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

Meeting of the Committee at 10:00 on 5th May via Skype and TEAMs

Present

Chairman:	Prof Alan Boobis	
COT Members:	Dr Phil Botham 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 Prof Matthew Wright Prof Gunter Kuhnle Dr Sarah Judge Prof John Foster Dr Stella Cochrane Ms Jane Case Ms Juliet Rix Prof Mireille Toledano Prof Paul Haggerty (SACN Liasion) Prof J O'Brien (Science Council Liaison)	
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland Dr D Gott Dr A Cooper Dr B Doerr 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
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary

Invited Experts and Contractors:	Dr K Vassaux	WrC
	Dr R Bevan	IEH
	Mr W McManus	WRAP
	Dr M Taylor James	Hutton Institute
	Dr R Hancock James	Hutton Institute
Assessors:	Ms V Swaine	HSE
	Prof T Gant	PHE
	Dr I Martin	EA
	Ms G McEneff	BEIS
	Mr S Fletcher	VMD
FSA and other Officials:	A Lorenzoni	EU Fora Fellow
	E Valanou	EU Fora Fellow
	R Annett	FSA NI
	K Gribbin	FSA NI
	T Chandler	FSA
	L Johnstone	BEIS

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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 James Coulson and Assessor Dr Daphne Duval from PHE.

Item 2: Minutes from the meeting held on 10th of March 2020 and the additional meeting held on 9th April to discuss PFAS

4. The minutes for both meetings were accepted as an accurate record subject to minor editorial changes.

Item 3: Matters arising from the meeting held on 10th of March 2020

Para 53: Draft EFSA opinion on PFAS

5. Following the additional meeting held on 9th April 2020 to discuss the paper by Abrahams *et al*., the COT's comments on the draft EFSA opinion on polyfluoroalkyl substances (PFAS) had been submitted to EFSA ahead of its deadline.

Para 67: Draft EFSA opinion on glycoalkaloids

6. The COT's comments on the draft EFSA opinion on glycoalkaloids had been submitted to EFSA ahead of its deadline.

Para 45: Discussion paper on the potential risks from almond drink consumption in children aged 6 months to 5 years of age

7. One Member informed the Committee that they had received data in relation to bitter almonds and almond drinks, which would be forwarded to the Secretariat.

Item 4: CBD - Draft COT position paper (TOX/2020/22)

8. Dr Stella Cochrane and Dr Natalie Thatcher declared non-personal, specific interests as their employers were interested in potentially developing CBD containing products. No further interests were declared.

9. Members were reminded that in February 2020, the FSA published consumer advice on the safety of CBD in food products, which drew on the outcomes of the COT discussions in July 2019 and January 2020.

10. Although adverse outcomes had been identified, including effects on the liver and reproductive system, as well as the potential for drug interactions, the Committee had not been able to draw final conclusions on CBD-containing products since there was a lack of published data and as the products themselves were likely to have variable effects depending on their composition. The Committee had been able to refine their initial views on CBD after reviewing data on the medicinal form of CBD, which is analytically well defined.

11. The COT was informed that since the FSA consumer advice was published, the FSA have received several enquiries about how it had been derived. Therefore, since a full statement was unlikely in the short term, it was considered timely for a position paper to be published setting out the COT's discussions and conclusions to date and to link to the way this was used in FSA consumer advice.

12. Members agreed with the overall structure and scientific content of the draft position paper. Members recommended that the possibility of dermal exposure to CBD from consumer products and cosmetics should be included in the CBD position paper since this would add to overall exposure.

13. Members discussed the consumer advice for healthy adults and how this could vary in individuals. The current advice is that consumers should think carefully before taking any CBD products, and as a precaution, healthy adults should not take more than 70 mg CBD per day, unless a doctor agrees more. The consumer advice further stated that this did not mean that these levels were definitely safe, but that the evidence suggested adverse health effects could potentially be seen above this intake. FSA also put out advice for potentially vulnerable groups (which included pregnant and breastfeeding women and people taking any medication), which recommended that CBD should not be taken. The recommendations were also intended to aid business when being asked for information by consumers.

14. It was explained to Members that the precautionary consumer advice of recommending no more than 70 mg/day was taken from the clinical trials of medicinal grade CBD, where doses of greater than 1 mg/kg bw/day were associated with adverse events and assuming a default body weight of 70 kg. Concerns were expressed that this might not be sufficiently precautionary for individuals with lower body weights. Members suggested this should be made clearer in the consumer advice. Furthermore, Members proposed the risk of the other possible cannabinoids in CBD products should be noted in the FSA consumer advice.

15. The Secretariat agreed to pass on the COT's comments as suggested. Additions and edits to the current FSA consumer advice were the responsibility of the FSA Communications and Novel Foods Policy Teams accordingly.

16. Members were informed that following the COM meeting in February, the Secretariat would be contacting GW Pharmaceuticals with a joint request for additional information. GW Pharma had kindly provided the current pre-clinical and

clinical data and provision of any further data would be at their discretion as they were not obliged to share it.

17. Members agreed that the minor edits for the position paper could be finalised via email correspondence.

Item 5: Potential risks from use of topically applied CBD-containing cosmetic products (TOX/2020/23)

18. Dr Stella Cochrane and Dr Natalie Thatcher declared non-personal, specific interests as their employers were interested in potentially developing CBD containing products. No further interests were declared.

19. The toxicity of oral CBD had been assessed in previous COT discussions (TOX/2019/32 and TOX/2020/02). Paper TOX/2020/23 focused on the potential risks arising from dermal exposure to CBD originating from dermally applied cosmetic products. These included serums; creams; washes/rinse-off products (cleansers, shampoos, conditioners, body washes, masks); bath products (capsules, oils, tablets and salts); deodorants; balms; and toothpastes. These products could contribute to systemic CBD exposure via dermal absorption and could also have local effects. The paper considered the available literature examining the potential exposure, bioavailability and toxicity of topically applied CBD to establish whether a risk assessment for dermal exposure to CBD could be performed.

20. Members noted the need to distinguish data on dermal pharmaceutical CBD products and cosmetic CBD products since these potentially had different specifications and formulations, in that some pharmaceutical forms were designed to maximise dermal absorption.

21. The possibility of using worst case exposure scenarios, such as assuming 100% dermal absorption (since some CBD products contain permeation enhancers) in a risk assessment if no specific data were available, was a possible option, with alternative options including ‘rough’ scaling based on lipophilicity and the partition coefficient (Kp). The Committee considered that the dermal absorption of CBD would be quite low but given the lipophilic nature of CBD, repeat application of these products could result in CBD accumulating in the stratum corneum from where it might slowly diffuse into the systemic circulation.

22. In addition to dermal exposure from dermally applied CBD products, inhalation exposure from some of the product types (e.g. deodorant, shower gel and bath salts) discussed in the paper could also be relevant. Inhalation, alongside oral and dermal exposure could contribute to aggregate exposure to CBD and therefore, the physicochemical properties of CBD and its propensity for inhalation following cosmetic use should be considered.

23. With regard to the Bartner et al 2018[1] study referenced in paper TOX/2020/23 (Table 1, page 7), it was highlighted that the C_{max} values in dogs were reported to be almost 300 ng/mL, which was similar to the C_{max} measured in humans following oral administration of CBD as a medicinal product. It was additionally noted that the application of CBD to the ears of dogs (which are relatively permeable) in this study might make extrapolation difficult to other dermal application sites. The relative bioavailability of dermal CBD, compared with oral administration, was less than 10%.

24. It was noted that in Figure 1B of the same study it appeared that at the final timepoint with the 150 mg dose, plasma CBD levels for CBD infused oil and oral microencapsulated CBD oil beads appeared to be in the elimination phase, however the plasma levels for the transdermal CBD cream appeared to still be rising. This point was not discussed by the paper's authors, although they did take it into account in determining whether extrapolation to infinity was possible when estimating plasma AUC values.

25. The committee considered that dermal absorption of CBD was likely to be less than 10% of oral absorption.

26. Members noted that providing CBD levels on product labelling would help consumers understand the aggregate CBD dose to which they may be exposed, and therefore make informed choices about controlling their intake and exposure to certain products.

27. It was acknowledged that there was insufficient information on the pharmacokinetics and toxicity of dermally applied CBD to allow an adequate risk assessment of the safety of CBD in cosmetics to be undertaken.

28. Given the available data, the Committee were unable to draw conclusions on the potential for drug interactions arising from dermal CBD exposure and how this related to the use of CBD in cosmetics.

29. Similarly, there was insufficient data to draw conclusions on the toxicity and pharmacokinetic profile of dermally applied CBD and the levels of CBD determined in various cosmetic products, and whether their use posed a potential safety concern.

30. The risk arising from aggregate exposure to multiple CBD products including cosmetics could not be determined by the Committee on the basis of the information available.

31. It was noted that there was currently no good quality *in vitro* or *in vivo* data to allow estimation of systemic doses of CBD from dermal application. The contribution of inhalation exposure from the use of such products was also unknown.

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[1] Bartner, L. R., Mcgrath, S., Rao, S., Hyatt, L. K. & Wittenburg, L. A. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. Can J Vet Res. 2018 Jul;82(3):178-183.

32. It was noted that dermally applied CBD products could have effects locally in the skin via the endocannabinoid pathways.

33. The Committee agreed that there were data gaps that needed to be addressed and that it would be worth contacting pharmaceutical companies to see if there were data on dermal absorption of pharmaceutical CBD products that could be used to help assess cosmetic and consumer products.

34. The Committee agreed that this topic should be revisited once more data became available.

Item 6: Scoping paper: alternatives to conventional plastics for food & drinks packaging (TOX/2020/24)

35. The following Members declared non-specific interests: Professor Alan Boobis is an Emeritus Professor at Imperial College London, where a research group is developing alternative plastic materials, although he has no involvement with the group, Professor Gary Hutchinson has received a grant to develop a nano-cellulose based scaffold for a drug delivery application and Dr Stella Cochrane and Dr Natalie Thatcher are employed by Unilever and Mondelez, respectively, companies which may have wider commercial interests in this topic. No further interests were declared.

36. There are various government initiatives to reduce the amount of conventional plastic used in packaging. This is due to the adverse environmental impacts of fossil-based plastics, and since a large proportion of the total plastic being used is in packaging. As a result of these initiatives, recent years have seen a major global increase in the development and use of biobased food contact materials (BBFCMs). The scoping paper introduced various toxicological hazards associated with the use of plastic alternatives, namely migration of chemicals, heavy metals and nanomaterials into food, in addition to allergy and formation of microplastics. The Committee were asked what further information on any of these aspects would be required to enable the provision of guidance on the corresponding risks.

37. A number of potential toxicological concerns were raised by Members. These included possible impurities introduced during manufacture, as there was a lack of information on the manufacturing process and cleanliness of the production line, the purity or otherwise of the finished material and a need for the assessment of uniformity, impurities and adsorption of extraneous substances onto the materials. The risk of bio-film type effects was noted as BBFCMs may provide substrates for microorganisms, as was the development of an outer protein ‘corona’, which may destabilise over time and thus affect how the BBFCM interacts with food, as well as providing a possible source of antigens.

38. There was a regulatory requirement to assess components of BBFCMs, including assessment of migration and breakdown products. Therefore, it was noted that quantitative information was needed on contamination, migration, and degradation of chemicals used during the manufacture of commercial bioplastics,

and on the impacts on the environment after disposal, for example upon entering landfill or from energy-from-waste processes. It would also be helpful to compare life-cycle impacts of both bio-based materials and conventional plastics. For example, if bio-based materials are generally inferior in terms of duration, it may be expected that more frequent food deliveries are required resulting in elevated greenhouse gas emissions compared to delivery of longer shelf-life products.

39. BBFCMs can be made from composite materials that incorporate both bio-based and plastic materials. However, it is unclear how the toxicity of such a complex material could be tested, and whether any toxicity would arise from the combined effect of the material or from its individual components. However, it was noted that BBFCMs are already used in various industries such as healthcare and these industries may be able to provide their in-house data.

40. There was a lack of information on micro- and nano-plastics that derive from both conventional and bio-based plastics. Numerous papers discussed the presence of nanomaterials in BBFCMs, however there was a general lack of toxicological information. Subsequently, it was agreed that research was required to fill the knowledge gap on the environmental impacts of nanoplastics derived from bioplastics. This research should include impacts on aquatic life due to the physical presence of the particle, and risks to consumers from foods that contain these particles.

41. Members asked whether any labelling on allergy had been applied. It was noted that some BBFCMs have not been thoroughly investigated for the presence of allergens, and it may be difficult to make precautionary allergenic statements on packaging labelling. However, it would be possible based on migration data to do a preliminary risk assessment on elicitation, but less so on the risk of allergenic sensitisation. The generation of novel antigens was also considered to present a possible health risk, whereby allergenic epitopes present in proteins used in the BBFCM are exposed during manufacture or degradation. A statement by DEFRA was available which provides a summary on the current situation.

42. The Committee was asked to advise on which BBFCMs require consideration in further detail. Due to the diversity of available BBFCMs, the Committee agreed that it would be helpful to focus on those BBFCMs that were most or most likely to be used in the UK, either directly or through import, such as PLA plastic. The FCM Policy team added that they receive many enquiries regarding chitin and wheat-based drinking straws; for example, on whether the allergenic content could be removed from them to ensure safety for the end user.

43. The Secretariat agreed to identify the most used materials and other higher priority materials for further review.

Item 7: Toxicological interactions between xenobiotics and the human microbiota -Second draft statement (TOX/2020/25)

44. No interests were declared

45. At previous COT meetings, the Committee expressed a wish to see a paper on the effects of xenobiotics on the gut microbiota and the effect of the microbiota on ingested xenobiotics and how these effects could be taken into account for risk assessment purposes. A scoping paper was presented in November 2019 and a First Draft Statement in January 2020. Following Members' comments, a Second Draft Statement was prepared

46. It was agreed that a paragraph specifically on intestinal barrier function should be included, rather than references to it throughout the text.

47. Members also suggested the following amendments and additions: 1) it should be highlighted that substances are often tested in animals at far higher final concentrations than humans would encounter from the diet: some mention should be made of the possible effects of antibiotic residues and artificial fibres in food and their effect on the microbiota, 2) highlight how the development of microbiological HBGVs could be used in COT work, and 3) incorporate the JMPR recommendations on considering the need to establish microbiological HBGVs for all xenobiotics.

48. Members were asked to send any minor editorial comments to the Secretariat. Major amendments would be circulated by correspondence and it was hoped that the Statement could then be finalised by Chair's Action.

Item 8: Draft revisions to COT Terms of Reference and Code of Practice (TOX/2020/26)

49. Greater consistency among the different FSA Scientific Advisory Committees (SACs) in their Terms of Reference (ToR) and Codes of Practice (CoP) is being encouraged by the FSA board. A template had been developed by the Chief Scientific Advisor's Team and the FSA Science Council and the current COT ToR and CoP have been revised to follow the common format. In general, the information included was the same, but the order in which it has been presented had been revised.

50. The COT differs from the other FSA SACs in that it is one of three sister Committees, along with COC and COM, that are jointly sponsored by the FSA and the Department of Health and Social Care (DHSC). Therefore, any changes would also need to be acceptable to these Committees to ensure consistency.

51. It was noted that the text used for the ToR was based on that published in the annexes to the COT/C/M Annual Report; some of the same information was also on the COT website.

52. Members agreed that the role of the lay members as representatives of the view of the general public should be made clear.

53. It was noted that the content of the paper should also be considered by the DHSC to ensure there was agreement as they were co-sponsors of the three

Committees. The COM and COC would have to consider how to produce a similar document with inclusion of the role of the FSA. It was noted that Other Government Departments might also have views to contribute.

54. A number of suggestions for minor alterations to the text were made, such as the use of gender-neutral terms such as “Chair” across the document and a change from “pollution of the environment” to “emissions to the environment”. It was also suggested that clarification was needed in the section of veterinary drugs and pesticides as those are considered to be residues rather than contaminants. Furthermore, it was noted that consumer products should be defined clearly within the document.

55. A description on the role of the Secretariat should be placed earlier in the COT CoP. This should include more clarity on the Secretariat’s role in preparation of the agenda, as well as on the decision process for items being included in the agenda.

56. Finally, it was requested that a number of additions should be made to the document, such as the timeframe for lapsed interests in topics and that contact with a company might represent a potential intellectual interest, even if below the threshold for a financial interest.

57. Members were advised that a revised version would be circulated in due course.

Item 9: WRAP study on potatoes and acrylamide (reserved) (TOX/2020/27)

58. No interests were declared.

59. The Committee discussed an unpublished study on the potential for acrylamide formation in potatoes. The item was reserved in order not to prejudice publication. The minutes will be published once publication of the study has been confirmed.

Item 10: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). (TOX/2020/29)

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

61. Mr Martin Dockrell and Ms Michelle Havill from the PHE Tobacco Control Policy team were in attendance.

Updated risk assessments for exposure of users to propylene glycol (PG) and glycerol from inhalation of E(N)NDS aerosols.

62. The Committee had previously agreed the draft statement on the potential toxicological risks from E(N)NDS, except for sections on propylene glycol (PG) and

glycerol. For these substances, refinement on the risk assessment had been sought to account for the unique exposure pattern associated with use of E(N)NDS. Input on this aspect has been obtained from external experts and proposed amendments to the relevant sections of the COT draft statement on E(N)NDS, based on the updated risk assessments, were presented to the Committee.

63. The modelling was discussed, and it was noted that standard values, e.g. for respiration rate, had been used. With respect to the toxicology, the endpoint of concern was a site of contact effect where repeated insult would be of concern. The Committee noted that there was no progression in pathology in the 13 week rat study, for either compound. Taking into account the need for repeated exposure, the Committee agreed that the average daily exposure, rather than the single puff exposure, should be compared to the modelled human equivalent concentration to determine the margin of exposure.

64. There remained uncertainty over the effect of heating of these compounds in E(N)NDS, and any potential long-term effects as the assessment was based on 13 week studies. These aspects were covered as data gaps more generally within the draft statement.

65. Overall, the available evidence was deemed sufficient to conclude that inhalation of propylene glycol or glycerol from E(N)NDS would be unlikely to be of concern following typical short- or medium-term use. Data were not available to comment on any potential health effects following long-term use.

Non-technical summary for E(N)NDS statement (TOX/2020/29 - Addendum)

66. A non-technical summary had been prepared to be published alongside the statement. The first draft of this summary was presented to the Committee.

67. A number of editorial amendments were suggested including to outline that the scope covered both the absolute risk of E(N)NDS use as well as comparing the risk of the use of E(N)NDS to conventional cigarettes. In addition, more clarity was required for the conclusion on the risk of dual use of e-cigarettes and conventional cigarettes to emphasise that this could result in an additional risk.

68. Some re-wording was proposed for the final conclusions and it was agreed that the statement should be harmonised with these.

69. The Committee agreed the non-technical summary and amended sections on propylene glycol and glycerol could be finalised by Chair’s action, as was agreed for the rest of the statement at the March 2020 COT Meeting.

70. Members were informed by the Secretariat that once the statement has been finalised arrangements for a press release will be made. However, the timeline for publication and communication of the conclusions was uncertain, due to the ongoing coronavirus pandemic. The Committee would be kept informed about the publication by the Secretariat.

Item 11: Update on the work of other scientific advisory committees and AOB (TOX/2020/28)

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

Item 12: Any Other Business

New ways of working

72. It was highlighted that Members are not always able to review all references cited in discussion papers and that as a result, for some agenda items, there may not be as much detailed discussion during meetings as ideal. Therefore, it was suggested that up to three Members could take responsibility for reviewing specific discussion papers on the agenda in depth and at the meeting, lead on the discussion. It was agreed that the Secretariat would assign the items to the Members, and that the process would be trialled for 2-3 meetings.

73. However, it was noted that as COT decisions were collective, Members would continue to need to be familiar with all items discussed.

COT Website

74. Members were informed of the re-vamping of the FSA Scientific Advisory Committee websites including that of the COT. This was to improve functionality, but also in order to comply with accessibility regulations by the 23rd of September 2020. The updated websites are due to be launched live in Autumn 2020.

75. Members discussed the advantages and disadvantages of publishing html and pdf files on the website. It was indicated that the Secretariat would still be able to publish discussion papers in pdf format, however, this would have to be accessible pdf format. Older COT documents are unlikely to comply without formatting of the source document, and therefore it is was proposed to focus on documents that were deemed critical (*i.e.* full and lay statements) as a priority with other items to be addressed at a later stage. Shorter documents such as agendas would be published as html web pages. It is likely that much of the older material will need to be archived and will not reside on the new website, though links will be provided to the documents.

76. Members highlighted that any existing output should remain accessible and discoverable. Indexing would be key to locating information in the National Archives where the current version of the website would be archived.

Virtual meetings

77. The Chair thanked Members for taking part in the first virtual COT meeting and asked any Members with suggestions on how to improve the online meetings, should send them to the Secretariat.

Date of next meeting

78. The next meeting of the Committee Meeting will be held at 10:00 on 7th July via TEAMs.