Minutes

Final minutes of the 12th July 2022 meeting

Meeting of the Committee at 10:00 on 12th July 2022 at Mercure Liverpool Atlantic Tower Hotel, Liverpool and on Microsoft Teams

Present

COT Chair	Professor Alan Boobis

COT Members:	Dr Phil Botham	
	Ms Jane Case	
	Professor Thorhallur Ingi Halldórsson	
	Dr Sarah Judge	
	Dr Gunter Kuhnle	
	Dr David Lovell	
	Professor Shirley Price	
	Dr Mac Provan	
	Ms Juliet Rix	
	Dr Michael Routledge	
	Dr Cheryl Scudamore	
	Professor Mireille Toledano	
	Professor Maged Younes	
	Dr Silvia Gratz	
	Professor John O’Brien	Science Council

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

UK HSA Secretariat:	Ms Britta Gadeberg	UK HSA Scientific Secretary
Invited Experts and Contractors:	Dr Sarah Bull	IEH
	Prof Jason Weeks	IEH (Item 10)
	Mr Mark Cairns	
Assessors	Ms Valerie Swaine	HSE
	Mr Tom Carter	HSE
	Ms Louise Dearsley	HSE (Item 11)
Assessor	Prof Tim Gant	UKHSA
Assessor	Dr Sam Fletcher	VMD
Assessor	Ms Liz Lawton	DEFRA
Assessor	Mr Ian Martin	Environment Agency
Assessor	Ms Frances Hill	BEIS
Assessor	Ms Susannah Brown	OHID
Assessor	Daragh Doyle	DHSC (Item 7)
Observers (Item 4 onwards)	Emma Bradley	FERA
	Dr Arthur de Carvalho e Silva	University of Birmingham
	Alexander Kalian	Kings College London

		FSA
		FSA
	Adib Khonkar	FSA
	Dr Amie Adkin	FSA
	Ms Natasha Gladstone	FSA (Item 6)
	Professor Rick Mumford	FSA (Item 6)
	Mr Vincent Greenwood	FSA
	Mr Tim Chandler	FSA
FSA Staff	Ms Nuala Meehan	FSA
	Ms Catherine Cleland	FSA
	Tasila Mwale	FSA
	Mr Miguel Guijarro	FSA
	Ms Eli Amanatidou	FSA
	Mr Mark Willis	
	Kam An Au	
Other Officials:	Mr Jack Brown	DEFRA
	Ms Lucy Smythe	FSS
	Ms Krystle Boss	
	Ms Sharon Gilmore	
	Ms Kerry Gribben	FSA NI
	Dr Marianne James	

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Announcements

1. The Chair welcomed Members and other attendees.

2. The Chair welcomed a new COT Member Dr Silvia Gratz. Dr Gratz is a senior Research Fellow at the Rowett Research Institute in Aberdeen with expertise in dietary exposure and mycotoxins. Dr Gratz briefly introduced herself.

3. Apologies were given for the late arrival of some of the papers

Interests

4. 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

5. Apologies were received from COT Members Dr Stella Cochrane, Professor Gary Hutchison, Dr Natalie Thatcher, Dr James Coulson, Professor Philippe Wilson and Ms Juliet Rix.

Item 2: Draft Minutes from the meeting held on 10th of May 2022 (TOX/MIN/2022/04)

6. The wording of paragraph 8 was changed from ‘this was not in accordance with the current NHS guidance, which recommends that supplementation is not needed if more than 500 ml infant formula is being consumed’ to read ‘current NHS guidance is that supplementation is not needed if more than 500 ml infant formula is being consumed.’

7. No other changes were made and the minutes and reserved minutes were agreed as a true record of the meeting.

Item 3: Matters arising from the meeting held on 10th of May 2022

Matters arising from previous meetings

Update on the process for the renewal of smoke flavourings authorisations -TOX/2022/34 - reserved

8. The Committee were updated on the workplan for the renewal of smoke flavourings authorisations. This item is currently reserved and the minutes will be published in due course.

JEGs Update

9. The Committee was updated on the current work of the Joint Expert Groups (JEGs).

AEJEG

10. The AE JEG were currently reviewing some extension of use applications along with the full dossier evaluation of blue microalgae. They were

in the process of clearing, by Chair's action, opinions on RP1057 and RP 217, which the COT had discussed at the March 2022 meeting, and were working on non-confidential versions of the assessments for publication. The latter part of 2022 would be largely spent reviewing the applications for the renewal of eight smoke flavouring authorisations.

FCM JEG

11. The Food Contact Materials (FCM) JEG have been discussing a plastic additive dossier along with further information on a recycling process dossier.

AFFA JEG

12. Members were informed that from October 2022, the Animal Feed and Feed Additives (AFFA) JEG will be replaced by the Advisory Committee on Animal Feeding stuffs (ACAF). ACAF is a FSA Scientific Advisory Committee (SAC), which was previously on hold but who will now undertake the assessment of regulated feed and feed products and will have the authority to issue their own opinions. Therefore opinions from ACAF would not need to go through the COT for verification. However, COT, COC and COM might be consulted for specialist advice as required.

CBD

13. The joint COT/ACNFP Working Group (WG) on cannabidiol (CBD) would be starting work over the summer. The FSA thanked COT Members who have volunteered to help. The Committee will be kept updated, but Members should be aware that the WG meetings will be held in closed session.

PBD

14. A third meeting of the plant-based drinks (PBD) WG was held in May with the next meeting scheduled for the autumn – the group were currently reviewing evidence gathered from manufacturers and will be starting work on a BRAFO analysis.

Publications

15. The COT position paper on bamboo composites has now been published on the COT website.

16. The COT statement on vitamin A is being finalised and will be sent to the Chair for clearance shortly.

Item 4: Discussion paper on the potential risk to human health of turmeric and curcumin supplements – following an updated literature review (TOX/2022/35)

17. No interests were declared.

18. 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.

19. 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.

20. 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.

21. The topic was most recently discussed at the March 2022 COT meeting, when the results of an analytical survey were considered. Members suggested that an updated literature review covering the bioavailability of curcuminoids would be beneficial, in particular reviewing the potential toxicokinetic changes that may, or may not, occur in the presence of adjuvant compounds such as piperine. It was also recommended that further market information for supplements that have unusual or novel contents such as synthetic or nano formulated curcuminoids claiming greater absorption should be obtained. It was also requested that all the trace element data, rather than just 4 heavy metals, from the 30 product survey discussed were scrutinised in greater detail.

22. Discussion paper TOX/2022/35 addressed Members’ suggestions from the March 2022 COT meeting.

23. The Committee concluded that the claim made for many supplements that the presence of piperine improved the bioavailability of curcuminoids was very questionable. There was little scientific evidence supporting these claims.

24. However, Members considered that some of the other ‘novel’ supplement types such as micellar nano and micro formulations should be looked at in further detail, in regards to their pharmacokinetics and the impact on curcuminoid bioavailability. 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.

25. Members concluded that after the results of the recent product surveys, lead contamination of turmeric products was unlikely to be the reason for incidents such as the hepatoxicity reported in the Italian incident. However, it was still uncertain why this cluster of adverse effects occurred.

26. The Committee requested that further hazard and risk characterisation data be included for the other trace elements reported after the 30 product survey discussed at the March COT meeting. This was not needed for lead, cadmium, mercury or arsenic which had already been discussed.

27. Members noted that the adulteration of turmeric powders by, for example, other Curcuma species was only briefly covered in past discussions and more detail around the potential significance of this should be included in future papers.

28. After discussion regarding the curcuminoid concentrations in supplements and the safety implications of long-term intake of these based on the studies presented, Members concluded that consumption of conventional turmeric supplements, if based on the label guidance, should not pose a significant risk to the population.

29. The Committee suggested a number of minor wording changes to the text of the current discussion paper to be included in later papers on the topic.

Item 5: The potential risks from ergot alkaloids in the maternal diet: Discussion paper (TOX/2022/36)

30. A declaration of interest was made by Dr David Lovell as a member of the 91st JECFA in 2021 quoted in the paper. The Committee agreed that he could still participate in the discussion. No other interests were declared.

31. The topic of ergot alkaloids was considered as part of the continuing programme of work reviewing nutrition and maternal health, focusing on maternal outcomes during pregnancy, childbirth, and up to 24 months after delivery, being conducted by the Scientific Advisory Committee on Nutrition (SACN), with the COT advising on the potential adverse effects of chemical contaminants and excess nutrients in the diet.

32. Ergot alkaloids (EAS) are fungal contaminants found in food, notably cereals. They have a number of direct and indirect physiological effects including vasoconstriction, uterotonic activity, serotonergic antagonism or adrenergic blockade, and central nervous system effects (induction of hypothermia and emesis or effects on the secretion of pituitary hormones). Due to their structural similarities, EAs are thought to act as agonists or antagonists of noradrenaline, dopamine and serotonin neurotransmitters.

33. Exposure to EAs has also been associated with pregnancy hindrance by interfering with egg implantation, along with embryotoxicity in rodents, negative effects on maternal blood supply to the placenta in ewes and possibly sirenomelia in humans. EAs can also negatively affect lactation due to their hormone mimicking activity.

34. Further information was requested on the exposure assessments, in particular what the standard deviations of the values were.

35. The Committee noted that there was only a single case study on sirenomelia associated with ergot alkaloids and asked if there were any animal studies to provide supporting evidence, if not the text should be rephrased to reflect the uncertainty.

36. It was suggested that the wording of paragraph 19, which reported observations from a rabbit colony should be rephrased, as these were incidental findings rather than observations from a toxicology study.

37. Members suggested some restructuring to clearly separate the neurotoxicity section from vasoconstriction and to ensure the data on reproductive performance was put together; more information was requested on the description of muscular atrophy in the discussion section.

38. The Committee requested that the units used for dopamine levels in paragraph 14 be checked.

39. A Member noted that ergotamine was currently used only for cluster headaches and no longer for migraines.

40. In the toxicokinetics section of the paper, Members requested additional information on the extent of gastrointestinal absorption given the systemic effects of EAs. The Committee asked which specific P450 enzyme was involved in EA metabolism. It was suggested it might be CYP3A4 but this needed to be confirmed. Members suggested that further information on toxicokinetics might be found in the JECFA review of EAs.

41. The Committee advised checking the IARC website to determine their precise status regarding the review process.

42. Further information on the prolactin effect mentioned in paragraph 29 was also requested.

43. Members asked for the exposure assessments for vegans and vegetarians to be checked as they may have been inverted.

44. The Committee questioned the comparison between the reference dose and therapeutic dose and highlighted this was not very informative, because determination of the therapeutic dose was based on different criteria from those used to establish the Acceptable Daily Intake. Members suggested that the phrase “below the therapeutic doses of natural or synthetic” in the conclusions should be substituted with “below the minimum effective doses used therapeutically of natural or synthetic”.

45. Overall, Members considered that EAs would not have adverse effects on maternal health at likely levels of exposure.

46. The Committee made a number of minor suggestions on wording and agreed that a statement should be prepared setting out their views.

Item 6: Discussion paper on Ocean Bound Plastic (TOX/2022/37)

47. Professor Boobis declared that he was a nominal Member of the Imperial Network of Excellence on Ocean Plastic Solutions, but had not undertaken any activities. No other interests were declared.

48. The FSA has recently become aware of plastic materials intercepted before entering the oceans (referred to as ocean bound plastic) being recycled for use in food contact applications on the UK market. The food contact materials policy team sought an initial opinion from the Joint Expert Group on Food Contact Materials (FCM JEG as to whether ocean bound plastic (OBP) could safely be used in food packaging, either directly or behind a functional barrier and whether exclusion of substances that are mutagenic, carcinogenic or toxic to reproduction (CMR) could be assured.

49. Following discussions held in 2021, the FCM JEG published an interim position paper on OBP in February 2022 and the FSA launched a call for evidence in March 2022 to obtain further information from industry, individuals as consumers, or interested parties. The COT discussed the draft interim position paper in May 2021 and were updated on progress in July 2021.

50. Paper TOX/2022037 briefly summarised the concept of OBP, its current uses on the UK market, the relevant UK regulations and its potential safety implications for human health.

51. FSA officials provided a policy perspective on OBP. As noted, the FCM JEG had considered OBP in 2021. Subsequently, the FSA policy team started to identify products on the market that were using OBP. They were then approached by a company concerned that businesses using recycled OBP would not be able to carry out an accurate risk assessment because they would not know what was in the starting material as well as the material itself not conforming to original EU standards. The Committee asked if the regulatory work for household plastic could be used for ocean-bound waste. Policy responded that Regulation 10/2011 and Regulation 282/2008 on plastic and recycled plastics covered this area.

52. The Committee considered that more data on the production process and supplier chain involved would be useful. Specific data on different types of OBP was also needed as the Committee agreed that the different types of OBP should not be grouped together.

53. The Committee raised particular concern about intentional misuse of plastic associated with incorrect storage of toxic materials such as pesticides as well as high levels of persistent organic compounds. Photooxidation coupled with redox cycling in the presence of contaminants such as polycyclic aromatic hydrocarbons (PAHs) may produce further toxic contaminants.

54. Members agreed that labelling plastic as OBP was not necessarily related to risk and was more related to sustainability and environmental impact. OBP is plastic that had been intercepted within a certain distance from the ocean and from a toxicological point of view it cannot be distinguished *per se* from environmental plastic that is located outside of the boundary defining OBP, if it is used in the same way. The Committee also concluded that “read across” from ocean-based microplastic was not possible as the adsorbed contaminant profile and biofilm would be very different from those of terrestrial plastic.

55. The Committee advised the addition of a preamble to the paper explaining that use of OBP was about sustainability and ecotoxicological issues and in terms of human health it has no impact different *per se* from the use of other environmental plastic waste. However, the Committee recognised that the increased use of labelling of plastic as OBP was an issue, for example with respect to its country of origin. Microplastic from the terrestrial environment reflected plastic waste and it would be useful to compare it to pristine plastic to determine the differences in toxicological profile.

56. Members agreed that from a toxicological perspective no case was made to distinguish OBP from other environmental plastic. The composition was important and not the distance from the ocean. The Committee further discussed different sources of plastic in the environment (such as plastic that was deliberately put into environment, such as for horticultural uses or fishing materials). However, it was concluded that OBP referred to waste plastic that can be harvested from the environment before it reached the ocean and then recycled into products, rather than deliberately added materials, which weathered.

57. The Committee agreed that defining OBP and environmental plastic was beyond their remit. It was noted that issues relating to how waste was managed in different countries contributing OBP requires discussion beyond the Committee, and would need to include consideration of international trade and legislation. Members identified that chemical characterisation and estimates of exposure would be necessary for a meaningful risk assessment.

58. Members concluded that there were gaps in information that needed to be addressed before the Committee could reach any conclusions.

Item 7: Statement on the bioavailability of nicotine from the use of oral nicotine pouches

and assessment of the potential toxicological risk to users – First Draft (TOX/2022/38)

59. Professor Boobis declared an interest as Chairman of TC 126, working group 10 at the ISO organization, and also as a Member of the World Health Organisation (WHO) Advisory Group on tobacco products. No other interests were declared

60. Paper TOX/2022/38 presented a first draft statement on oral nicotine pouches, drawing together the conclusions made by the Committees during discussions of the topic in May 2021 and March 2022.

61. The Committee made a number of comments for minor changes and edits in the document. In particular, it discussed an appropriate oral bioavailability factor to use.

62. The Committee recommended including an explanation of the basis of the EFSA oral bioavailability factor of 0.44, which it was suggested might be based on the data for oral capsules. Given the present insufficiency of data, the Committee advised using a range of values rather than the single value for oral bioavailability. Based on the information presented in the paper for other products that might have similar buccal and oral absorption routes, the Committee agreed that a range from approximately 20 to 80% for oral bioavailability should be used. Using this range for oral bioavailability would then result in a range of estimates for exposure to be compared to the reference value.

63. The Committee agreed on the overall conclusions presented in the statement, and considered they reflected the present data. The Committee agreed that the further changes to the statement can be finalised via correspondence, prior to approval by Chair’s Action.

Item 8: EFSA consultation: Draft opinion on review of existing Health Based Guidance Values for copper (TOX/2022/39)

64. Professors Maged Younes and Thorhallur Ingi Halldórsson declared an interest as part of the EFSA Working Group. It was agreed that this did not prevent them from taking part in the discussion of this item.

65. This paper provided a summary of the approach used by the EFSA Scientific Committee to establish an ADI for copper and a brief summary of the approaches and studies used to reach the conclusions in order for Members to discuss and submit their comments.

66. The Committee discussed the previous Health Based Guidance Value (HBGV) for copper that was based on a traditional No Observed Adverse Effect Level (NOAEL) where no effect was observed on liver enzyme levels after copper supplementation.

67. Members highlighted that the pivotal studies used by EFSA included a limited number of participants who were all male and questioned how reliable the new HBGV would be based on these small numbers. More clarification was needed as to why these studies were chosen.

68. The Committee asked if there would be any differences in response between male and females. It was explained that the homeostatic response would not vary due to sex, age or pregnancy.

69. Members commented that copper sequestration in the liver can result in copper release and cause liver toxicity in other organs.

70. The use of copper as a plant protection product was discussed by the Committee and although not seen currently at a high amount, there was concern that the levels in the soil could rise in future, increasing the concentration present in plant crops.

71. It was highlighted that there was no uncertainty factor in the new EFSA HBGV and therefore it did not account for inter-individual variability. However, the Committee agreed that because the homeostatic mechanism was used as an endpoint, the HBGV was conservative.

72. Members noted that copper was an essential element, referencing the recommended adult intake of 1.3 mg/day for a 70 kg adult given in the EFSA opinion, although the margin between safety and adequacy was quite narrow.

73. The Committee agreed that there was evidence of the homeostatic mechanism being overwhelmed at exposures of 10 mg per day, but the new HBGV of 5 mg per day was acceptable and that the harmonised approach used seemed reasonable. Members commented that the justification for using the homeostatic approach was that it should predict the effects of longer term exposure.

74. Members noted that the wording in paragraph 32 on Wilson's disease and accumulation was incorrect and needed to be rectified.

75. Members were asked to send any additional comments to the Secretariat or add them to the document on the Teams site for submission to EFSA.

Item 9: Updated literature on potential health risks from organophosphate exposure in aircraft cabin air (TOX/2022/40)

76. No interests were declared.

77. Members were informed that this paper was the first in a series considering the potential health risks from aircraft cabin air exposures, and this paper presented a more detailed review of five studies investigating organophosphate effects published since the 2013 COT position paper on the topic.

78. It was highlighted that the 5 newly identified studies had a number of methodological limitations. Members noted that the tests used by Reneman et al. (2016) appeared to have been restricted to those that reflected the authors' *a priori* hypothesis that neurotoxic effects were related to OPs from engine oil fume exposure. It was also noted that the number of flying hours in the Reneman et al. (2016) study were self-reported, limiting their reliability.

79. Members disagreed with the uncertainty factor (UF) of 4000 in the de Ree et al. (2014) study used to account for differences in paroxonase-1 and cytochrome P450 activity. The authors of the study derived the UF value by applying UF values of 40 and 100 for each enzyme, respectively, and multiplying them together. However, since both enzymes are known to work in series, rather than in parallel, the Committee did not consider it appropriate to multiply UF factors for both enzymes together. The Committee was also not aware of any specific information on the involvement of paroxonase-1 in tri-ortho-cresyl phosphate (ToCP) metabolism. Therefore, the Committee considered the UF of 4000 was not appropriate, but noted that despite the large uncertainty factor the hazard quotient (HQ) value of 0.0004 was still below 1.

80. Overall, the Committee agreed that this paper did not alter the conclusions from the 2007 COT statement nor the 2013 COT position paper on

this topic, that the adverse effects reported by cabin crew were unlikely to be due to exposure to triaryl phosphates (or other organophosphates) in aircraft cabin air.

81. The Committee noted the referral from DfT and CAA had been clarified and would cover a broader review of potential chemical causes of the effects reported, which would be covered by future papers in the series.

Item 10: Draft document on how the Committees evaluate the relevance and reliability of data when assessing a chemical of concern – draft 0.e (TOX/2022/41)

82. No interests were declared.

83. This paper presented an updated draft of a non-technical document on how the COT, COC and COM objectively consider evidence, taking on board comments provided by COT, COC and COM previously.

84. A number of further changes were suggested for the next draft, in particular suggestions were made to clarify and improve the statistics section, though the Committee considered that it should be kept non-technical, based on to the intended audience. In addition, terms such as Good Laboratory Practice and peer review should be explained, use of ‘clinical relevance’ should be amended to human relevance, and the document should be amended to reflect that the Committees consider the relevance and reliability of the evidence as a whole, rather than considering whether an individual study is relevant or reliable as an absolute outcome.

85. Members were informed that the paper would be reviewed by the Committee on Carcinogenicity at its meeting on 21 July 2022. The document would then be sent to Members of COC, COM and COT for comment by correspondence, prior to approval by the three Chairs.

Item 11: First draft statement on the safety of ginger supplement use in pregnancy (TOX/2022/42)

86. No interests were declared.

87. As part of the current programme of work on the maternal diet, the Committee considered the use of dietary supplements during pregnancy. A discussion paper (TOX/2020/51) was presented in October 2020, reviewing the commonly used dietary supplements during pregnancy. These were supplements that were not officially recommended by the relevant authorities, but which were promoted by anecdotal evidence and unofficial sources as having various purported benefits.

88. In May 2021, the Committee considered the potential effects of ginger and ginger supplements during pregnancy and lactation. Paper TOX/2021/26 reviewed the available data on toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with drugs as well as data on potential exposure.

89. Based on the Committee's suggestions, an additional literature search was performed to further inform the available database on the points raised by the Committee and in October 2021, the COT considered additional data on the effect of ginger on prostaglandins, reproductive and developmental toxicity and the possible contaminants present in ginger (TOX/2021/51).

90. The Committee concluded that, based on the previously considered studies and the newly available information, it was not possible to determine a point of departure to use in the risk assessment of ginger. They also noted that while there was some equivocal evidence for the possible effect of ginger on reproduction, it was not possible to characterise this based on the data available. There is no clear indication that ginger is detrimental to consumers. It was concluded that the next step would be the preparation of a statement drawing together information from the two discussion papers which was presented in the current statement.

91. The Committee noted that ginger had been reviewed and approved by the National Institute for Clinical Excellence (NICE) and the European Medicines Agency (EMA) and is recommended by NICE for nausea and vomiting in pregnancy, which seemed contradictory to the message of the draft statement. It was agreed that information from the existing NICE guidelines on the use of ginger for nausea in pregnancy should be added to the statement.

92. The Committee noted that although ginger was recommended for use for nausea in pregnancy, clarification was required on exposure to ginger in the

form of concentrated products such as food supplements, drinks or shots. Members noted that some food supplements marketed for general use contained considerably higher doses of ginger than those marketed for use in pregnancy. For example, one general purpose supplement was labelled as containing 1100 mg of ginger, with a recommended serving size of 2 capsules per day. This was considerably higher than the amount of ginger found in supplements marketed for pregnancy, which contain 10 mg of ginger extract. Although not marketed as a pregnancy supplement, it was unknown if these might be used by pregnant women for the treatment of nausea.

93. A few of the trials cited by NICE were of short duration which was considered to be a limitation. The Committee noted that there were also some studies such as Weidner & Sigwart, 2000 that should be included in the draft COT statement. The Committee noted that there were studies with contradictory outcomes to some of those cited, for example, an in vivo study in hamsters (Plengsuriyakarn et al, 2012)., which found no adverse effects following administration of ginger.

94. The Committee noted that the cytotoxicity studies discussed in the statement were not intended to study the safety of ginger *per se* but rather aimed to identify potential anti-cancer agents and agreed that this should be mentioned.

95. The Committee stated that there were a number of studies documenting spontaneous abortion as an outcome but also a number of studies contradicting this finding. They concluded that the weight of evidence for this effect should be considered, and the probability of this effect addressed. It was also noted that clarification was required on the extent of birth defects as an outcome.

96. In terms of ginger's effect on P450 enzymes and the potential for herb-drug interactions, the Committee noted that inhibitory effects could occur at concentrations as low as 1 µm, depending on the extract and P450 enzyme.

97. Members discussed some of the reported interactions of ginger with medicines in some of the studies cited in the draft statement, for example one study investigating the effect of ginger on the pharmacokinetics of metronidazole using rabbits, saw a 4-fold increase in Cmax and a 10-fold increase in the area under the curve (AUC), which was a considerable increase. (Okona et al, 2008). Similarly, a study investigating the effect of ginger on tacrolimus pharmacokinetics conducted in rats, also reported a significant increase in AUC values but only used a single dose of tacrolimus intraduodenally (Egashira et al,

2012). In a case report on the effect of ginger on the INR of a patient taking warfarin, the patient had been taking multiple medicines concomitantly that could have inhibited warfarin (Rubin et al., 2019), however the patient's consumption of ginger tea was the only factor that had been reported to have changed. A paper contradicting the findings of this report was also highlighted (Jiang et al, 2005).

98. The Committee asked that additional papers on the anti-platelet effect of ginger should be reviewed.

99. Overall, the Committee agreed with the conclusions of the statement but commented that more detail should be included on the use of highly concentrated shots and how these compared to doses recommended by authoritative bodies. The Committee added that reference to guidelines on the use of ginger as a remedy for nausea in pregnancy should be added to the statement conclusion.

Item 12: Paper for information: Update on the work of other Scientific Advisory Committees (TOX/2022/43)

100. This paper was circulated for information and Members were invited to send any comments and questions via email.

Item 13: Any other business

101. There was no other business.

Date of next meeting

102. The next meeting of the Committee will be at 10:00 on the 6th of September 2022 at Broadway House, London and via Skype and Teams.