estimated concentration of 0.51 µg T-2 and HT-2/ kg oat milk from occurrence data in European-harvested oats and using the analytical result from the 2015 FSA retail survey which reported that the concentration in an oat milk sample (n = 1) was 2.6 µg (LB) and 3.6 µg T-2 and HT-2/ kg oat milk (UB).

37. These occurrence data were combined, separately, with acute and chronic consumption data from the DNSIYC and NDNS surveys to estimate the corresponding exposures for 3 to <36-month olds. A small number of infants and toddlers were reported to drink oat milk in these surveys (n = 2-3), so these data were unlikely to be representative for this age group in the UK. Therefore, consumption data for cows’ milk were used instead for the exposure assessment, since a much greater number of individuals were reported to consume it.

38. For acute health risk assessment, mean acute exposure estimates were less than the ARfD using the estimated or analytical occurrence data of T-2 and HT-2.

39. For chronic health risk assessment, use of the estimated occurrence data leads to mean chronic exposure estimates < TDI. However, if the higher analytical concentration was used, mean chronic exposure estimates > TDI. It was unclear whether the exposure estimates using the analytical occurrence data represented a risk to health since the analytical concentration was measured from one sample of oat milk, which was expected to comprise of oats from the 2014 UK oat crop harvest where higher than usual levels of T-2 and HT-2 were found in whole oats. In addition, the exposure estimates were based on the assumption that all dietary cows’ milk was replaced with oat milk which was unlikely to be the case for all individuals in these age groups.

40. Members were asked if the exposure assessment should be based on the analytical or estimated concentration of T-2 and HT-2 in oat drink. It was agreed that the estimated concentration using European occurrence data in oats should be used for exposure assessment. The analytical data derived from one sample of oat drink is unlikely to be representative for the UK given the lack of surveillance data and variability of contamination levels in the UK oat harvest. Furthermore, it was noted

that there was no indication that mycotoxin concentrations in UK oats would be substantially different to those reported in other European countries by EFSA.

41. It was noted that although there were uncertainties regarding the use of cows' milk consumption data for the exposure assessment of oat drink, it was nevertheless a conservative approach for the risk assessment.

42. Aside from the nutritional adequacy of oat drink used to replace dairy milk, it was questioned whether there might be a difference in mycotoxin concentration levels between organic and inorganic oats. A Member noted that mycotoxins in oats had been analysed for the Scottish Government and this might provide further relevant data.

43. It was agreed that follow-up work should 1) assess the contribution of mycotoxin exposure from oat drinks in relation to exposure from total oats in the general diet, and 2) estimate the amount of oat drink one would need to consume in relevance to the rest of the diet to approach the TDI.

Item 7: Toxicological interactions between xenobiotics and the human microbiota - First draft statement - TOX/2020/04

44. No interests were declared

45. A scoping paper (TOX/2019/57) on the toxicological interactions between xenobiotics and the human microbiota was discussed by the Committee in October. Based on those discussions, a draft Statement had now been prepared. As requested, more emphasis was given to the human microbiota, although the animal data from the earlier paper had been tabulated for comparison.

46. The Committee decided that several points needed more emphasis. It was agreed that a clearer indication should be given of what was known about the effects of xenobiotics on the microbiota, and downstream effects on the host, and what was currently speculative. How changes in the taxonomic balance of the microbiota were reflected in functional change, i.e. the level of functional redundancy in the system and whether these changes were pathological or adaptive should also be considered.

47. It was also agreed that effects on the integrity of the intestinal barrier function and the expression of antimicrobial resistance genes should be included and that some mention should be made of the other non-bacterial components of the microbiota – fungi, viruses, archea and protozoans.

48. The Committee considered that although gnotobiotic animals could more closely mimic the human situation, the model was still beset with problems relating to the health status of the animals and the fact that such colonies were expensive and difficult to maintain. Members noted that pigs probably provided a system that was qualitatively closer to humans than did rodents. Moreover, the use of 'representative'

species of bacteria in *in-vitro* systems could provide the basis for a regulatory risk assessment but was not a risk assessment for the microbiota as a whole.

49. The Committee decided that the microbiota was a potential subject for FSA funded research but it would also be useful to keep a watching brief on developments in the area – such as moves from 16S RNA genetics to functionality assays and the effects of the dietary use of artificial modified starches.

50. A second draft of the Statement would be presented to the Committee in due course.

Item 8: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes).

51. In addition to those interests already declared in December 2018, Dr Coulson declared a personal specific interest in that he has recently became an investigator and advisor on a contract research organisation-led study sponsored by British American Tobacco. He was present for the discussion but did not contribute.

52. A number of papers were provided to the Committee for information and to be included into the discussion of the draft Statement as necessary:

Reviews by UK and International organisations - TOX/2020/05

53. Paper TOX/2020/05 considered reviews from authorities including WHO, PHE, the National Institute for Public Health in the Netherlands, BfR, and the US National Academies of Science, Engineering and Medicine. Apart from a few anomalies, most reviews of the health effects of E(N)NDS were consistent with the conclusions being made by the COT. It was observed that the interpretation of the evidence did not vary significantly between countries, but the regulatory positions taken did.

Relevant UK regulatory aspects - TOX/2020/06

54. Paper TOX/2020/06 set out details of the regulatory regime in the UK. The Committee noted that there were differences in regulatory requirements between nicotine (ENDS) and non-nicotine (ENNDS) delivery systems.

55. Members considered that flavourings should be tested prior to use in these products. The Committee highlighted the reference made to skin sensitisation in paragraph 10, which implied that skin sensitisation was a greater concern with flavourings than was highlighted in the draft statement discussed later.

Update on Yellow Card Scheme data for E(N)NDS - TOX/2020/07

56. Paper TOX/2020/07 provided an update on adverse drug reaction reports from the Yellow Card Scheme ENDS products as well as some recent vigilance reporting from manufacturers requested by the Medicines and Healthcare Regulatory Agency (MHRA). The Yellow Card Scheme reports were current up to early January

2020. Comparator Yellow Card reports were also provided for nicotine replacement therapies and the drugs bupropion and varenicline, which are used to aid smoking cessation.

57. Members asked how the data were monitored and analysed. MHRA advised that statistical analyses were conducted and that adverse outcomes likely to be drug-induced also raised flags.

58. Members observed that reports of nausea and vomiting were reported commonly for all nicotine sources; but this was commonly reported for many medicinal products.

Paper for discussion: First draft statement - TOX/2020/08

59. The Committee agreed that in general the draft Statement was well presented.

60. It was agreed that a distinction between ENDS and ENNDS products should be made in context of their role in cessation of nicotine addiction and the legal position that each device has in the UK framework, in comparison to other EU Member States and other countries.

61. It was also made clear that Good Manufacturing Practices (GMP) should not only be applied to avoid metal contamination but to consider the whole device production as a whole since their malfunctioning have been reported (e.g. device explosions and defective devices delivering e-liquid material directly to the mouth of users).

62. Potential adverse effects from E(N)NDS use were discussed. Specifically, on the potential of inhaling solvent/carrier vapours from E(N)NDS and their potential to localise tar deposits (as a consequence of conventional cigarette smoking) in the lungs. It was hypothesised that this risk would be negligible, however, it was acknowledged that specific data was lacking.

63. In terms of propylene glycol, it was agreed that repeated exposures still need to be considered. It was requested that a recalculation be made, to take into account the inhalation correction factor for differences in breathing rates between mice and humans (as carried out by the EPA) for the second draft Statement.

64. A number of further editorial amendments would be made to the draft statement, and a second draft would be brought back to the Committee for further discussion.

Item 9: Horizon scanning - TOX/2020/09

65. The annual horizon scanning paper was presented to the Committee. It detailed planned agenda items for 2020 and potential discussion topics. The latter included possible public consultations from EFSA, which would require consideration by the COT and new suggestions for topics.

66. Members were asked to comment on the items detailed in the paper, whether there were any additional topics that should be addressed, or any proposals for research that should be funded in order to improve COT risk assessments, and to consider whether there were any important gaps in expertise amongst the current COT membership or in light of possible future developments.

67. The first suggestion for a new topic was that of residues in human pharmaceuticals in food. It was suggested that the toxicological screening values (TSVs) proposed by EFSA in their guidance on establishing Reference Points for Action (RPAs) for residues of non-allowed veterinary medicines in food should be considered, though it was noted that these were conservative.

68. A programme of work on the maternal diet was planned at the request of PHE and SACN. This would specifically consider the health of the mother not the offspring. The timeline would be from 6 months prior to conception to post-delivery. The time between pregnancies would need to be considered and the window of sensitivity of offspring versus the window of benefit to the mother.

69. The main concern was the effects of excess vitamins as this population group tends to have a high use of vitamins. It would also be necessary to consider the recommendations for oily fish, toxins versus nutrients (nutrients to the mother and the infant and the adverse effects on the offspring). When considering oily fish, the nutrients could be obtained through supplementation to avoid toxins, but SACN would rather recommend foods to supply these nutrients, fish being a high quality, lean protein source.

70. Initially a scoping exercise would be undertaken on a number of chemicals looking at maternal toxicity only, mobilisation of fat and its associated toxins. Possible sources of data as well as the immune system would need to be considered.

71. Pesticides were included on the list of chemicals that could be considered. It was noted that maternal toxicity would be looked at in reproductive toxicity studies. It was suggested that the work concentrate on the legacy pesticides as contaminants, and dietary residues of pesticides. Clear terms of reference will be needed for any work undertaken on pesticide assessment.

72. The Committee had been asked to consider alternatives to plastic packaging; particularly those from plant materials. The environmental degradation products would need to be assessed as these were likely to be different from the parent compounds. Associated chemicals e.g. pesticide residues in plant-based cups would need to be considered.

73. With regards to new topics there were two suggestions from Members. These were developments in dietary exposure assessment and evaluation of the exposome.

74. For balance of expertise on the Committee, Members were informed that a central recruitment exercise for the FSA Scientific Advisory Committees was

underway and that expertise in clinical pharmacology and additional expertise in epidemiology was being sought for COT.

75. The Committee also discussed potential ideas for research including looking at blood levels of chemicals in relation to levels in breast milk and monitoring and undertaking a dietary survey of plant-based milks to support the ongoing Committee work in this area.

76. The Committee were informed that the epigenetics statement was awaiting publication and would be kept updated with progress.

Item 10: 2019 COT Annual Report - TOX/2020/10

77. No substantive comments were received from members on the draft annual report. The Committee agreed that they would discuss the work of the Committee in relation to the Code of Practice for Scientific Advisory Committees at the next meeting due to lack of time. The Secretariat agreed to provide each member with an individual summary of their current affiliations and declarations of interest for Members to review and update before the next meeting.

Item 11: Paper for information: Update on actions taken subsequent to COT advice - TOX/2020/11

78. COT statements have been published and, where appropriate, forwarded to the European Food Safety Authority (EFSA) to inform its evaluations. COT Opinions are frequently cited by the relevant Government Departments and Agencies in dealing with correspondence. The Food Standards Agency (FSA) routinely uses the Committee's conclusions and opinions in risk assessments following food safety incidents, responding to queries from consumers and in assessing emerging risks.

79. This paper presented to the Committee actions taken following COT publications in the last year.

80. The Committee asked what was happening with the advice it had given regarding potential adverse effects from fortification of wheat flour with folic acid to improve folate status and reduce the incidence of neural tube defect affected pregnancies and were informed that the results of the recent public consultation were with the Department of Health and Social Care (DHSC) but an outcome had not been announced. The Committee requested that representation be made to DHSC for an update including what the final conclusions are and the basis for them.

Item 12: Update on the work of other Scientific Advisory Committees - TOX/2020/12

81. This paper was tabled for information.

Item 13: Any other business: EFSA consultation on PFAS

82. “Any other business: EFSA consultation on PFAS” was covered in the matters arising section of this meeting and there was no other business from the Secretariat or Members.

Date of next meeting

83. The next meeting will be held on Tuesday 10th - 11th March, Manchester Conference Centre & The Pendulum Hotel, Weston Building, Sackville Street, Manchester, Greater Manchester, M1 3BB.