Meeting

Final Minutes of the 21st October 2024 COT Meeting

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited

Meeting of the Committee at 10:00 on the 10th of December 2024 on Microsoft Teams.

Present

Chair:	Professor Alan Boobis	Committee on Toxicity

Members:

Dr Stella Cochrane	
Professor James Coulson	
Professor Gary Hutchison	
Professor Thorhallur Ingi Halldórsson	
Dr Gunter Kuhnle	
Dr David Lovell	Committee on Toxicity
Professor Shirley Price	
Dr Mac Provan	
Dr Michael Routledge	
Dr Cheryl Scudamore	
Dr Natalie Thatcher	
Dr Simon Wilkinson	
Professor Philippe Wilson	
Professor Maged Younes	
Dr Steven Enoch	
Professor Peter Barlow	
Dr Meera Cush	
Mr Gordon Burton	
Dr Andreas Kolb	
Dr Alison Yeates (from Item 4)	

Liaison Member	Mr Tom Oliver (from Item 3)	Science Council

		FSA Scientific Secretary
Food Standards	Ms Cath Mulholland	
Agency (FSA)	Dr Tahmina Khan	
Secretariat:	Dr Alex Cooper	
	Mr Barry Maycock	
	Ms Claire Potter	
	Dr Barbara Doerr	
	Dr Olivia Osborne	
	Ms Sabrina Thomas	
	Dr Gail Drummond	
	Ms Chara Tsoulli	
	Ms Frederique Uy	
	Ms Jocelyn Frimpong-Manso	
	Ms Sophy Orphanos	
	Dr Gaetana Spedalieri	
	Mr Thomas Hornsby	
	Dr Emily Hudson	
	Dr Aaron Bradshaw	
	Ms Natasha Adams	
	Dr Katie Schulz	
	Ms Rachel Kerr	
	Mr James Metcalfe	
	Ms Polly Bevan	
	Ms Alba Ureña Rusillo	
	Mr James Metcalfe	
	Ms Abigail Smith	

UK HSA Secretariat:	Ms Britta Gadeberg	UK HSA Scientific Secretary
Assessor	Mr Stephen Robjohns	UK HSA
Assessors	Mr Ian Martin	Environment Agency
Assessors	Ms Akosua Adjei	MHRA
Assessors	Mr Leon Jackson	DEFRA
FSA and other officials	Ms Pamela Iheozor-Ejiofor	FSA
FSA and other officials	Ms Colleen Mulrine Ms Catherine Hardy	Food Standards Northern Ireland
FSA and other officials	Ms Krystle Boss Ms Lucy Smythe	Food Standards Scotland
FSA and other officials	Ms Nive Raja Ms Sanyukta Pallavi	UK HSA
Observer	Dr Emma Bradley	FERA/FCM JEG
Observer	Dr Michael Walker	FCM JEG

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Announcements

1. The Chair welcomed Members and other attendees.

2. It was announced that Professor Gary Hutchison, Dr Cheryl Scudamore, Dr Stella Cochrane and Dr David Lovell have accepted one-year extensions to their current second terms.

3. Members were informed that COT Deputy Chair, Professor Shirley Price will be acting as a formal liaison between the JEGs and the COT as part of continuing efforts to strengthen links and aid the evaluation of regulated products.

4. It was announced that Mr Tom Oliver and Ms Jacqueline Healing have taken over from Professor John O'Brien as Science Council liaison: Mr Tom Oliver would be attending the present meeting in the afternoon.

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 COT Members Dr Silvia Gratz, Mr Nick Richardson, Dr Chris Morris, and SACN Liaison Member, Professor Paul Haggarty.

Item 2: Draft minutes and reserved minutes of the 3rd of September 2024 meeting. (TOX/MIN/2024/05)

7. The Committee reviewed the draft minutes and the reserved minutes of the 3rd of September 2024 meeting (TOX/MIN/2024/05). It was noted that there were spelling/grammar mistakes in paragraphs 16 and 19 of the reserved minutes. These would be amended by the Secretariat.

8. Subject to the above amendments, the minutes and reserved minutes were accepted as an accurate record.

Item 3: Matters arising

Joint Expert Group (JEG) updates

AEJEG

9. The last meeting of the full Additive and Enzyme Joint Expert Group (AEJEG) was held on the 16th October 2024.

10. The AEJEG discussed an update paper and a second Draft Committee Advice Document (CAD) on the "Application for the Authorisation of Blue Microalgae Extract (Blue *Galdieria* Extract) for Use as a New Food Additive in the "Colour" Functional Class (RP507)". It was agreed that the Secretariat would present a revised CAD document to the AEJEG meeting in December for their final approval.

11. An update paper on an Application on the Extension of use of curcumin (E100) to a new food category "egg analogues" (RP41) was also considered. The AEJEG agreed that RP41 could return to the Expert Group as a draft CAD.

12. The AEJEG were also informed that the CAD for RP1457 (glycolipids) would be first presented to the Advisory Committee on the Microbiological Safety of Food (ACMSF) for review of the AEJEG conclusions on the microbiome and would then be presented to the COT in December 2024.

13. The next AEJEG meeting would take place on the 4th December 2024.

14. The Smoke Flavourings Working Group would meet next on the 23rd October 2024 to continue Phase 3 of the assessment.

FCMJEG

15. The most recent Food Contact Materials JEG (FCMJEG) meeting was held on the 2nd October 2024, where they discussed applications for the authorisation of two plastic additives. The next meeting would be on the 2nd December 2024, where the FCMJEG would be discussing one of the new plastic additive applications (RP229) and the response received to a Request for Further Information (RFI) for a plastic additive application (RP1898).

16. There were currently two new plastic additive applications in the suitability check stage – poly(2-ethyl-2-oxazoline) and agar palmitate. Both were being prepared and would be reviewed by the JEG in upcoming meetings.

17. There were currently four applications at the RFI stage -RP262, RP1415, RP1898 and RP2229. Of these, a response had been received for RP1898, a response was expected for RP 262 in November 2024. A RFI was due to be issued for a plastic additive application (RP2147) following the October 2024 FCMJEG meeting.

18. Three applications for the authorisation of recycling processes have been finalised by correspondence.

19. The FCMJEG statement on tetra-methyl bisphenol F diglycidyl ether (TMBPF-DGE), a can coating used as an alternative to bisphenol A, has now been published.

COT Statement on Lead in the Maternal Diet

20. Members were informed that the recently published statement on lead in the maternal diet had been revised after the Secretariat's attention had been drawn to an error in the exposure calculations. This error has now been corrected and the revised statement was cleared by Chair's action as it did not materially affect the conclusions.

21. The Chair informed Members that he had been quoted in the media following correspondence with an MP regarding the potential effects of environmental lead entering the food chain.

Publications

22. The COT review of titanium dioxide was published on the 3rd October 2024. The accompanying COM statements were published on the 11th October 2024.

23. The FSA and COT Roadmap for NAMs has been accepted as a peer reviewed publication in Regulatory Toxicology and Pharmacology. It can be found at:

Food for thought- Paving the way for a UK Roadmap towards optimum consumer safety: Development, Endorsement and Regulatory Acceptance of New Approach Methodologies (NAMs) in Chemical Risk Assessment and Beyond

Subgroups and working groups

24. The last meeting of the ACNFP/COT working group on Cannabidiol (CBD) took place on the 11th September 2024 where an “introduction to Group C products” was discussed. These are products that contain between 2.5 and 67% CBD. The next working group meeting would be held on the 6th November 2024.

25. A date for the next meeting of the per- and polyfluoroalkyl substances (PFAS) sub-group has not been set.

26. The joint SACN/COT Working Group on plant-based drinks will be meeting on the 5th November 2024 to discuss the outcome of the peer review of the draft report. This topic would be covered in item 5 of the agenda.

SAC recruitment

27. Recruitment to the FSA Scientific Advisory Committees (SACs) had now closed. Members were thanked for their suggestions on individuals and institutions to contact directly and for circulating information on the recruitment to their networks.

Item 4: RP1741 - Draft Committee Advice Document on the evaluation of the safety of the process for the recycling of post-consumer PET into food contact material (Reserved) (TOX/2024/36)

28. No interests were declared for this item.

29. This item is currently being treated as reserved, as the data are commercially confidential and it is an area of developing policy.

30. Members reviewed and commented on the Committee Advice Document (CAD).

31. The CAD will be reviewed again by the FCMJEG once the Secretariat has addressed the comments made by COT.

Item 5: Joint Scientific Advisory Committee on Nutrition (SACN)/COT draft report on plant-

based drinks - response to peer review (Reserved) (TOX/2024/37)

32. Dr Alison Yeates noted a potential conflict of interest due to her involvement with the School Milk and Nursery Alliance. It was agreed that she could contribute to discussions but would not participate in formulation of the conclusions. Dr Meera Cush noted a conflict of interest, as she had been involved in a project for a manufacturer, where she had provided toxicology information on the safety of isoflavones for use in medical foods for the elderly; the company concerned had commented on the draft report. It was agreed that she could contribute to discussions but would not participate in formulation of the conclusions.

33. No other interests were declared.

34. Members were reminded that the draft report of the joint COT and SACN Working Group on assessing the health benefits and risks of consuming plant-based drinks was published for peer review in July 2024. The responses received from the peer review were set out in paper TOX/2024/37 for COT Members to consider. It is being treated as reserved business as it is developing policy.

Item 6: Deriving a health-based guidance value for antimony to support development of UK Drinking Water Standards (TOX/2024/38)

35. No interests were declared.

36. Paper TOX/2024/38 presented a summary of the toxicity of antimony to support the review of the current drinking water regulatory standards by the Drinking Water Inspectorate (DWI). The UK Health Security Agency, which advises the DWI, were seeking advice from the COT with respect to an appropriate health-based guidance value (HBGV) for antimony.

37. The Committee discussed the interpretation of a 90-day rat drinking water toxicity study on antimony potassium tartrate by Poon et al. (1998) (Food and Chemical Toxicology, 36(1), pp.21-35). The World Health Organization (WHO), the US Agency for Toxic Substances and Disease Registry (ATSDR) and Health Canada (2024) have all used this study as the basis to establish HBGVs, but these

are all different. The differences are primarily due to variations in the interpretation of the study findings, particularly in the identification of the No Observed Adverse Effect Level (NOAEL).

38. The Committee raised several concerns highlighting significant issues with the pathology assessment of this study. These included the use of unusual pathology scoring, which combined severity with tissue distribution of the lesions, and unusual terminology for lesions particularly those observed in the thyroid. This complicated the interpretation of the identified outcomes.

39. The Committee agreed the Poon et al. (1998) study showed no clear evidence of changes in thyroid hormone levels and the thyroid weights were not measured in the study. The Committee considered that liver changes were minor and not indicative of adverse effects as there was no evidence of an increase in liver weight across a large range of doses, or in the activity of serum enzymes such as alkaline phosphatase and aspartate aminotransferase. The changes in the levels of liver enzymes like ethoxyresorufin-O-deethylase (EROD) and glutathione-S-transferase (GST) were minor and inconsistent with a hepatotoxic effect. The effects on serum glucose levels in females showed limited dose-response for a decrease and there was a lack of historical control data to support the interpretation. There was also difficulty in interpreting findings in the spleen due to high background variation and the findings were not considered to be of toxicological significance.

40. Many of the concerns raised by the COT had also been noted in a commentary by Lynch et al. (1999) (Regulatory Toxicology and Pharmacology, 30(1), pp.9-17), and the Committee considered this provided a reasonable assessment of the interpretation of the study findings in Poon et al. (1998).

41. Overall, for the Poon et al. (1998) study, the Committee agreed that the significant body weight changes observed at the highest dose would be the critical effect; this finding had also been utilized by the WHO in establishing a health-based guidance value. The COT agreed with the NOAEL of 6,000 µg/kg bw/day proposed by Lynch et al. (1999) for this study, which was also the value identified by the WHO.

42. The Committee considered the other studies summarised in the paper. It was noted that the US National Toxicology Program (NTP,1992) intraperitoneal study on antimony potassium tartrate, although of less relevance for risk assessment of exposure via the oral route, contributed to the weight of evidence, as despite higher systemic exposure, the liver effects observed in the Poon et al.

(1998) study, were not observed in this study.

43. The Committee noted that while there are multiple studies reporting changes in body weight gain following oral administration of antimony salts, often the changes were marginal. Rossi et al. (1987) (Teratogenesis, Carcinogenesis and Mutagenesis, 7(5), pp.491-496) administered antimony trichloride in drinking water to pregnant female rats and to their pups post-weaning. An 18% decrease in body weight gain was measured in dams, with a more marked effect on pups immediately before weaning (53% decrease at post-natal day 22). This raised concerns about potentially susceptible populations; however, it was noted that with reducing maternal body weight, this might possibly have impacted on lactation and therefore pup body weight. The Committee requested further information on any other reproductive and developmental toxicity studies.

44. For a number of the other studies there were concerns about study quality, the exposure route and the form of antimony used. It was also suggested that there might be useful information on the acute toxicity of antimony from data on tartar emetic.

45. It was suggested that a more in-depth review of studies on antimony was required, focusing on distinguishing between different forms of antimony and their bioavailability. There was a need for further information, if available, on the solubility of different antimony forms, valence states, and their endpoints. Information on other reproductive and developmental toxicity studies was also requested. The Committee was unable to reach a conclusion on what point of departure to use for antimony and suggested that provision of a summary table, including information such as details on study duration, administration routes, and form of antimony used, would be of value in the assessment.

46. It was agreed that a further discussion paper on this topic would be brought to a future meeting.

Item 7: Citrinin in the maternal diet (TOX/2024/39)

47. No interests were declared.

48. In 2019, the Scientific Advisory Committee on Nutrition (SACN) agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this

would include the effects of chemical contaminants and excess nutrients in the diet. COT would assess the toxicological effects, to assist SACN in this review.

49. A scoping paper was presented to COT in July 2020. This included background information on a provisional list of chemicals proposed by SACN. Following discussions at the September 2020 meeting, COT agreed that papers on a number of compounds should be prioritised, which included several mycotoxins, one of which was citrinin.

50. Citrinin (CIT) is a mycotoxin produced by several species of fungi and is generally formed during storage following harvest. CIT is acutely nephrotoxic in mice and rats, rabbits, pigs and poultry, causing swelling and eventual necrosis of the kidneys. Adverse reproductive effects have been reported, but these were potentially secondary to maternal toxicity.

51. In 2012, EFSA assessed the risks to public and animal health related to the presence of CIT in food and feed and concluded that the derivation of a health-based guidance value (HBGV) would not be appropriate, given the available data on genotoxicity and the limitations and uncertainties in the current database. A summary of the EFSA opinion (2012) and new data published since the EFSA opinion were presented in the COT paper.

52. The aim of paper was to request the advice of COT on whether exposure to citrinin would pose a risk to maternal health.

53. In interpreting the *in vivo* reproductive toxicity studies, the Committee discussed whether direct toxic effects on the developing fetus could be distinguished from maternal toxicity. Members noted that the doses used in these studies were substantially higher than the level of no concern for nephrotoxicity established by EFSA in 2012, as well as the estimated levels of dietary exposure.

54. The Committee highlighted that from the toxicokinetic data on citrinin labelled with C14 it was unclear whether citrinin could reach the fetus. However, the toxicological effects reported in other studies indicate some citrinin could reach the fetus. Members noted that the findings of the studies assessing exposure using labelled citrinin and those assessing toxic effects were not consistent and questioned whether there was an apparent difference in kinetic behaviour between labelled and unlabelled citrinin, due to the position of the label and the fate of the molecule.

55. It was noted by the Committee that mycotoxins do not occur in isolation and there was likely to be exposure to multiple mycotoxins when contaminated

food was consumed. This should be acknowledged in the paper.

56. EFSA (2012) was unable to reach a conclusion on the genotoxicity of citrinin but noted that it did not cause gene mutations. The Committee considered the data published since 2012 and agreed that there was no evidence for the genotoxicity of citrinin in *vivo*. However, Members considered citrinin to have a potential effect on microtubules and/or spindle assembly, which could result in aneugenicity; an effect that would have a threshold. The Committee concluded that CIT was unlikely to be genotoxic *in vivo* at dietary exposure levels.

57. The Committee considered whether to characterise the risk from citrinin using a margin of exposure (MOE) approach. Since studies indicate that citrinin was carcinogenic, the MOE could be expressed using the upper bound exposure level and a conservative estimate of the point of departure (POD) for tumours. It was noted that exposure was likely to be orders of magnitude lower than this POD.

58. Members noted that the level of no concern for nephrotoxicity established by EFSA had been based on a 90-day study. A few additional 90-day studies had been published since the 2012 EFSA opinion and whilst they did not follow standard guidelines, it was agreed they should be included in the review.

59. It was noted by the Committee that the EFSA opinion (2012) included studies on immunogenicity, but no such studies were included in TOX/2024/39. The Secretariat agreed to add any immunogenicity studies published since the EFSA opinion to the review of citrinin for the Committee’s consideration at a future meeting.

60. The discussion paper summarised the uses of red yeast rice (RYR) in Asian cuisine and as a dietary supplement to reduce plasma cholesterol and triglyceride levels, which is often contaminated with CIT. The Secretariat informed the Committee that RYR supplement packaging states that the product is unsuitable for women who are pregnant or who are breast feeding. The Secretariat also noted that RYR is used in China as a food colouring. The Committee questioned whether exposure to CIT from RYR should be included in the assessment.

61. When considering the exposure data, Members noted that all the values were below the limit of quantification and 100-fold lower than the level of no concern for nephrotoxicity established by EFSA for citrinin. As the commodities described in the exposure assessment were all below the LOQ, the Committee

could not determine whether any of the food groups would specifically contribute to exposure from citrinin.

62. The Committee asked how citrinin levels might change over the next 10 years due to climate change and similarly whether the exposure data from 10 years ago was representative of current exposures. Higher temperatures might affect harvest and storage conditions, which could lead to increased growth of the fungi which produces citrinin, and therefore higher levels of citrinin, though it was noted that badly contaminated produce should be identifiable and removed before entering the food chain. The literature in this area focused mostly on changes in crop production and no more recent data were available on the occurrence of citrinin in the UK diet.

63. It was highlighted by the Committee that the list of commodities used for the exposure assessment did not include plant-based drinks.

64. Members agreed that the level of no concern for nephrotoxicity established by EFSA in 2012 was adequately protective for maternal, reproductive and developmental toxic effects; this was not affected by any of the newer data.

65. The Committee highlighted that the paper relates to maternal effects but includes discussion on male reproductive endpoints, which might need to be removed, due to lack of relevance. However, these effects might reflect potential mechanisms, but if included this would need to be explained.

66. From the information presented, Members concluded that there was no evidence of a risk from citrinin in the maternal diet at current exposure levels. The Committee confirmed that the paper would return as a first draft statement with the requested changes. If additional information on immunogenicity were found, this would be presented to Members in a separate annex.

Item 8: Update on the work of other FSA Scientific Advisory Committees - for information (TOX/2024/40)

67. This paper was circulated for information, but Members should contact the Secretariat if they have any questions.

Item 9: Any other business

68. There was no other business.

Date of next meeting

69. The next meeting of the Committee will be held on the 10th of December via Microsoft Teams.