Meeting

Draft Minutes of the 16th May 2023 COT Meeting

Meeting of the Committee at 10:00 on Tuesday16th May 2023 via Microsoft Teams

Present

Chair:	Prof Alan Boobis

COT Members:	Dr Phil Botham	
	Professor James Coulson	
	Professor Gary Hutchison	
	Professor Thorhallur Ingi Halldórsson	
	Dr Michael Routledge	
	Dr Natalie Thatcher	
	Dr Sarah Judge	
	Ms Juliet Rix	
	Dr Simon Wilkinson	
	Professor Maged Younes	
	Professor Mireille Toledano	
	Professor Philippe Wilson	
	Ms Jane Case	
	Professor Gunter Kuhnle	
	Professor Shirley Price	
	Dr Cheryl Scudamore	
	Dr Stella Cochrane	
	Dr David Lovell	
	Professor Matthew Wright	
COT Co-Opted Members:	Professor Paul Haggarty	SACN Liaison

	FSA Scientific Secretary
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland
	Mr Michael Dickinson
	Dr David Gott
	Dr Alex Cooper
	Mr Barry Maycock
	Ms Claire Potter
	Dr Barbara Doerr
	Dr Olivia Osborne
	Ms Chara Tsoulli
	Ms Frederique Uy
	Ms Emma French
	Ms Rhoda Aminu
	Ms Sabrina Thomas
	Dr Gail Drummond
	Ms Cleanncy Hoppie
	Ms Jocelyn Frimpong-Manso
	Ms Sophy Wells
	Dr Gaetana Spedalieri
	Mr Thomas Hornsby
	Dr Emily Hudson
	Mr David Kovacic
	Ms Kaitlyn Jukes
	Dr Aaron Bradshaw
	Dr Lorean Browne

UK HSA Secretariat:	Ms Britta Gadeberg	UK HSA Scientific Secretary
Invited Experts and Contractors:	Dr Sarah Bull	Institute for Environment and Health (IEH)
Assessors	Dr Ovnair Sepai	UKHSA
	Ms Valerie Swaine	Health and Safety Executive (HSE)
	Ms Liz Lawton	Department for Environment, Food and Rural Affairs (DEFRA)
		Environment Agency
	Mr Ian Martin	Department for Business and Trade
	Ms Frances Hill	
Observers	Dr Emma Bradley	FERA
FSA and other Officials:	Mr Vincent Greenwood	FSA
	Ms Kerry Gribbin	FSA NI
	Mr Elliot Dews	FSA NI
	Ms Coleen Mulrine	FSA NI
	Dr Ovnair Sepai	UKHSA
	Ms Krystle Boss	Food Standards Scotland (FSS)
	Ms Lucy Smythe	FSS DEFRA
	Ms Holly Alpren	

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Date of the next meeting – Tuesday 11th July at Broadway House, London and via Teams

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 were received from COT Members Dr Mac Provan and Dr Silvia Gratz and from Dr John O'Brien, Science Council liaison. Apologies were also received from Dr Joseph Shavila of the Secretariat.

Item 2: Draft Minutes from the meeting held on 28th of March 2023 (TOX/MIN/2023/01)

4. It was noted that there appeared to be two item 6s, but this was two related papers, which should be under the same agenda item. This would be amended.

5. The minutes and reserved minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 28th of March 2023

JEGs Update

6. Members were updated on the current work of the Joint Expert Groups (JEGs)

AEJEG

7. Members were informed that there were a number of dossiers under evaluation by the Additives, Enzymes and other Regulated Products (AE) JEG and two items on steviol would be presented to the COT later in the agenda.

8. Review of the smoke flavourings dossiers were progressing and most of the applicants have responded to requests for further information. A second round of AEJEG smoke flavouring meetings would take place later in the year.

FCMJEG

9. The Food Contact Materials (FCM) JEG will be having their next meeting on the 24th May 2023. The FCMJEG are considering a number of responses providing additional information for two recycling dossiers. The overview of the regulation on recycling processes is currently ongoing.

Publications

Oral nicotine pouches

10. Members were informed that the statement on oral nicotine pouches has now been published.

Working Groups

Per- and polyfluorinated alkyl substances (PFAS)

11. A PFAS subgroup was being set up and any Members who are interested in joining this group should let the secretariat know by the end of the month (May).

Dioxins

12. The Secretariat would like to thank members who provided comments on the first draft of the dioxins review and the final review will be presented at a future meeting.

UK New Approach methodologies - third draft roadmap - TOX/2023/22

13. Members were informed that if they had any comments on the third draft of the UK New Approach Methodologies Roadmap they should let the Secretariat know by the end of the month (May).

Scientific Advisory Committee recruitment

14. The FSA Scientific Advisory Committees (SACs) have been recruiting and recommendations have been made to appoint both full and associate Members to COT. The appointment of Associate Members was a new scheme to encourage mid-career applicants who would be in post for 1 year and would learn about the work of the SACs, with a view to considering application for full Membership in due course. If any COT Members wished to act as mentors for the Associate Members, they should contact the Secretariat.

15. It was announced that Professor Philippe Wilson had been re-appointed to serve a second term on the Committee. Dr Phil Botham, Ms Jane Case, Dr Sarah Judge, Ms Juliet Rix, and Professor Matthew Wright have been re-appointed to serve a third terms on the Committee. However, this will be for 1 year to ensure adherence to CopSAC guidelines.

COT Workshop

16. Members were informed that the round table discussion questions for the COT workshop on 17 May have been posted on the COT Teams site. Members were asked to let the Secretariat know if they had any final additions or suggestions.

Item 4: Can coating (Reserved) – (TOX/2023/23)

17. The item was reserved as it includes commercially confidential data.

18. Professor Alan Boobis was a member of ILSI Europe expert groups, which included participants of the company (Velspar) producing the epoxy resin. However, as the discussions held by the expert groups were not related to the compound discussed nor company specific, Prof Boobis was free to chair this item. Dr Emma Bradley, who was attending the COT meeting as an observer, declared a personal specific interest as she was directly involved with the tests conducted at FERA and assisted the company in putting the dossier together for the Dutch assessment. Dr Bradley was therefore absent for this item. No other interests were declared.

Item 5: EFSA opinion on BPA – (TOX/2023/25)

19. Professor Thorhallur Ingi Halldórsson and Professor Maged Younes of the Committee and Dr David Gott of the Secretariat were Members of the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP panel) and BPA Working Group. They were able to answer questions and provide clarification but could not otherwise take part in the discussion. Professor Matthew Wright is an EFSA panel Member but was not involved in the BPA evaluation and was able to take part. Dr Stella Cochrane and Dr Natalie Thatcher declared non-personal specific interests, as their employers would have an interest in the use of BPA in packaging. No other interests were declared.

20. Following public consultation in December 2021, the EFSA CEP panel published their final opinion on the re-evaluation of the health risks arising from the presence of bisphenol A (BPA) in food in April 2023.

21. The Panel established a new Tolerable Daily Intake (TDI) of 0.2 ng BPA/kg bodyweight (bw) per day. This reduction would mean that average and high level consumers for all age groups would exceed the new TDI by 2-3 orders of magnitude, whereas consumer exposure was within the previous temporary TDI.

22. As the diverging views between EFSA and the European Medical Agency (EMA) and the Bundesamt fuer Risikobewertung (BfR) could not be resolved, according to the respective founding regulations, EFSA and the EMA/BfR were obliged to present a joint document to the European Commission (EC) clarifying the contentious scientific issues and identifying relevant uncertainties in the data.

23. The COT had discussed the draft EFSA opinion at their extraordinary meeting in February 2022 and submitted comments to EFSA’s public consultation, raising a number of concerns, including the use of an intermediate endpoint on

which to establish a health-based guidance value (HBGV).

24. Paper TOX/2023/25 set out the basis for the final TDI established by EFSA, and the diverging opinions from the EMA and BfR.

25. The Committee noted that while the EMA's approach to risk assessment differs from that of the COT and BfR in that it also considers benefit when reviewing human medicines, both the EMA and BfR raised scientific concerns with respect to the endpoint used by EFSA in their opinion. These aligned with the concerns and comments highlighted by the COT during the public consultation. Members also noted that there was currently work underway at international level regarding the safety of BPA.

26. EFSA utilized a predetermined method/protocol, which included a defined time period for the inclusion of studies. While Members acknowledged that it would not be possible to consider every single study published and every endpoint available, they agreed with the BfR's criticism that EFSA's protocol restricted the data set assessed in the EFSA opinion. While other studies may not be infallible and would have uncertainties attached to the data, there was a wider data set available for BPA, which should have been considered in the evaluation, for the relevant endpoint selection but also the derivation of the human equivalent dose (HED) factor.

27. Looking at the study selected by EFSA for the establishment of the TDI, Members specifically questioned whether an intermediate endpoint of uncertain pathophysiological significance would be sufficiently robust. While this was a wider discussion, the Committee did not agree with EFSA that the change seen in Th17 cells was a sufficiently relevant and scientifically robust intermediate endpoint on which to base the establishment of a HBGV.

28. The Committee noted that by focussing on a single study, the EFSA opinion lacked transparency in evidence integration. In addition, given the uncertainties over the endpoint, a weight of evidence approach should have been clearly applied in the EFSA opinion to fully assess the data and derive a robust point of departure.

29. As a default EFSA recommends a 5% change for BMDL modelling, however EFSA deviated from this default in the in the draft opinion (20% change) and the final opinion (40% change), based on the coefficient of variation in the response. Members also noted that given the wide range of uncertainty, the TDI could be 3-4 times the order of magnitude than the current TDI. EFSA applied a

number of assumptions in their derivation of a point of departure over which Members raised concerns, specifically the use of a single figure/number applied to the overall outcome.

30. Members highlighted that while not explicitly asked to perform an exposure assessment, the exposure data used in the new EFSA opinion was the same as that used in the 2015 opinion. Hence, the data and conclusions on exposures may not accurately reflect the current exposures of consumers, as permitted migration levels of BPA had been reduced, something EFSA acknowledged in their opinion.

31. The Committee previously agreed with EFSA's assessment of the safety of BPA in 2006, 2008 and 2015. However, while the Committee considered it possible that the TDI would need to be revised to account for new evidence and ensure it was sufficiently protective, on balance the weight of evidence did not support the conclusions drawn by EFSA, or a TDI as low as that established by EFSA.

32. It was agreed that an interim position paper, capturing the COT's view and the proposed next steps should be published.

Item 6: Second draft statement on green tea catechins – (TOX/2023/26)

33. Professors Maged Younes and Matthew Wright declared personal non-specific interests relating to flavanols as the Chair and a Member, respectively, of the EFSA ANS Panel that produced the original opinion on the safety of green tea catechins (GTCs). They were able to provide comment and clarification on the EFSA opinion but not to contribute to the conclusions of the COT's discussions. Professor Gunter Kuhnle declared that he was currently involved in performing industry-funded research on flavanols, therefore left the meeting while this item was being discussed. No additional interests were declared.

34. In 2017, following a series of reports of adverse effects on the liver following the consumption of green tea supplements, the European Commission requested EFSA to assess the available information on the safety of green tea catechins (principally - epigallocatechin-3-gallate (EGCG)) from all dietary sources including preparations such as food supplements and traditional infusions, with a focus on liver toxicity. At that time, and at the request of the Department of Health and Social Care (DHSC), who have the policy lead for food supplements in

England, the FSA Chemical Risk Assessment Unit team reviewed the EFSA opinion informally and agreed with its conclusions.

35. Following the adoption of the EFSA opinion, the EU Commission are proposing amendments to EU legislation to restrict or prohibit the use of green tea catechins to ensure that foods containing these substances are safe for human consumption. The proposed risk management measures could include prohibiting the substance, restricting the permitted dose, or placing it under Community scrutiny for a period of time under Article 8 of Regulation (EC) 1925/2006.

36. Following a request to FSA from the Nutrition Labelling Composition and Standards (NLCS) Common Framework on behalf of the UK, COT have been asked to evaluate whether the conclusions of the 2018 EFSA opinion are still applicable, in view of any new data that have become available since its adoption, to enable them to consider the next steps. The 2018 EFSA opinion itself and its evaluation by the COT, focus on green tea catechins and the associated cases of probably idiosyncratic hepatotoxicity, rather than being a safety assessment of either green tea catechins or green tea infusions and extracts more generally.

37. A discussion paper was presented to the Committee in September 2021, since which drafts of the statement have been reviewed, with the final substantive discussion being held in February 2023.

38. Following discussion of the statement, Members requested the Secretariat to summarise the cited studies in a table format to provide a general overview of the doses consumed and adverse effects observed.

39. Members also requested the Secretariat to ensure that references to legislation were up to date.

40. A number of minor editorial changes were also proposed.

41. Members agreed that the statement could be cleared by Chair’s action following the addition of the requested information above.

Item 7: Discussion paper on novel formulations of supplement compounds designed to increase oral bioavailability- TOX/2023/27

42. No interests were declared.

43. In their second draft statement on the safety of turmeric (TOX/2022/68), the COT identified novel formulations, particularly those with the potential to increase oral bioavailability, as a key area of uncertainty in the assessment of dietary supplements. Such formulations include micellar, nano- and micro-formulations, including colloidal dispersions and liposomal systems. Therefore, the Committee decided that novel formulations designed to increase the oral bioavailability of supplements should form the basis of a general discussion paper.

44. Paper TOX/2023/27 gave an overview of the structure and physicochemical properties of several novel supplement formulation types, including colloidal, liposomal, and micellar systems. The biological mechanisms through which such formulations may alter bioavailability were also summarised. The paper reviewed pharmacokinetic studies in human subjects with novel formulations of three different supplements, as exemplars: vitamin C, curcumin, and cannabidiol (CBD). In reviewing these case studies, Members noted that the pharmacokinetic behaviour of xenobiotics such as curcumin and CBD can differ from that of essential constituents of the diet, such as vitamin C, due to the role of homeostatic regulation in the latter. At standard doses (up to 200 mg), vitamin C was fully bioavailable, so there was little scope for any increase in systemic exposure by changing absorption. Any changes observed with novel formulations must therefore involve more complex interactions with homeostatic mechanisms. With lipophilic xenobiotics exhibiting low bioavailability in their standard form, there is more scope for increased bioavailability by formulating them in novel ways to increase their solubility, uptake and escape of presystemic metabolism. Members commented that other novel formulations such as those containing vitamin A, vitamin D, iron and iodine were currently available and would require consideration.

45. In reviewing potential systemic exposure from novel lipid-based formulations Members stated it was important to distinguish between studies conducted in the fed and fasted state, because absorption involves carrier lipids and bile acids that are modulated by feeding state. The interaction between lipid-based formulations and the GI tract was also raised, and it was argued that some formulations might prevent the absorption of dietary nutrients during equilibration in the gut.

46. Members discussed the challenges in translating findings from conventional toxicology studies to the potential impacts of novel formulations. In this respect, Members raised the question of potential non-linearity in the dose-

responses of these formulations and the point at which increases in area under the curve became toxicologically relevant. Members also noted that the mechanisms underlying any increase in bioavailability were important to consider, and how they relate to increases in absorption, saturation of efflux transport, saturation/inhibition of metabolism, and/or other kinetic parameters. Considering these discussions, Members stated that interspecies differences in these processes are also important to consider when evaluating the safety of novel formulations.

47. The Committee noted that the bioavailability of formulations will depend on particle size, and formulation of supplements with nanoparticle technologies may have impacts on circulation time and tissue distribution. Changing physiological stability in this way, may distort pharmacokinetic parameters and/or have toxicological relevance. The route of exposure, for instance inhalation, may also be important to consider regarding bioavailability. The Committee agreed that this fell outside the scope of the current discussions, however, which related to dietary supplements.

48. In terms of establishing health-based guidance values (HBGVs) for novel supplement formulations, Members noted that this was important for consumer safety, as maximum dosage levels for certain compounds may not be applicable for novel formulations. Members stated that the critical factor was understanding how external dose relates to internal exposure for standard and novel formulations, and when/if these diverge.

49. Members reiterated the issues of cross-species differences and extrapolation of no observed adverse effect levels. In cases where kinetic data were available relating to changes in bioavailability, this may inform the uncertainty factor applied in establishing HBGVs for standard formulations of compounds, where they exist. In the absence of specific kinetic data, Members stated that a worst case approach would be to assume 100% bioavailability of the active compound. The Committee discussed how these data are often unavailable, and that the pharmaceutical industry is likely to have more extensive datasets that might aid in these kinds of assessments.

50. Based on these data gaps the Committee also discussed the regulatory issues regarding supplements in general. Members raised the issue of consumer perceptions of safety, the use of high doses of supplements, and the role of misinformation, influencers, and marketing in this process. Members suggested that products should not be marketed for use at doses above safe levels, where they have been established. Supplements exist in a ‘grey space’, Members

suggested, where they are claimed to promote some benefit but do not make direct health claims and hence are currently not covered by specific legislation.

51. The Committee discussed the emerging usage of intravenous vitamin drips which provide 100% bioavailability of an active compound but for which the regulatory context is not clear. The Care Quality Commission may have some regulatory oversight, but these drips were not regulated by the Medicines and Healthcare Products Regulatory Agency.

52. Members considered the paper contained sufficient information to reach general conclusions regarding novel formulations, and that no further and/or specific information was required for this purpose. The Committee also agreed, given that supplements will vary on a case-by-case basis, it was not necessary to provide further case studies and/or exposure assessments to reach general conclusions.

53. In discussing the potential conflicts of interest relating to the literature on novel formulations and bioavailability, Members noted that, if present, these would more likely to result in a positive reporting bias, in that there would be an advantage in providing evidence of increased bioavailability for low-bioavailability compounds. The Committee agreed that it was not necessary to see further information regarding conflicts of interest for the current paper.

54. It was agreed by the Committee that purchasing a market report summarising the projected trends of the novel formulation market for supplements was not necessary for reaching general conclusions. Members noted that in assessing these formulations it is prudent to act on what is already occurring in the market, and, furthermore, that any market report will contain omissions and assumptions. Moreover, Members argued that supplement companies should be disclosing what they sell.

55. Some minor editorial issues were raised regarding the glossary definition of ‘micelles’ which incorrectly identifies the direction of the hydrophobic/hydrophilic faces of the molecules.

56. As a next step, a Position paper will be drafted that addresses Members questions and comments, which could potentially be included in future guidance documents.

Item 8: Committee Advice on the safety of the extension of use of steviol glycosides (E 960) from stevia leaf extract produced by enzymatic conversion (RP1084) (Reserved) - TOX/2023/28

57. The item was reserved as it includes commercially confidential data.

58. Dr Stella Cochrane declared a non-personal specific interest as her employers Unilever, may use stevia in their products; this did not preclude her for taking part in the discussion of this item. No other interests were declared.

Item 9: Committee Advice on the approval of steviol glycosides (E 960) produced by Yarrowia lipolytica (RP1140) – (Reserved) – TOX/2023/29

59. The item was reserved as it includes commercially confidential data.

60. Dr Stella Cochrane declared a non-personal specific interest as her employers Unilever, may use stevia in their products; this did not preclude her for taking part in the discussion of this item. No other interests were declared.

Item 10: Update on the work of other FSA Scientific Advisory Committees - for information - (TOX/2023/30)

61. This paper was circulated for information. Members were encouraged to contact the Secretariat for any additional information.

Item 11: Any other business

62. There was no other business.

Date of next meeting

63. The next meeting of the Committee will be at 10:00 am on the 11th of July 2023 at Broadway House, London and via Microsoft Teams