Meeting

Draft minutes of the 25th October 2022 meeting

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

Present

Chair:	Prof Alan Boobis

Dr Phil Botham

Dr Stella Cochrane

Professor James Coulson

Professor Gary Hutchison

Professor Thorhallur Ingi Halldórsson

Dr Mac Provan

Ms Juliet Rix

COT Members:

Dr Michael Routledge

Dr Natalie Thatcher

Dr Simon Wilkinson

Professor Philippe Wilson

Professor Matthew Wright

Professor Maged Younes

Professor Paul Haggarty — SACN Liaison

Professor John O’Brien — Science Council Liaison

Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland	FSA Scientific Secretary
	Mr Michael Dickinson	
	Dr David Gott	
	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 Cleanncy Hoppie	
	Ms Jocelyn Frimpong-Manso	
	Ms Sophy Wells	
	Dr Gaetana Spedalieri	
	Mr Thomas Hornsby	
	Mr Lawrence Finn	
	Dr Emily Hudson	
	David Kovacic	
	Ms Kaitlyn Jukes	
	Dr Aaron Bradshaw	

UK HSA Secretariat:	Ms Britta Gadeberg	UK HSA Scientific Secretary
Contractor for UKHSA	Dr Sarah Bull	IEH
Invited Expert:	Mr Mark Cairns	Civil Aviation Authority (CAA)
	Dr Sibylle Ermler	
Invited Experts: FSA JEG Members	Dr Gill Clare	FSA FCMJEG
	Professor Michael Walker	
Invited Expert: Commitee on Mutagenicity	Professor Gareth Jenkins	COM Chair
Assessors	Ms Valerie Swaine	Health and Safety Executive (HSE)
	Ms Rachel Elsom	
Assessors	Susannah Brown	Office for Health Improvement and Disparities, (OHID), DHSC
	Estella Hung	
Assessors	Dr Tim Gant	UKHSA
Assessors	Dr Sam Fletcher	Veterinary Medicines Directorate (VMD)
Assessors	Ms Liz Lawton	DEFRA
Assessors	Mr Ian Martin	Environment Agency (EA)
Assessors	Ms Julianna Berrie	Department for Business Energy and Industrial Strategy (BEIS)

Observers	Dr Emma Bradley	FERA
	Mr Alexander Kallian	Kings College London (presenting)
	Dr Christer Hogstrand	Kings College London
	Dr Miao Guo	Kings College London
	Professor John Colbourne	Birmingham University
	Professor Mark Viant	Birmingham University
	Dr Arthur de Carvalho e Silva	Birmingham University (Biosciences) (Presenting)
	Dr Stephen Ruckman	TSG consulting

	Mr Adib Khonkar	
	Dr Amie Adkin	
	Ms Natasha Gladstone	
	Professor Rick Mumford	
	Mr Vincent Greenwood	
	Mr Tim Chandler	
	Mr Nuala Meehan	
FSA Officials:	Ms Tasila Mwale	FSA
	Mr Miguel Guijarro	
	Ms Elli Amanatidou	
	Mr Mark Willis	
	Ms Kam An Au	
	Dr Andy Axon	
	Mr Gareth Thompson	
	Mr Ciaran Weir	
	Ms Jenny Lika	
	Ms Sharon Gilmore	
FSA Northern Ireland	Ms Kerry Gribben	FSA NI

Food Standards Scotland	Dr Marianne James Ms Catherine Cleland Ms Fiona Comrie Ms Lucy Smythe	FSS
Other Officials:	Mr David Ebbrell Ms Beth Glennie	HSE
Other Officials:	Mr Stephen Robjohns Ms Helen Nakeeb Ms Kerry Foxall Ms Dorothy Ubong Mr Matthew Symington Dr Ovnair Sepai Dr Tim Marczylo Ms Krystle Boss	UKHSA
Other Officials:	Ms Debby Webb Ms Bethany Knowles	DHSC
Other Officials:	Ms Lynn Larkin	Health NI (HNI)

Contents

Date of the next meeting	Wednesday 14th December 2022

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 Ms Jane Case, Dr Sarah Judge, Prof. Shirley Price, Dr Silvia Gratz and Dr David Lovell. Apologies were also received from Dr Emily Hudson of the Secretariat.

Item 2: Draft Minutes from the meeting held on 6th of September 2022 (TOX/MIN/2022/06)

4. It was agreed that the reference to the International Life Sciences Institute (ILSI) should be removed from paragraph 19 and a minor editorial amendment was made to paragraph 29.

5. No other changes were made and the minutes were accepted as an accurate record of the meeting.

Item 3: Matters arising from the meeting held on 6th of September 2022

Matters arising from previous meetings

PFAS

6. No Interests were declared.

7. The COT statement on EFSA's opinion on perfluoroalkyl and polyfluoroalkyl substances (PFAS) had now been published. However, from discussions between the FSA, EA, and UKHSA, it was clear that in the UK, further work on PFAS was required. In particular, given the caveats expressed by the Committee regarding the EFSA opinion, it was necessary to consider how the risk assessment of PFAS could be supported. Therefore, the COT were asked to consider what further guidance could be provided to support in-house risk assessments of PFAS undertaken by UK Government Departments and Agencies.

8. The paper provided a brief summary of COT's work on these substances, summarised the uncertainties that COT had identified in respect to risk assessments undertaken using EFSA's tolerable weekly intake (TWI) for a group of four PFAS, and described some of the challenges facing UK Government Departments and Agencies in their risk assessments of PFAS.

9. Members noted that it would be worth considering the use of new approach methodologies (NAMs) and bringing together the available information on these to reduce uncertainties. It was also suggested that the use of adverse outcome pathways (AOPs), which related to effects on nuclear receptors, be considered to investigate whether this information could inform the dose response relationship and relevance to humans.

10. The COT agreed that an interim position paper should be prepared, followed by a longer-term piece of work on the human health risks from PFAS using the SETE approach, by a sub-group. It was noted that the Committee would consider the human health risk assessment of PFAS, but there was wider work on risk analysis, including for example work by the Hazardous Substances Advisory Committee (HSAC) on environmental risk, to be undertaken by UK Government.

Maternal Diet - Vitamin D

11. Members were informed that at the Scientific Advisory Committee on Nutrition (SACN) Subgroup on Maternal and Child Nutrition (SMCN) meeting held on the 29th September 2022, the current programme of work on the maternal diet was discussed.

12. This included discussion of the COT statement on vitamin D and it was noted by SMCN Members that the effects of calcidiol (25-hydroxyvitamin D2) in supplement form had not been considered. SMCN Members considered that calcidiol should be reviewed due to its increased availability in supplement form and as consumption of calcidiol resulted in a more rapid and sustained increase in

serum 25(OH)D concentrations than consumption of other forms of vitamin D.

13. COT agreed that calcidiol should be reviewed as part of its work on the maternal diet.

Maternal diet - tea

14. The Members of the SACN Working Group noted that intakes of tea can be high in some pregnant women and therefore suggested the COT review it. The COT had previously agreed that while Raspberry leaf tea should be reviewed as a single supplement, for normal tea, caffeine was the key concern and therefore it was not necessary to review tea consumption per se. It was noted that assessing tea (green and black tea) would involve reviewing a broad range of epidemiological studies which were likely to be confounded and potentially of limited value in addressing this concern. However, the COT agreed that they could provide a short summary/review of tea for inclusion in the overarching statement rather than a comprehensive evaluation.

Item 4: Discussion paper on the request for authorisation of a can coating to be approved in the UK (RESERVED) (TOX/2022/54)

15. The COT Chair Prof 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 ILSI expert groups were not related to the compound discussed nor were company specific, Prof Boobis was able to chair this item and participate in the discussions. No other interests were declared.

16. This item was reserved as the data are commercially confidential.

17. Members discussed the information provided to the Committee on a can coating as well as the assessment and discussions of the Joint Expert Group on Food Contact Materials (FCM JEG) and sister Committee on Mutagenicity (COM).

Item 5: Presentations from FSA Fellow and PhD Student (TOX/2022/61)

18. The FSA and COT have been considering New Approach Methodologies (NAMs) to understand the best scientific methodologies available for use in the risk assessment of chemicals, and to consider how these can be incorporated and accepted in a regulatory context.

19. In 2021, the FSA started funded a computational toxicology postdoctoral Fellow at the University of Birmingham and a PhD Student at King's College London as part of their Interdisciplinary Doctoral Program (LIDo-TOX AI). Paper TOX-22- 61 introduced the work of the student and the fellow but is currently being treated as confidential as the data it contains is pre-publication. The fellow and PhD student have been working alongside other Government Departments to understand how NAMs will improve indicative levels of safety in chemical risk assessment.

20. In addition, these new partnerships have helped with networking, research collaboration, training opportunities and other activities in this area. The Fellowship and studentship also compliment the work set out in the COT FSA UK Roadmap towards using new approach methodologies in chemical risk assessment.

21. The Postdoctoral Fellow and the PhD student prepared a yearly review and gave presentations to the Committee on their progress to date.

22. The Postdoctoral fellow presented two case studies. The first of these focused on the plasticiser di-2-ethylhexyl terephthalate (DEHTP). The main objective was to derive a health-based guidance value. Concentration-response data obtained from ToxCast studies, via the Chemicals Dashboard (US EPA), were used. The second case study had, as chemical of choice, a perfluorinated substance, perfluorooctanoic acid (PFOA). The main objective was to integrate an *in silico* workflow with transcriptomics data to derive a health-based guidance value for PFOA that could be compared with that previously recommended by the European Food Safety Authority (EFSA). Transcriptomics data published by Health Canada were used as a data source from *in vitro* exposures of Human Liver Microtissues (a commercial preparation of spheroids comprising primary hepatocytes and Kupffer cells) to PFOA.

23. The PhD student presented on the hybrid Quantitative Structure Activity Relationship (QSAR) model of mutagenicity they have developed, which is, on average, 78% accurate at predicting mutagenicity. The hybrid model consists of two constituent QSAR models which individually are approximately 70% accurate on average. The first QSAR model used molecular fingerprint- based similarity

index calculations, whereas the second QSAR model used molecular fragmentation, to identify pro-mutagenic characteristics. Principal component analysis (PCA) was successfully used to identify the key determinants of the predictions.

24. The COT Members were impressed with the progress to date and gave feedback to the fellow and PhD student.

Item 6: Review of the guidance levels for fortificants in the bread and flour regulations (BFR) (TOX/2022/48)

25. No interests were declared.

26. In 2022, consultees of the Bread and Flour Regulation (BFR) 1998 and Bread and Flour Regulations (Northern Ireland) 1998 review were asked whether they agreed with the proposal to raise the minimum levels of calcium carbonate, iron and niacin to align with the provisions of retained Regulation (EU) 1925/2006 on the addition of vitamins and minerals and other substances to food which requires that nutrients must be present in a “significant amount”. A “significant amount” is defined for each added nutrient in retained Regulation (EU) 1169/2011 on the provision of food information to consumers as providing 15% of the nutrient reference value (NRV). NRVs are established guidelines for the recommended daily energy and nutrient consumption. The minimum levels for three of the four added nutrients which are required to be added to 100g of non-wholemeal wheat flour in the BFR 1998 are currently lower than the required 15% of the NRV, calcium 11.75%, iron 12% and niacin 10%, thiamin provides 19% of the NRV. On behalf of the UK government and devolved administrations, the Department of Health and Social Care (DHSC) requested the COT provide an assessment of the dietary exposure of calcium carbonate, iron and nicotinic acid (the form of niacin added to non-wholemeal wheat flour) and thiamin (Vitamin B1) at the current and proposed minimum fortification levels.

27. Members questioned why the UK were adopting an increase in the minimum fortification level of calcium, iron and niacin permitted in non-wholemeal wheat flour to harmonise with EU legislation on fortification. It was confirmed that this was all retained EU law and the measure would harmonise with other legislation on fortification of foods. Making this amendment would reflect changes which have already been made on a voluntary basis by the

majority of industry ensuring a level playing field in the market and minimise the burden on manufacturers as it would allow manufacturers to have one production line of flour which can be marketed on both domestic (GB) and export markets (nutrients must be present at least at 15% of the NRV when exporting to EU member states). Although the proposed change would have the benefit of increasing nutrient intakes in the population, this was not the aim.

28. It was noted that exposures to the nutrients at the proposed levels were within recommended maximum levels, except where supplements were also being consumed when in some instances maximum recommended levels were exceeded for total intakes.

29. It was highlighted that the supplement data presented in the paper were not derived from the National Diet and Nutrition Survey (NDNS) making it hard to determine the proportion of the population consuming these supplements.

30. The Committee noted the advice from the Department of Health and Social Care (DHSC) is that calcium, iron, niacin and thiamin supplements were not required unless an individual has certain underlying health issues for which these supplements are recommended.

31. Members questioned why some of the 97.5th percentile consumer intakes were the same or less than the mean consumer intakes; the Secretariat agreed to check this.

32. The Committee concluded that an increase in the minimum fortification level of calcium, iron, and niacin to 15% of the NRV would not result in any excess risk *per se* but agreed there would be a possible exceedance of recommended maximums in individuals that consume supplements. This would also be true for thiamin at the current level of fortification.

Item 7: Aircraft Cabin Air – Volatile organic compounds in aircraft cabin air comparison with work environment (TOX/2022/55)

33. No interests were declared.

34. The COT had been asked by DfT to investigate whether any new data have been published and to re-evaluate their previous view in their statement from 2007 and position statement from 2013 on the cabin air environment, ill-

health in aircraft crews and the possible relationship to smoke/fume events in aircraft. Following the May 2022 COT meeting, the request made of COT had been further refined to: “Is there evidence of exposure to chemical contaminants in cabin air that could have long-term health impacts, either from acute exposures or due to long-term low level exposures including mixtures, e.g. of VOCs?”. Paper TOX/2022/55 was one of a series of papers considering the topic, and this one focussed on Volatile Organic Compounds (VOCs) in aircraft and other work environments.

35. Members agreed that, subject to advice from the Civil Aviation Authority (CAA), focus should be on UK and EU airlines and comparisons with working environments, and modes of transport, within UK and EU rather than wider afield, as exposures to VOCs were likely to be very different in some other parts of the world. The Committee also raised the question of whether it is possible to separate data from the CAA based on whether the reports are for flights coming from EU or from non-EU airspace.

36. The Committee discussed whether exposures in the aircraft cabin were comparable to exposures in other workplaces; the next step would be considering whether the levels of individual chemicals were deemed acceptable, e.g. because they were lower than workplace exposure limits. It was noted that according to a review by EASA (European Union Aviation Safety Agency), the quality of cabin cockpit air is similar to or better than that of normal indoor environments (childcare, educational environment, etc.) with no occupational guidelines being exceeded.

37. Clarification was sought on whether the Committee review should be focussed only on pilots and cabin crew, or whether it should also include passengers. It was noted that cabin crew would be exposed to cabin air for longer and more often. However, it was agreed that it is still important to consider impact on passengers because of the different age groups potentially present, and as aircraft would be considered in the context of workplace exposure limits for cabin crew, which might not be as protective for passengers.

38. It was agreed that the data from the two papers on VOC exposures in aircraft, modes of transport and work environments would be reassessed and provided as a comparison focussed on data from the UK and EU. The data would, where possible, be compared to workplace standards or indoor air quality guidelines. It was agreed that any VOCs not exceeding such values would be of low priority. Initially, individual chemicals would be assessed and subsequently, a decision on how to assess mixtures would be made.

39. A number of other factors potentially confounding a possible association between the symptoms reported with chemicals in the aircraft cabin air environment include stress, radiation and shift work were noted. It was also noted that recent literature indicated that levels of tricresyl phosphate and particularly the ortho-isomer are much lower than they had been previously and it was unlikely that these compounds would be responsible for effects currently being reported.

Item 8: COT FSA Paving the way for a UK Roadmap: Development, Validation and Regulatory Acceptance of New Approach Methodologies (NAMs) in Chemical Risk Assessment – Workshop Report (TOX/2022/56)

40. No Interests were declared.

41. The COT and FSA held a 2-day workshop online in October 2021 with the intention of gaining insights from a variety of perspectives to help develop the COT FSA UK Roadmap for NAMs in chemical risk assessment.

42. The aim of the workshop was to receive insights, comments and ideas from a wide variety of stakeholders, industry, academia and government, on the roadmap. The idea was to develop it into a useful and engaging document that is of value to more than just the FSA and COT. The workshop addressed issues such as: what might be holding back the progress of NAMs being used in the regulatory space, including a range of areas such as socio-technical barriers, regulatory frameworks and current legislation.

43. Paper TOX/2022/56 contained the first draft of the workshop report. It was noted that it had not yet been published on the COT website as the final text of the speakers' section was still being agreed.

43. Members were content with the first draft of the workshop report. Some suggestions on restructuring the introduction were made along with some minor edits.

44. Members suggested that it would be useful to arrange a short meeting of a few COT Members with the COT Secretariat to help prepare a new section or document on New Insights, to highlight key themes.

45. Members were invited to submit any further comments to the COT Secretariat.

Item 9: First draft statement on the potential risk to human health of turmeric and curcumin supplements (TOX/2022/57) (Partially Reserved)

46. No interests were declared.

47. Turmeric has been widely used for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases for centuries.

48. Many of the proposed pharmacological properties of turmeric have been attributed to curcumin, a compound naturally present in turmeric rhizomes. These properties are claimed to include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities.

49. Due to its purported health benefits, the consumption of curcumin/turmeric supplements is becoming increasingly popular. However, there have been a number of reports of hepatotoxicity linked to the consumption of curcumin supplements in Italy, France and the United States (US).

50. The topic was most recently discussed at the July 2022 COT meeting. From this meeting further detail was requested on hazard and risk characterisation data for the other trace elements reported after the 30-product survey undertaken in 2021 by Fera. Further occurrence and toxicity data on adulterants such as other curcumin species were also requested. In the July 2022 meeting, Members suggested that novel supplement delivery mechanisms such as micellar nano and micro formulations should be looked at in further detail. Although these products made up only a small percentage of the supplement market at present, they may become more popular in the future and should be discussed.

51. After the meeting in July 2022, it was agreed with the Chair that a new paper discussing novel supplement delivery mechanisms, i.e. to potentially increase the bioavailability of an active substance, would be prepared for discussion in 2023, separate to the discussion and conclusions on the safety of turmeric in the diet and in supplements in common use.

52. The first draft statement, TOX/2022/57, summarised the current conclusions from the Committee since turmeric safety had first been discussed in December 2019. It highlighted recent conclusions from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), an update from the Italian authorities on their incident of acute hepatitis cases in 2019, and a very recently published 18 year study in October 2022 from the US Drug-Induced Liver Injury Network (DILIN) looking at correlations between turmeric exposure and hepatotoxicity (which was attached as a reserved Annex since the version available to the Secretariat was an unpublished draft).

53. Members highlighted that further emphasis should be placed on the apparent idiosyncratic nature of the liver toxicity cases relating to turmeric consumption. The Committee concluded that minor exceedances of the Acceptable Daily Intake (ADI), whilst generally of minimal concern, may be significant for those in the population who were susceptible to curcuminoid toxicity. However, these individuals would not know they were susceptible before taking such supplements. As highlighted in the recently published DILIN study, this susceptibility appears to be due to genetic factors, such as the presence of the HLA-B*35:01 allele in some individuals, although not all who suffered liver injury from use of curcumin supplements carried this allele. The HLA-B*35:01 allele has been linked to increased susceptibility to hepatotoxicity from a number of polyphenols.

54. The Committee concluded that a fully translated document from French to English of the 2022 ANSES opinion was not required at this time as there was sufficient information available from other sources to reach conclusions.

55. The Committee suggested a number of minor wording changes to the text of the current statement to be included in a second draft to be presented at a future date.

Item 10: EFSA draft Nitrosamine Opinion (TOX/2022/58)

56. The Committee was asked to comment on a draft EFSA Opinion concerning N-nitrosamines (N-NAs) in food, which was open for public consultation. Members were presented with TOX/2022/58, which provided an overview of the draft Opinion.

57. It was considered that the draft Opinion provided a good summary in terms of ADME and genotoxicity data. It was commented that the main issues open to question were the method of benchmark dose (BMD) analysis and how compounds were aggregated (grouped).

58. The Committee considered EFSA's statement that attributing a different, often lower, potency factor to the various compounds evaluated in the Opinion did not change the overall conclusions. Members questioned whether EFSA had provided numerical data to support this, noting that there was a sizeable difference in potency between some compounds.

59. Members added that the BMD analysis in EFSA's opinion was complex. It was noted that the Brantom study from which the BMD Limit (BMDL) was derived - which used the critical effect of liver tumour incidence, had a large number of dose groups (16 doses and controls). The problem with this, it was explained, was that even with a good dose-response, it was hard to fit an acceptable curve to the data. The Committee questioned whether experimental data to which it was easier to fit a dose-response curve would have changed the conclusions.

60. Overall, it was agreed that positive feedback should be given on the draft Opinion, which Members considered to be a comprehensive review of the topic.

61. Members were asked to provide any additional comments on the draft Opinion by Wednesday 16th November by uploading them to a document that would be made available on Microsoft Teams.

Item 11: Paper for information: Update on the work of other scientific advisory committees (TOX/2022/59)

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

Item 12: Any other business

63. There was no other business.

Date of next meeting

64. The next meeting of the Committee Meeting will be at 10:00 on Wednesday the 14th of December 2022 at Ministry of Justice, 102 Petty France, London in person and via Skype and Teams.