Meeting

Final minutes of the 14th December 2022 meeting

Meeting of the Committee at 10:00 on 14th December 2022 at Broadway House, London and on Microsoft Teams

Present

Chair:	Prof Alan Boobis

COT Members:	Dr Phil Botham
	Ms Jane Case
	Dr Stella Cochrane
	Dr James Coulson
	Professor Gary Hutchison
	Professor Thorhallur Ingi Halldórsson
	Dr Mac Provan
	Ms Juliet Rix
	Dr Michael Routledge
	Dr Natalie Thatcher
	Professor Matthew Wright
	Professor Maged Younes
	Dr Simon Wilkinson
	Professor Philippe Wilson

SACN Liaison	Professor Paul Haggarty
Science Council Liaison	Professor John O’Brien

	Ms Cath Mulholland	
	Ms Claire Potter	
	Dr Alex Cooper	
	Dr Olivia Osborne	
	Mr Michael Dickinson	
	Ms Emma French	FSA Scientific Secretary
Food Standards Agency (FSA)	Ms Rhoda Aminu	
	Ms Sabrina Thomas	
Secretariat:	Dr Gail Drummond	
	Ms Cleanncy Hoppie	
	Ms Sophy Wells	
	Dr Gaetana Spedalieri	
	Mr Thomas Hornsby	
	Mr Lawrence Finn	
	Dr David Gott	
	Mr Shaddad Saleh	
	Dr Emily Hudson	
	Dr David Kovacic	
	Mr Alexander Smith	
	Ms Aisling Jao	
	Ms Victoria Balch	
	Mr Barry Maycock	
	Dr Barbara Doerr	
	Ms Chara Tsoulli	
	Ms Frederique Uy	
	Ms Cleanncy Hoppie	

UK Health Security Agency (HSA) Secretariat:	Ms Britta Gadeberg	UK HSA Scientific Secretary
Invited Experts and Contractors:	Dr Sarah Bull	Institute of Environment and Health (IEH) Consulting
	Dr Sibylle Ermler	FSA FCMJEG
	Dr Gill Clare	FSA FCMJEG
	Professor Michael Walker	FSA FCMJEG
	Professor Gareth Jenkins	FSA FCMJEG
Assessors:	Ms Valerie Swaine	Health and Safety Executive (HSE)
	Ms Rachel Elsom	Office for Health Improvement and Disparities, (OHID), DHSC
	Ms Susannah Brown	
	Prof Tim Gant	UK Health Security Agency (UKHSA)
	Dr Sam Fletcher	Veterinary Medicines Directorate (VMD)
	Ms Liz Lawton	Department for Environment Food & Rural Affairs (DEFRA)
	Mr Ian Martin	Environment Agency (EA)
	Ms Julianna Berrie	Department of Business, Enterprise and Industrial Strategy (BEIS)
	Ms Mindy Dulai	
Observers	Dr Emma Bradley	FERA

Mr Alexander Kalian (Presenting)	
Dr Christer Hogstrand	Kings College London
Dr Miao Guo	
Professor John Colbourne Professor Mark Viant Dr Arthur de Carvalho e Silva (Biosciences) (Presenting)	Birmingham University
Dr Stephen Ruckman	TSG Consulting

FSA and other Officials:	Mr Adib Khondkar	Food Standards Agency (FSA)
	Dr Amie Adkin	
	Prof Rick Mumford	
	Mr Vincent Greenwood	
	Mr Tim Chandler	
	Ms Nuala Meehan	
	Ms Tasila Mwale	
	Mr Miguel Guijarro	
	Ms Eli Amanatidou	
	Mr Mark Willis	
	Natasha Gladstone	
	Ms Kam An Au	
	Dr Andy Axon	
	Ms Jenny Lika	
	Mr Gareth Thompson (Item 4)	
	Ms Sharon Gilmore	Food Standards Agency Northern Ireland (FSA NI)
	Ms Catherine Cleland	
	Ms Kerry Gribben	
	Mr Ciaran Weir (Item 4)	

Ms Fiona Comrie	
Mr Will Munro	Food Standards Scotland (FSS)
Ms Krystle Boss	
Ms Lucy Smythe	
Dr Alison Gowers	UKHSA/ Committee on the Medical Aspects of Air Pollution (COMEAP) Secretariat (Item 4)
Mr Nigel Dowdall	Civil Aviation Authority CAA (Item 7)
Ms Lynn Larkin	HNI
Ms Debby Webb	Department of Health and Social Care (DHSC)
Ms Bethany Knowles	
Mr Mark Cairns	Civil Aviation Authority (CAA)
Mr Stephen Robjohns Ms Helen Nakeeb Ms Kerry Foxall Ms Dorothy Ubong	UK Health Security Agency (UKHSA)
Dr Ovnair Sepai	
Dr Tim Marczylo	
Mr Matthew Symington	
Mr David Ebbrell Ms Beth Glennie	Health and Safety Executive (HSE)

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Announcements

1. The Chair welcomed Members and other attendees.

Interests

2. The Chair reminded those attending the meeting to declare any commercial or other interests they might have in any of the agenda Items.

Item 1: Apologies for absence

3. Apologies were received from COT Members Professor Matthew Wright, Professor Maged Younes, Ms Juliet Rix and Professor Þórhallur Ingi Halldórsson. Apologies were also received from Ms Chara Tsoulli and Ms Emma French of the Secretariat.

Item 2: Draft Minutes from the meeting held on 25th of October 2022 (TOX/MIN/2022/07)

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

Item 3: Matters arising

Matters arising from previous meetings

SETE update on discussion with COMEAP

5. The Secretariat updated the Committee on the discussion held by the Committee on the Medical Effects of Air Pollutants (COMEAP) on the recommendations of the Working Group on the Synthesising Epidemiological and Toxicological Evidence (SETE). Members were informed that COMEAP

assessed the guidance from the SETE report using some of their recent statements that have already been published, as examples of how it could be used, and going forward agreed to apply the process to some of their assessments from start to finish.

Review of the Codex's report on food allergen threshold levels TOX/2022/62

6. Dr Stella Cochrane declared a non personal, non-specific interest as her employers manufacture foods and have a general interest in allergen levels. This did not preclude her being involved in the discussion of this item. No other interests were declared.

7. FAO and WHO were asked to provide scientific advice on threshold levels in foods of the priority allergens by establishing an Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens.

8. The Summary and Conclusions report was published in August 2021. It suggests that the Expert Committee agreed and defined reference doses (RfD) as mg of protein at the Eliciting Dose (ED) 05 based on VITAL 3.0.

9. Food allergen risk assessments performed by the FSA and some of the food industry are based on the use of ED01. Moving from ED01 to ED05 was potentially a significant change and when COT previously considered the issue of adventitious contamination of soya in wheat flour the Committee advised that the limits should not be relaxed to the ED05. Therefore, the Food Hypersensitivity Policy Team have commissioned a review of Codex's full report on threshold levels to understand whether it is appropriate for the recommended reference doses to be applied to the UK 14 regulated allergens.

10. The Secretariat proposed that a sub-group of the COT should be established in order to review the report shortly after its publication and invited volunteers from the Committee. There was wide support from Members for this proposal and it was agreed that an expert review was critical. Members suggested that experts from outside the Committee should also be considered, particularly those with statistical knowledge.

JEGs Update

11. Members were updated on the current work of the various Joint Expert Groups.

12. The Joint Expert Group for Additives, Enzymes and other Regulated Products (AEJEG) were progressing with a number of applications for manufacturing methods which were expected to be ready to be viewed by the COT early next year. The majority of AEJEG work has been based around smoke flavourings. The first smoke flavourings meetings will be in January and applications are expected to be brought to COT in the spring.

13. The Food Contact Materials Joint Expert Group (FCMJEG) have been considering data received via a call for information into ocean bound plastics.

14. The Advisory Committee on Animal Feedstuffs (ACAF), which supersedes the Joint Expert Group on Animal Feed and Feed Additives (AFFAJEG), have discussed a number of applications and requests for further information, which had been received. The terms of reference were still being drafted.

2023 COT Workshop

15. At the October COT meeting it was agreed that the annual COT workshop scheduled for May 2023 should consider the proposed revision of the COT guidelines on the testing of chemicals for toxicity. A provisional agenda was tabled and the Committee were asked for any additional suggestions for topics, speakers or any other comments.

16. Members agreed that while the process of risk assessment was not expected to change, it would be appropriate to ensure the revised testing guidelines were flexible so that they could adapt to future changes in toxicity testing without need for further amendment or adaptation.

17. The Committee asked if the expected outcomes of the workshop were to have a new set of testing guidelines or to generate ideas. The Secretariat stated that the workshop was the first step in what was likely to be a lengthy piece of work developing new and/or revised testing guidelines and the main aim initially was to gather ideas. Members noted that it would be helpful to have clear aims for the workshop and suggested that facilitation could be useful if small group discussions were planned.

18. It was agreed that the Committee on Carcinogenicity (COC) and the Committee on Mutagenicity (COM) should be involved. Members added that a common section of testing guidelines between Committees should be considered in order to allow for a more holistic approach to toxicity assessment.

19. Members suggested that considering how risk assessment is conducted in other industries/sectors may be helpful.

20. Members were asked to send any additional suggestions to the Secretariat.

Item 4: Discussion paper on the request for assessment of a can coating (RESERVED) (TOX/2022/63)

21. 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 expert groups were not related to the compound discussed nor company specific, Prof Boobis was able to chair this item and participate in the discussions. Dr Emma Bradley, who attended the main COT meeting as external 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; she was therefore absent for this item. No other interests were declared.

22. This item is currently being treated as reserved, as the data are commercially confidential.

23. Members discussed information on the can coating along with the assessment and discussions of the Joint Expert Group on Food Contact Materials (FCM JEG) on the same coating.

Item 5: Microplastics - inhalation route 2nd draft statement (TOX/2022/64)

24. Professor Boobis declared an interest as one of the authors of the 2022 WHO report Dietary and inhalation exposure to nano- and microplastic particles and potential implications for human health (who.int). He is also involved in an ILSI Europe-convened multi-stakeholder group to identify data gaps in the assessment of the risk to human health of microplastics. Professor Shirley Price declared an interest as she was also one of the authors of the 2022 WHO report Dietary and inhalation exposure to nano- and microplastic particles and potential implications for human health (who.int). No other interests were declared.

25. In 2019, as part of horizon scanning (TOX/2019/08), the COT identified the potential risks from microplastics as a topic it should consider, subsequently informing FSA discussions on this area. Since then, several discussion papers have been presented to the COT and in 2021, the COT published an overarching statement on the potential risks from exposure to microplastics. This provided a high-level overview of the current state of knowledge on microplastics also identifying data gaps and research requirements. This was followed by a sub-statement which considered oral exposure to microplastics in more detail.

26. As there is evidence for the presence of plastic particles in both indoor and outdoor air, inhalation is a possible route of exposure to microplastics. The purpose of the draft sub-statement presented was to provide supplementary material to the overarching statement and to consider in detail the potential toxicological risks of exposure to microplastics via inhalation.

27. The Committee discussed to what extent particles arising from tyre wear should be included in the paper and it was decided that a brief overview was needed for completeness and context but that the separate review conducted in 2020 should be highlighted.

28. Members made a number of comments on the structure and content of the paper and the weighting given to certain studies.

29. Members asked for an introductory paragraph to be included to describe the factors affecting indoor exposure to microplastics and the behaviour of particles.

30. The Committee suggested that the research priorities should be ranked as there was currently no order of priority and to consider whether the scope of the work could be broadened to examine less traditional areas.

31. The Committee noted that the conclusions drawn by the 2022 WHO review were similar and that this report should be referenced along with the Chief Medical Officer’s 2022 Annual report which considered microplastics.

32. Members concluded that some restructuring of the document was required, and it should be brought back to the Committee in due course.

Item 6: Carbon monoxide and carbon dioxide in aircraft cabin air (TOX/2022/65)

33. Interests were declared by Britta Gadeberg (UKHSA Secretariat) who was an author on one of the papers cited in paper TOX/2022/65. No other interests were declared.

34. The COT had been asked by Department for Transport (DfT) to investigate whether any new data had 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/2022/65 was one of a series of papers considering the topic, and focussed on carbon dioxide (CO2) and carbon monoxide (CO) in aircraft.

35. Members noted that levels of CO2 were lower than the workplace exposure limit and the aircraft regulatory limit of 5000 ppm but higher than the ASHRAE limit of 1100 ppm. Members raised questions about the bases for the derivation of such regulatory values used as comparators and requested more information before conclusions could be made. In general, CO levels were below regulatory values for aircraft and air quality standards.

36. The Committee discussed the adverse health effects associated with exposure to CO and CO2. The Committee agreed that effects of CO2 should be assessed in terms of acute and chronic exposure as adverse effects may be different. Members also commented that CO2 could have a consequence on decision making, which was considered to be an adverse effect, following acute exposure but there is little evidence available for adverse effects following low level chronic exposure. It was noted that although CO2 could be considered a toxicant, it was also important in respiratory drive. In contrast, chronic exposure to CO can be associated with adverse health effects, including on cognition.

37. Members queried the origin of CO2 in cabin air other than from passengers and requested information regarding air changes in aircraft, especially after the smoking ban was implemented, and how engines compress air. It was agreed that information would be sought from the Civil Aviation Authority (CAA).

38. Regarding CO, Members noted that little information is available correlating CO levels *per se* with adverse effects, but rather effects have been

compared with carboxyhaemaglobin levels in blood, which may not be the best biomarker to use as there is considerable uncertainty about the relationship between exposure to CO and blood levels of carboxyhaemaglobin.

39. Overall, Members concluded that levels of CO in aircraft are unlikely to be associated with ill health. For CO2, more information was needed regarding the derivation of regulatory levels before a conclusion could be made.

Item 7: Discussion paper on EFSA's 2022 assessment of the genotoxicity of acrylamide (TOX/2022/66)

40. No interests were declared.

41. In response to a request from FSA policy colleagues, paper TOX/2022/66 considered EFSA's 2022 assessment of the genotoxicity of acrylamide. In this, the EFSA Panel considered the Modes of Action (MoA) underlying the carcinogenicity of acrylamide (including both genotoxic and non-genotoxic effects). The European Commission had requested EFSA review their 2015 conclusions in response to a review article published by Eisenbrand (Archives of Toxicology, 94, 2399–2950, 2020) that argued against a genotoxic mode of action for the carcinogenic effects of acrylamide. It is anticipated that the FSA will carry out a full review of acrylamide in 2023.

42. EFSA did not consider Eisenbrand's review to be comprehensive, and so also conducted a literature search on the genotoxicity of acrylamide to retrieve information that had been published since their 2015 review. Overall, EFSA upheld their 2015 opinion on the genotoxicity of acrylamide, concluding that a margin of exposure approach (MOE) was still appropriate. COT Members agreed with EFSA's conclusions, and offered some further comments and context on the statement. It was noted that acrylamide was well established as a genotoxic compound, with a large body of evidence available *in vivo*, especially at higher doses.

43. Members questioned what the specific contribution of the Eisenbrand paper was to the understanding of the topic as it did not add new mechanistic data on acrylamide and used a somewhat selective approach to reinterpret previously published studies. The erratum to Eisenbrand's paper (Archives of Toxicology, 94, 3935, 2020) noted some previously undeclared conflicts of interest. Members noted that several groups have reviewed the Eisenbrand paper

and concluded that it did not add any information or insights. It was further noted that the EC's request to EFSA was part of a wider review of acrylamide, and not catalysed solely by the Eisenbrand paper.

44. Members noted that the EFSA opinion lacked critical discussion on the interpretation of a mutational signature for acrylamide (and its degree of specificity) and there was little mention of toxicokinetic studies performed in knock-out CYP21 mice (conversion of acrylamide to glycidamide), which have an important bearing on conclusions regarding the relative role of the parent compound and this metabolite in genotoxicity.

45. It was noted that the updated literature review conducted by EFSA provided more supporting evidence for the genotoxicity of acrylamide and does not alter the prevailing opinion.

46. The Committee agreed that although there was uncertainty about the relative contribution of genotoxic and non-genotoxic mechanisms to the carcinogenicity of acrylamide, the genotoxic effects cannot be discounted. The current weight of evidence points to a conclusion that both genotoxic and non-genotoxic effects have the potential to contribute to the overall carcinogenicity of acrylamide. It was noted that EFSA's endorsement of the MOE approach applies to substances that are both genotoxic and carcinogenic, which is certainly the case for acrylamide, and therefore there was no reason to depart from this approach.

Item 8: Summary of health-based guidance values for per- and polyfluoroalkyl substances (TOX/2022/67)

47. No interests were declared.

48. 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 to support risk assessment of PFAS was required. Therefore, the COT was asked to consider what further guidance could be provided to support in-house risk assessments of PFAS undertaken by UK Government Departments and Agencies.

49. An initial paper on further work on PFAS was discussed at the October 2022 COT meeting (TOX/2022/53). That paper noted that a number of health-based guidance values (HBGVs) from other countries and international bodies were available for PFAS. In outlining a plan for a series of papers for COT consideration on PFAS, it was noted that a summary of available HBGVs and their derivations would be useful, which was presented in this paper.

50. Members noted it was useful to see the range of HBGVs and discussed the variation across the values based on the same data, due to differences in modelling approaches used.

51. Based on the HBGVs presented, the Committee agreed the critical effects to be assessed by the planned subgroup included hepatic, endocrine, immunological and developmental effects. Members also requested a future paper with more information on the physiologically based pharmacokinetic modelling and benchmark dose modelling as well as the critical effect and uncertainty factors used to determine the HBGV to further understand the values derived.

52. The Committee agreed that the planned interim position paper would be prepared next, followed by a longer-term programme of work on the human health risks from PFAS to be undertaken by the planned subgroup.

Item 9: Second draft statement on the potential risk to human health of turmeric and curcumin supplements (TOX/2022/68)

53. No interests were declared.

54. 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.

55. 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.

56. 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).

57. Turmeric was initially considered by the Committee in December 2019, with the topic being most recently discussed at the July 2022 COT meeting. Following discussions at that 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.

58. At the July 2022 meeting, members suggested that novel supplement delivery mechanisms e.g. 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. Following this meeting, it was agreed that a paper discussing novel supplement delivery mechanisms that could potentially increase the bioavailability of an active substance, would be prepared as a separate paper in 2023.

59. The first draft statement (TOX/2022/57) discussed at the October 2022 COT meeting, summarised the conclusions to date reached by the Committee. It highlighted recent conclusions from the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), an update from the Italian authorities on their cases of acute hepatitis reported in 2019, and a recently published (October 2022) 18-year survey from the US Drug-Induced Liver Injury Network (DILIN) looking at the correlations between turmeric exposure and hepatotoxicity.

60. This second draft statement, TOX/2022/68, contained a rewording of the description for idiosyncratic drug response of curcuminoids, reflecting the Committees' final conclusions relating to this. An updated description of the recently published United States Drug Induced Liver Injury Network (DILIN) study was also included along with a number of other minor wording changes.

61. Members stated there should be a re-emphasis on the lack of evidence for piperine increasing the bioavailability of curcuminoids, with a recent review article providing further emphasis that all uses of piperine for this purpose appeared to be derived from one study. This should be referenced in the statement.

62. With regard to the potential contamination of turmeric supplements by lead, the COT suggested a review of the 2013 conclusions in their ‘Statement on the potential risks from lead in the infant diet’, to cross check with the wording regarding the relevant margins of exposure against the BMDL01.

63. Members highlighted that the conclusions on curcumin dietary exposure (through food and drink rather than supplements) which currently stated that they generally lead to exposures that are below the dietary ADI should be re-worded to reflect more accurately the exposure data presented in Table 2 in Annex B of the draft statement.

64. The Committee suggested a number of other minor wording changes to the text of the current statement to be included in a final draft which would be finalised by Chair’s action.

Item 10: Paper for information: Update on the work of other scientific advisory committees (TOX/2022/69)

65. This paper was circulated for information. Members were notified that the paper was available online and were invited to share any comments with the Secretariat.

Item 11: Any other business

66. Members were asked if any volunteers could provide feedback on an urgent ongoing incident.

67. There was no other business.

Date of next meeting

The next meeting of the Committee Meeting will be at 10:00 on the 7th of February 2023 at Broadway House London and via Skype and Teams.