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

Meeting of the Committee at 10:00 on 23rd March 2021 on Microsoft Teams

Present

Chair:	Prof Alan Boobis	
COT Members:	Dr Phil Botham	
	Dr Caroline Harris	
	Dr James Coulson	
	Prof Gary Hutchison	
	Dr David Lovell	
	Dr Mac Provan	
	Prof Faith Williams	
	Dr Michael Routledge	
	Dr Cheryl Scudamore	
	Dr Natalie Thatcher	
	Dr Stella Cochrane	
	Ms Jane Case	
	Ms Juliet Rix	
	Prof Mireille Toledano	
	Prof Philippe Wilson	
	Prof Gunter Kuhnle	
	Prof Paul Haggarty	SACN Liaison
	Prof John O'Brien	Science Council Liaison
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland	FSA Scientific Secretary
	Ms Jocelyn Frimpong-Manso	
	Dr Douglas Hedley	
	Ms Cleanncy Hoppie	
	Dr Olivia Osborne	
	Ms Claire Potter	
	Ms Chloe Thomas	
	Ms Sabrina Thomas	
	Ms Chara Tsoulli	
	Ms Frederique Uy	
Public Health England (PHE) Secretariat:	Ms Britta Gadeberg	PHE Scientific Secretary
Invited Experts and Contractors:	Dr Sarah Bull	IEH
	Dr Ruth Bevan	IEH
	Dr Kate Vassaux	IEH
	Professor Paul Harrison	IEH

	Professor Len Levy	IEH
Assessors	Prof Tim Gant	PHE
	Ms Rachel Elsom	PHE
	Mr Ian Martin	Environment Agency
	Dr Sam Fletcher	Veterinary Medicines Directorate (VMD)
	Ms Valerie Swaine	HSE
	Ms Susannah Brown	PHE
Observers	Dr Mindy Dulai	OPSS at BEIS
	Dr Emma Bradley	FCM JEG Member
FSA and other Officials:	Ms Sophy Wells	FSA
	Dr Ovnair Sepai	PHE
	Mr Will Munro	FSS
	Ms Krystle Boss	FSS
	Mr Liam Johnstone	BEIS
	Prof Rick Munford	FSA
	Dr Amie Adkin	FSA
	Ms Sharon Gilmore	FSA NI
	Dr David Mortimer	FSA
	Ms Erica Pufall	FSA

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Announcements

1. The Chair welcomed Members and other attendees.

2. Members were informed that this was the last meeting for Professor Faith Williams whose term of appointment to the Committee has expired. Professor Williams has served three terms on the Committee and the Chair, Members and Secretariat thanked her for her valuable contribution over the years and wished her well in the future.

3. It was announced that the Chair and Members Dr James Coulson and Professor Mireille Toledano have been reappointed to serve further terms on the Committee.

4. Members were informed that a finance drop-in session would be available at lunchtime. Members were reminded to submit any claims for fees for the 2020-2021 Financial Year before the end of the month.

Interests

5. 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

6. Apologies were received from Members Professors Matthew Wright and Maged Younes and Drs Rene Crevel, Sarah Judge and Mac Provan. Apologies were received from David Gott, Barry Maycock and Joseph Shavila of the Secretariat

Item 2: Draft Minutes from the meeting held on 2nd of February 2021 (TOX/MIN/2021/01)

7. There were no comments and the minutes and reserved minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 1st of December 2020

Matters arising from previous meetings

EFSA opinion on HBCDD

8. Members were informed that the EFSA opinion on HBCDD, for which COT had contributed comments, has now been published.

Dioxin position paper

9. Members were informed that the dioxin position paper has been finalised and cleared by Chair's action. It will be published on the COT website in due course.

COT statement on microplastics

10. Members were informed that the COT statement on microplastics has now been published on the COT website.

Update from the Office for Product Safety and Standards at BEIS

11. Dr Mindy Dulai from the Office for Product Safety and Standards at BEIS updated Members on their plans for risk assessment of regulated consumer products such as cosmetics and consumer products. An independent Scientific Advisory group had been established to undertake this work; the terms of reference were currently being agreed. It was noted that there is potential overlap with the work of COT, and BEIS will work with FSA to ensure that the terms of reference take this into account. The Group was expected to meet every 2 months.

Maternal diet – comments from SACN WG

12. The Secretariat gave Members a brief summary of comments from the SACN Working Group on the maternal diet (WG) in response to the COT's selection of chemicals for review following the discussion of the first prioritisation paper at the February COT meeting. The SACN WG expressed their thanks to the COT for their work in contributing to this process and noted this would be reflected in the WG minutes.

13. The WG made the following comments based upon the table of substances covered by the prioritisation paper:

- The WG enquired whether the COT might be considering pica[1], assuming that there was sufficient robust data to do so. Even though not minuted, pica was also briefly mentioned by COT Members when the compounds were being prioritised, though a final decision was not made.

- The WG noted the importance of assessing the evidence on whole foods or drinks as well as constituent parts, for example in relation to caffeine as a constituent of coffee and polyphenols as constituents of tea. However, COT members were of the view that this would be difficult and potentially misleading. For example, there is a need to consider aggregate exposure to substances such as caffeine, from all dietary sources. COT proposes to provide risk assessments for individual substances, so that overall risk can be assessed. If there are contrary effects of other constituents in the diet, this would need to be part of a more holistic assessment, led by SACN, to which COT would be happy to contribute.

- On the question of whether women of childbearing age can be taken as surrogate for pregnant women, one of the WG members had suggested

[1] Pica is a psychological disorder characterized by an appetite for substances that are largely non-nutritive.

that it could be the case, though probably not for caffeine, considering there is specific intake advice for caffeine in pregnancy. COT noted that it would use surrogate information only when there is no alternative, and would take account of any specific information available for pregnant women, such as caffeine avoidance.

- Members of the WG questioned whether the COT had considered undertaking a toxicological assessment of alcohol. From the SACN WG meeting in December 2019, it was minuted that Members were reminded that alcohol per se was outside SACN's remit, but that it might be considered in relation to energy intake depending on the evidence available. The COT Secretariat noted that the most recent review of alcohol in pregnancy was a Chief Medical Officers' report from 2016, where the uncertainties around the effects of low levels of drinking were set out and a prudent recommendation that it was best to avoid alcohol altogether was made. This report would be presented to the COT in May or July so that they can decide how they want to proceed

14. Members suggested investigating the possibility of using data from the Children of the 90s study.

15. Members discussed pulling together a comprehensive list of chemicals of potential concern and any data that is available on monitoring.

EFSA draft opinion

16. The Secretariat thanked Members who provided comments on the draft EFSA opinion on the Development of Integrated Approaches to Testing and Assessment (IATA) on developmental neurotoxicity (DNT) risk assessment. These have now been submitted to EFSA.

JEGS update

17. Members were updated on regulated products and the current activities of the JEGS. Over 700 applications for regulated products have now been received by the FSA. The vast majority of these were for novel food authorisation of CBD products. Some applications for food additives, animal feed additives and food contact materials have been received and were undergoing validation checks but have not yet been allocated to the JEGs for review. It was unlikely that the COT would be seeing any output from the JEGs before July at the earliest.

Item 4: The potential effects that excess iodine intake may have during preconception, pregnancy and lactation - Second draft statement. (TOX/2021/14)

18. No interests were declared.

19. The COT had been asked to consider whether exposure to excess intake of iodine would pose a risk to maternal health in a discussion paper (TOX/2020/54) in

July 2020 as part of the COT contribution to the SACN review of the maternal diet. The first draft of the statement was presented to the COT in October 2020 (TOX/2020/61). The second draft statement setting out the issue and the COT's conclusions was attached at Annex A to paper TOX/2020/61.

20. A number of comments were provided on the structure and content of the draft statement.

21. It was suggested that a note be added on nomenclature, clarifying the use of the terms iodine and iodide in the document.

22. The Committee noted that paragraph 2 stated that the only known biological function of iodine is in hormonal synthesis. It was suggested that any role of iodine, independent of that of thyroid hormones, in cognitive development, should be clarified.

23. The Committee commented on the Danish fortification scheme noting that it would be useful to include the levels of iodine used in the fortified products. Members noted that although iodide salt was available in the UK, it was not part of a fortification scheme. The Committee requested consumption data on iodine from iodised salt in the UK be included in the statement if this was available.

24. Members noted that appreciable levels of iodine were still being detected in cows' milk. The Committee suggested that the Veterinary Medicines Directorate should be contacted to find out when iodophors were discontinued in the UK. It was agreed that if the use of iodophors was stopped in 2014 then it would suggest that this had not resulted in a large change in iodine levels in milk.

25. The limited information on iodine in tap water and how it compared to other environmental levels in other countries was also discussed. The Committee requested that some values on iodine levels from medication should be provided to give some more context. It was noted that paragraph 40 should include the uncertainties regarding the exposure calculations for seaweed.

26. Members suggested that the risk characterisation section should include some discussion on other routes of exposure. The Committee agreed that there should also be mention that there was a lack of data in relation to pregnancy and lactation.

27. The committee noted that according to the exposure calculations there were toxicological concerns about the levels of iodine intake that might arise from consumption of seaweed, which could potentially pose a toxicological concern to maternal health. It was agreed that excess iodine would not lead to toxicological concerns in the UK diet overall.

28. It was agreed that the statement could be cleared by Chair's action.

Item 5: Development of Human Biomonitoring Guidance Values in the HBM4EU Project (TOX/2021/15)

29. No interests were declared.

30. The paper outlined the methodology for the derivation of human biomonitoring guidance values by the European Human Biomonitoring Initiative, referred to as HBM4EU, which is a project designed to develop a harmonised and systematic strategy for the derivation of human biomonitoring guidance values (HBM-GVs). Information was provided concerning other types of human biomonitoring guidance values to allow comparison with established methods, and the potential application of the HBM4EU strategy and values, and their relevance to the UK discussed.

31. Appendix A provided some background information on human biomonitoring and Appendix B background information regarding environmental and consumer exposure monitoring schemes, such as NHANES in the US.

32. Four illustrative case studies, conducted by the HBM4EU partners, were included for discussion: Butylbenzylphthalate (BBzP); Diisononylcyclohexane-1,2-dicarboxylate (DINCH); Bisphenol A; Cadmium.

33. The paper had been presented to the COC earlier in March, to gain their feedback on the approach. COC Members were informed that key comments would be summarised as part of the briefing for COT. COC agreed that the framework was a robust and scientifically valid way to determine HBM-GVs, with suggestions to make some components more explicitly stated. Application of the framework to derive UK values as UK-specific HBM data becomes available was also encouraged.

34. Dr Ovnair Sepai (PHE) gave a short overview presentation on the HBM4EU project as background for the paper and Members were provided an opportunity to ask general questions on the project overall prior to focusing on the contents of the paper. Members enquired about the UK's involvement in the European project in terms of data collection and were informed that from a general population perspective there were no UK-specific data as the UK does not collect such information. Members commented that there were two aspects that needed to be considered: the generation of the human biomonitoring guidance values and the application of these values to the population. It was also noted that, similar to determining any guidance value, the derivation of the human biomonitoring guidance values would depend on the type of data available and on establishing the relationship between the exposure and the effect. UK specific biomonitoring data would be useful for risk assessment and more information (such as appropriate auxiliary data) would be required before being able to use these values for this purpose.

35. In terms of the methodology for deriving the human biomonitoring guidance values, it was noted that the values would need to be validated from a toxicological perspective. It was also suggested that it would be ideal if exposure could be correlated to environmental levels in combination with human biomonitoring data, for example by collaborating with the Environment Agency or Defra to collect environmental biomonitoring exposure data. A suggestion was made that correlation of National Diet and Nutrition Survey (NDNS) data with environmental biomonitoring data would be useful to refine exposures.

36. With regards to the paper itself, Members questioned whether there would be sufficient toxicological data to establish human biomonitoring guidance values and

suggested a continuation project with targeted studies to allow for the generation of suitable data. The provision of examples was considered very useful.

37. It was noted that, on occasion, both external and internal guidance values will need to be used - for example in cases where there is variability in the exposure depending on product, and therefore monitoring of both product levels and internal levels in humans would be needed. It was agreed that this would need to be done on a case by case basis and that the human biomonitoring guidance values often do not stand alone. But they add value when they can be used in combination with other approaches.

38. The Committee considered that more information would be useful in the paper on the pharmacokinetic requirements to establish a biomonitoring equivalent. The sampling and exposure scenarios need to fit sampling time. Members noted that requirements for marker substances were not included in the paper. The Committee agreed that the strategy developed by HBM4EU robust and scientifically valid; depending on kinetics information and data availability. The importance of appropriate dermal data in ensuring assumptions were correct was also highlighted. Finally, the Committee agreed that, in principle, the use of HBM-GVs derived by the HBM4EU in the UK would be possible. In practice, and in line with any other guidance value, detailed evaluation of the human biomonitoring value would be needed to determine whether the critical endpoint was appropriate for the UK population. The Committee agreed that going forward, the use of human biomonitoring guidance values in risk assessment could be helpful to the FSA and that the Committee was happy to look at future case studies and offer their perspective. If endorsement of these values was needed, the Committee would have to perform a detailed evaluation to offer their perspective.

Item 6: Update to the COT Position paper on the potential risk of CBD in CBD food products: additional text summarising committee discussions relating to dermal and inhalation exposure. TOX/2021/16

39. No interests were declared.

40. The COT 'Position paper on the potential risk of CBD in CBD food products' summarised discussions and conclusions of the COT and COM from July 2019 to May 2020 on the available toxicological information of relevance to cannabidiol (CBD) in non-medicinal food products and was published in July 2020. At the May 2020 COT meeting, the Committee had discussed data of relevance to dermal exposure to CBD from CBD-containing cosmetic products and at the December 2020 COT meeting, information on inhalation exposure to CBD was considered.

41. The Committee discussed data from three additional publications relating to dermal and inhalation exposure to CBD presented in paper TOX/2021/16. The dermal absorption study, which used human skin *in vitro*, provided some additional information on ranking of dermal absorption using various drug delivery systems but this was not related to exposure via the products and scenarios that COT had reviewed previously. The Committee requested that the previous conclusion that dermal absorption of CBD was lower than oral absorption should be checked before

agreement of the additional text on dermal exposure was added to the position paper.

42. The data in the papers by Spindle *et al*. (2020a and 2020b)[2] did not change the previous conclusions. The data suggested that vaped (i.e. the inhalation route) CBD could be more bioavailable than from the oral route. The studies summarised in the paper were difficult to interpret. There was insufficient information available to obtain reliable estimates of systemic exposure, for which a full bioavailability study would be needed if this needs to be explored further. The Committee agreed the text on inhalation exposure to CBD should be added to the position paper.

43. It was agreed that the additional text could be agreed by Chair's action and then included in the position paper.

Item 7: Draft report on the synthesis and integration of epidemiological and toxicological evidence in risk assessments (TOX/2021/17)

44. The Committees on Toxicity and Carcinogenicity (COT and COC) published a joint report on synthesising epidemiological evidence (SEES) in 2019. During their meetings the subgroup also discussed the approaches on the synthesis and integration of epidemiological and toxicological evidence and recognised that current approaches in risk assessment usually consider epidemiological evidence separately from toxicological evidence. Guidance on the integration of the two evidence streams was scarce and the way in which this is done by the Committees has not been clearly explained to date.

45. Consequently, the Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE) Subgroup was formed in November 2019. The aim of the subgroup was to report in a transparent fashion on the approaches taken by the Committees and to give practical guidance on how to integrate the two evidence streams.

46. The draft SETE report presented to the Committee in Appendix 1 of paper TOX/2021/17 set out the considerations and deliberations of the SETE subgroup. This included a practical and directly applicable guidance document on evidence integration contained in Annex 1 of the SETE report.

47. Annex 2 of the SETE report had not yet been finalised but aimed to provide practical examples applying the procedures for the integration of evidence and SETE

[2] Spindle, T. R., E. J. Cone, E. Goffi, E. M. Weerts, J. M. Mitchell, R. E. Winecker, G. E. Bigelow, R. R. Flegel & R. Vandrey (2020a) Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. *Drug Alcohol Depend,* 211**,** 107937.

Spindle, T. R., E. J. Cone, D. Kuntz, J. M. Mitchell, G. E. Bigelow, R. Flegel & R. Vandrey (2020b) Urinary Pharmacokinetic Profile of Cannabinoids Following Administration of Vaporized and Oral Cannabidiol and Vaporized CBD-Dominant Cannabis. *J Anal Toxicol,* 44**,** 109-125.

guidance. The Committee would have the opportunity to comment on the examples in a future meeting.

48. The COC had the opportunity to comment on the current report and guidance document at their meeting on 4th March 2021, where it was favourably received.

49. Lay members of the COC had asked for additional discussion on the weight of evidence approach and Members of the COT suggested cross-referencing available guidance, if possible, or an extension of the glossary entry to address this. Members further echoed the observations made by the COC on the potential accessibility issues regarding the colour scheme of the figure illustrating the visual matrix of the likelihood of a causal relationship.

50. Members discussed the quality assessment of studies, particularly of epidemiological studies and ways in which bias and confounding could be assessed. The approach for assessing epidemiological studies in the scientific community has largely moved away from simply applying a numerical score with the help of check lists but rather focuses on the totality of the evidence. The Committee endorsed this approach, assessing the strengths and weaknesses of all epidemiological studies.

51. Members welcomed the section on *in vitro* methods. Text on *in silico* methods was currently embedded in a later discussion of PBPK models but Members felt it would be better earlier in the document and suggested renaming the section on *in vitro* methods to new approach methodologies (NAMs) and to include *in silico* methodology in this section.

52. The Committee endorsed the principles and considerations laid out in the report and the guidance document and looked forward to seeing worked case study examples at a future meeting to put these principles into practice.

53. Members were asked to send any additional/editorial comments they may have to the Secretariat after the meeting.

Item 8: First draft non-technical statement on how the Committees evaluate the relevance and reliability of data when assessing a chemical of concern? (TOX/2021/18)

54. No Interests were declared.

55. The topic of 'biological relevance and statistical significance' had been raised as an area of interest during Committee horizon scanning activities for a number of years. A scoping paper was presented at the Joint COC/COM meeting in November 2020 also attended by some COT members, where it was agreed that guidance aimed at the lay audience would be prepared, providing clarity on how the expert Committees evaluate data with respect to consideration of biological relevance and statistical significance.

56. Paper TOX/2021/18 presented a draft document providing a brief outline of the Committee evaluation process focussing on the relevance and reliability of data,

written specifically to inform the lay person. It had been revised following review by lay members of the COC, COT and COM.

57. The Committee was informed that the paper had been presented at the March 2021 COC meeting where feedback had been provided that the document was overly technical for a lay audience. It was proposed that two documents be developed; one aimed at the lay audience about the process used by the Committees to evaluate evidence and reach conclusions, and another on statistical significance testing and the consideration of biological relevance that is aimed at a more informed audience.

58. The COT considered the paper was largely fit for the purpose of describing the mechanisms of ascribing biological and statistical significance to the assessment of the risk posed to the consumer by a chemical. It was acknowledged that the statistical assessment described was overly complex for a lay readership, however it was emphasised there should be no simplification of the definition of concepts such as the null hypothesis and p-value to the extent that their meaning was lost.

59. There was support for a second statement, or area on the website, describing the workings of the sister committees. Some aspects would need more development to take this forward, in particular, how a particular chemical or issue is added to the agenda and the steps taken to assess the risks to the consumer associated with it. Such a paper should also clearly define the basis of the conclusions reached.

60. The Committee agreed that the paper could go forward to the COM for their assessment as to whether it should be split into two separate documents, and a number of suggestions were made for amendments for the next version of the current paper.

Item 9: Paper for information: Update on the work of other scientific advisory committees (TOX/2021/19)

61. This paper was circulated for information.

Item 10: Any other business

62. There was no other business.

Date of next meeting

63. The next meeting of the Committee Meeting will be at 10:00 on the 4th of May 2021 via Skype and Teams.