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

Meeting of the Committee at 10:30 on the 26th of October at the Holiday Inn Bloomsbury and via Microsoft Teams

Present

Chair:	Professor Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr Stella Cochrane Dr Caroline Harris Professor Gary Hutchison Professor Thorhallur I. Halldórsson Dr Sarah Judge Dr Gunter Kuhnle Dr David Lovell Professor Shirley Price Ms Juliet Rix Dr Michael Routledge Dr Natalie Thatcher Dr Simon Wilkinson Professor Philippe Wilson Professor Matthew Wright Professor Maged Younes Prof Paul Haggarty Prof John O'Brien	 SACN Liaison Science Council Liaison
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland Mr Michael Dickinson Dr Alex Cooper Ms Claire Potter Dr Barbara Doerr Dr Douglas Hedley Dr Olivia Osborne Dr Joseph Shavila Ms Emma French Dr Rhoda Aminu 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	FSA Scientific Secretary

	Mr Thomas Hornsby Mr Lawrence Finn Mr David Kovacic	
Public Health England (PHE) Secretariat:	Ms Britta Gadeberg	UK Health Security Agency Scientific Secretary
Invited Experts and Contractors:	Dr Sarah Bull	Institute of Environment and Health
Assessors	Susannah Brown	Department of Health and Social Care (DHSC) (nutrition)
	Ian Martin	Environment Agency
Observers		
FSA and other Officials:	Ms Sharon Gilmore Ms Kerry Gribben Ms Natasha Gladstone Dr Marianne James Mr Josh Hunt Dr James Donarski Dr Elli Amanatidou Ms Lucy Smythe Mr Shaddad Saleh Mr Tim Chandler Ms Vikki Cohen Dr Ovnair Sepai Ms Krystle Boss Ms Rachel Elsom Mr Colin Ramsay	FSA NI FSA NI FSA FSS FSA FSA FSA FSA FSA FSA FSA UK HSA FSS DHSC Public Health Scotland

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Announcements

1. The Chair welcomed Members and other attendees.

2. The Chair welcomed Lawrence Finn and David Kovacic who have joined the COT Secretariat team at the FSA.

3. It was noted that this was the first hybrid COT meeting and that the Secretariat would be seeking feedback from Members after the meeting.

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 James Coulson, Dr René Crevel, Dr Mac Provan, Dr Cheryl Scudamore and Professor Mireille Toledano. Apologies were also received from Dr David Gott and Mr Barry Maycock of the Secretariat.

Item 2: Draft minutes and reserved minutes from the meeting held on 7th of September 2021 (TOX/MIN/2021/05) and reserved minutes from 6th of July 2021

6. There were no comments and the minutes and reserved minutes for September, and the reserved minutes for the July meeting, which had not been previously circulated, were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 7th of September 2021

Plant based drinks: Proposed Joint COT and SACN Working Group

7. The Committee was informed that the proposed joint working group between COT Members and the Scientific Advisory Committee on Nutrition (SACN) on plant based drinks had been established, but with one Member still to be confirmed from SACN. The COT Members taking part were Professor Alan Boobis, Dr Caroline Harris and Professor Gunter Kuhnle. The first meeting is due to be held on the 2nd of December 2021. No questions were raised by the COT.

NAMs workshop

8. The workshop entitled “Development, Validation and Regulatory Acceptance of New Approaches Methodologies in Chemical Risk Assessment” was held virtually on the 6th and 7th of October 2021. It included international speakers from across academia, industry, and other regulatory agencies as well as breakout sessions with

a number of themes to aid discussions. The outcomes of the workshop will be used to further develop the UK Roadmap and promote collaboration across regulatory agencies, academia and industry.

9. The Committee were informed that the Secretariat were currently using the notes compiled - during the workshop to prepare a report of the meeting that would be brought to the Committee at a future date. Potential research project ideas would also be identified to take forward for further development, on how NAMs can be used in future chemical risk assessment.

10. The Committee congratulated the organisers for arranging an excellent workshop.

11. Members asked about the European dimension of NAMs and the initiatives from EFSA, and whether consideration has been given to working with others to help avoid unnecessary divergence. The Committee were informed that this was a UK initiative in the first instance, and hence the FSA would be engaging with Whitehall, but also internationally. A Member noted that there was a lack of global harmonisation, with national groups pushing forward separately, however the UK could make an important contribution to these discussions

12. As part of the related work in this area, a FSA funded computational toxicology fellow and PhD studentship have also started.

13. A Member noted some public concern with respect to the testing of cosmetic ingredients on animals being allowed if the ingredient was to be used not only in cosmetics. The Committee was informed that there would be engagement with consumers/public on their views on these testing methods to help gauge consumer acceptability to help in determining how to take this issue forward.

14. It was noted that the British Toxicology Society (BTS) were very keen to support this work and that there was an information workshop on NAMS for the Interdepartmental Group on Health Risks from Chemicals (IGHRC) and BTS Members in November. The session will be recorded to enable access for other groups/attendees.

Public Health England

15. The Committee were informed that on 1st of October 2021, Public Health England transferred its health protection function into the UK Health Security Agency (UKHSA). The PHE Scientific secretariat for the COT has now moved to UKHSA with support continuing as before. The health improvement/healthcare public health functions have been transferred into the Office for Health Improvements and Disparities (OHID), which is part of DHSC. The PHE Diet, Obesity and Physical Activity division (DOPA), which includes the team providing secretariat support to SACN, has transferred to OHID, and interaction with SACN is expected to continue as previously.

Publications

16. The COT statement on combined exposure to mycotoxins has been published on the COT website

17. A poster was presented on the Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE) work at Eurotox. It was noted that the World Health Organisation (WHO) will have a session at the International Congress of Toxicology in 2022, with one of the presentations being on the COT's work on synthesis of information.

JEGs Update

18. The Committee were informed that there is no new information on the Joint Expert Groups (JEGs), but meetings of all three JEGS are due to take place in the near future.

Item 4: The potential effects that excess vitamin D intake may have during preconception, pregnancy and lactation. Third draft statement (TOX/2021/50)

19. No interests were declared.

20. The COT had been asked to consider whether exposure to excess vitamin D would pose a risk to maternal health, as part of the COT contribution to the SACN review of the maternal diet. The topic was initially discussed in paper TOX/2021/08, with a draft statement then being prepared. Annex A of paper TOX/2021/50 presented the third draft of the statement. Members were invited to comment on the draft statement, which had been revised to reflect their previous consideration.

21. In paragraph 12 where the conversion of 25(OH)D to $1,25(OH)_2$ was discussed, the Committee asked that it be made clear that it was the quantity of $1,25(OH)_2D$ produced during pregnancy that was unique and not the conversion itself.

22. The Committee made reference to the Burt *et al*., 2019 study cited in paragraph 24, clarifying that 17% of participants receiving 400 IU had hypercalciuria on at least one occasion over the study duration. It was also noted that the study results on hypercalcemia and hypercalciuria did show a significant dose dependent effect of vitamin D. It was further noted that the study authors dismissed only the findings on bone mineral density (BMD) but did not dismiss an effect of vitamin D on hypercalciuria and hypercalcemia.

23. Other recommendations made by Members were to state how the 25(OH)D deficiencies in individuals (discussed in paragraph 34 of Annex A) were assessed according to the 2016 SACN report on vitamin D, and to highlight that the deficiencies reported were on the basis of rickets.

24. In reference to paragraph 2 of Annex A, the Committee requested the secretariat to check why the leaves of plant species belonging to the *Solanaceae* family are not commonly consumed and if it was due to any potential toxicity. The wording in paragraph 44 of Annex A was amended to reflect that the edible portions of this plant were unlikely to "represent a significant source of vitamin D".

25. The Committee highlighted that there could be uncertainty in the exposure assessment for mushrooms, as the consumption data was based on all types of mushrooms but the concentration of vitamin D present in mushrooms was based on wild mushrooms. It was additionally noted that UV treated mushrooms can contain high amounts of vitamin D, and thus how much vitamin D was present can also vary with the producer of the mushrooms, adding to the overall uncertainty.

26. The Committee queried paragraph 49 of the statement which set out the dosage of vitamin D supplements available on the market and noted that the higher end of the quoted dose level may be lower than what is currently available.

27. The Committee discussed paragraph 51 where it was noted that the exposure data may not be entirely representative of the maternal diet. Members suggested that while there be a potential underestimate of up to 30% due to under-reporting in the NDNS, this would depend on the type of food, and for some of the foods considered there may have been over-reporting.

28. In reference to paragraph 70, discussing the reasons for consumers' supplement use, the Committee asked the secretariat to look at NHS surveys to see if the reasons for supplement intake amongst consumers might include that it is NHS advice. This information might be useful in assessing the effectiveness of NHS messaging to consumers.

29. The Committee agreed that paragraph 79 of the risk characterisation should address the potential of UVA to photodegrade excess pre-vitamin D_3 produced in the skin and not just UVB.

30. The Committee concluded that it was unclear whether UV exposure in the summer when combined with high-dose vitamin D containing supplements could lead to excess levels of vitamin D.

31. The Committee suggested the wording in paragraph 86 be amended to make it clear that high vitamin D exposure was driven by high supplement use and not by dietary sources.

32. A number of additional comments were provided on the structure and content of the draft statement.

33. The Committee agreed that the statement could be cleared by Chair's action.

Item 5: Safety of Ginger Supplement use in Pregnancy–An Update (TOX/2021/51)

34. Dr Stella Cochrane declared that her employers, Unilever, manufacture teas containing ginger. This was a non-personal specific interest, and she was able to contribute to the discussion. No other interests were declared.

35. As part of the current programme of work on the maternal diet, the Committee was considering the use of dietary supplements during pregnancy. A discussion paper (TOX/2020/51) was presented, 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. Following this initial review, the COT agreed that ginger required further assessment, noting that human, animal, and *in vitro* data were available.

36. 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.

37. Overall, it was concluded that the data were limited. The human data presented were not strongly indicative of any toxicological concern but there were some indications of possible adverse effects and considerable uncertainty. In general, ginger did not appear to be systemically toxic but did appear to have reprotoxic effects at high supplemental doses.

38. Paper TOX/2021/51 provided further information with respect to *in vitro* studies of ginger and studies in laboratory animals, and on contaminants and exposure to ginger supplements. The paper was primarily centred on the effect of ginger on prostaglandins, reproductive and developmental toxicity and the possible contaminants present in ginger.

39. Members noted that more clarity was required on what form of ginger was being discussed, as the papers reviewed covered ginger in a range of forms including fresh, dried, aqueous, and alcohol extracts.

40. Members noted that although the different ginger extracts were not comparable, there did appear to be some biological activity in the early stages of pregnancy. It was reiterated that in general there was no indication of systemic toxicity from the use of ginger.

41. Members noted that the possibility of a window of susceptibility was of concern as women would most likely use ginger in the early stages of pregnancy, a critical period of development, to alleviate morning sickness.

42. Members noted the potential effect of ginger on the prostaglandin pathway, in particular cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) inhibition and considered how this might affect early pregnancy.

43. The Committee expressed concern about the robustness of the available evidence. Effects on maternal weight were noted, which is known to have an indirect effect on reproductive outcome. In some studies, reprotoxic effects were seen; however, no specific teratogenic, embryotoxic, or fetotoxic effects were observed. Early pregnancy loss and spontaneous abortion are difficult to assess in humans; however, it was noted that the study by Smith *et al.* 2004 (Obstetrics and Gynecology. 103. 639-45) attempted to link effects observed in animal toxicology with human data on pregnancy outcome.

44. With regard to a point of departure, the Committee noted that using animal toxicology data would be difficult given the quality of the studies and their reporting, In addition, further understanding of the quality and quantity of ginger and the type of preparation (e.g. fresh or dried) used in these studies would be required. Where the information was not available**,** it should be made clear that it could not be specified.

45. It was suggested that a table in which fresh ginger, dried ginger and ginger extracts were converted to a common comparator would be useful in making comparisons across studies. It was noted that some of the studies did not mention how much ginger or ginger extract was used, referring only, for example, to ginger administered in drinking water.

46. It was noted that, in paragraph 20, the discussion focused on cytotoxicity , rather than to effects on prostaglandin production (Lantz *et al.,* 2007, Phytomedicine 14: 123-128). It was observed that the most potent effect of ginger was on prostaglandin synthesis, occurring at concentrations less than 0.1 µg/ml. Half maximal inhibitory concentration (IC50) values for a range of components in ginger were reported and it was demonstrated that these acted mainly on COX2.

47. The Committee suggested adding more data from human studies to paragraphs 19 to 21 to highlight the effect of ginger on the prostaglandin pathway and to look further at the role of this pathway in pregnancy. It was noted that quantitative data would be useful.

48. The Committee noted in paragraph 26 it should be clarified that in the study by Shalaby and Hamowieh, 2010 (Food and Chemical Toxicology, 48, 10, 2920-2924) lethality was determined in mice and effects on fertility were determined in rats. The effects of ginger on the sperm of diabetic rats were investigated since this was putatively beneficial on male fertility in diabetic subjects.

49. There was concern with reference to the study by Wilkinson (2000) (Reproductive Toxicology, 14, 507-512) mentioned in paragraph 31. Members expressed some uncertainty about the histopathological results detailed in the study.

50. The number of fetuses was considered but not the number of litters, which could give rise to spurious findings due to spontaneous litter to litter variation, and no significant trend with dose was observed, making the evidence equivocal.

51. The Committee were not able to comment fully on the results of the Hosseini et al, 2015 study (Journal of Gorgan University of Medical Sciences. 17, 29-34) since only the abstract was available in English. The findings on the histopathology could not be verified based on the data available. It was noted that the Dissabandara & Chandrasekara (2007) study (Ceylon J Med Sci 2007, 50: 1-7) used a ginger powder extract dissolved in water.

52. The Committee suggested that the statement that ovarian follicle atresia was observed should be deleted from paragraphs 31 and 56 as the data was not conclusive with respect to this effect on the ovary.

53. Appendix C (paragraph 36) considered the human studies. The Committee noted more clarity was required on the lack of power in the study by Smith. Members asked if the number of participants in the observational study detailed in paragraph 39 could be included.

54. Overall, the Committee questioned if there was good evidence for any effects of ginger on pregnancy outcome in humans.

55. The Committee discussed the potential presence of contaminants and noted that the ginger products used in the studies reported were sourced locally in markets or herbalists. Members queried whether there were any specific data on contaminants in ginger supplements available in the UK.

56. It was noted that the statement in paragraph 33 on possible contamination by microorganisms, pesticides, heavy metals and residual solvents was considered strong, and it was questioned if this was representative of what is being consumed in the UK, particularly by pregnant women, and therefore it was suggested this be amended to reflect that there is uncertainty in the data available.

57. It was noted that the Getaneh (2021) paper (Heliyon, 28;7,4) contained conflicting messages regarding the risk to health of consumers associated with exposure to heavy metals through ginger consumption. The Committee suggested reporting only the levels of heavy metals detected and not summing the hazard quotients of all of the metals, for which there is no mechanistic basis. The Committee also questioned if ginger had been included in previous UK surveys of heavy metals in food.

58. The Committee noted it was unknown how much ginger and particularly, highly concentrated juice extracts, would contribute to overall contaminant exposure in the UK. It would be useful to know how the levels of contaminants in ginger compared to bulk foods, such as cereals and in other spices.

59. Members questioned if, based on the IC50 values noted for COX inhibition, it would be possible to look at potency relative to that of other COX inhibitors, and what advice or evidence there is for the effects of COX inhibitors during pregnancy.

60. The Committee concluded that the message being communicated to those planning to become pregnant, consuming food containing ginger, should be clear. It was agreed that the evidence from the epidemiology data was that the dietary use of ginger during pregnancy does not pose a risk, but there was a lack of information with regard to high strength extracts. The Committee queried whether it would be appropriate, based on the available limited information, to urge some caution based on the uncertainty and lack of data on consuming high strength ginger extract products.

61. Members noted that the stage of pregnancy should also be taken into account, as it is possible that these extracts would be taken for a short period of time, e.g., to alleviate morning sickness, which occurs at the beginning of pregnancy – a time when the fetus could be most sensitive to any effects of ginger.

62. Members questioned if any of the ginger products had been assessed as novel foods and, if so, what was the nature of evidence used to support their health claims.

63. It was asked whether closer consideration should be given to populations known to consume larger amounts of ginger. It was noted that people from ethnic backgrounds were under-represented in the National Diet and Nutrition Survey (NDNS) and thus there were limited consumption data. The Committee asked whether high consumers in under-represented groups would be covered by the 97.5th percentile NDNS value.

64. Overall, the Committee concluded that based on the newly available information it was not possible to determine a point of departure to use in the risk assessment of ginger. It was also not possible to determine a point of departure based on the previously considered studies. The Committee 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. The Committee also noted that from the evidence presented, the potential for contamination of ginger with heavy metals and/or mycotoxins cannot be excluded, but there is a dearth of UK-relevant information.

65. The Committee concluded that the next step would be the preparation of a statement, which would require particular input from the Committee lay Members to ensure the clarity of the message being conveyed.

Item 6: Sub-statement on the potential risk(s) from exposure to microplastics: Oral route (Second draft) (TOX/2021/52)

66. Professor Alan Boobis previously declared that he is involved in discussions with ILSI, JRC and others in the possible development of a reference bank for microplastic samples. No other interests were declared.

67. Earlier in 2021, the COT published an overarching statement on the potential risk(s) from exposure to microplastics (COT Statement 2021/02 and Lay summary). The first draft sub-statement on the potential risk(s) from exposure to microplastics: Oral route was presented in September 2021 (TOX/2021/38), when the Committee requested several changes to its contents and structure.

68. The revised draft was presented at this meeting (in Annex A) aimed to address these requests.

69. Members noted that the statement should also highlight the lack of empirical data for dosimetry purposes, which further compounds the difficulty of study comparison.

70. Regarding recent news articles concerning microplastic studies, Members were of the opinion that these were often not peer-reviewed and/or present preliminary data with small sample numbers and that these studies do not affect the conclusions reached by the Committee thus far.

71. Both the Committee and Secretariat are aware that the field of micro- and nanoplastic research is continually evolving, and therefore will continue to review the scientific literature on an ad hoc basis.

72. Members agreed that the statement could be cleared via Chair's action

Item 7: Discussion paper for the risk assessment of cows' milk in children aged 1 to 5 years, in the context of plant-based drinks evaluations – Part 1 (TOX/2021/53)

73. No interests were declared.

74. The Committee had previously been asked to consider the potential for adverse effects arising from the consumption of plant-based drinks by young children (aged 6 months to 5 years) who were following a plant-based diet. The drinks considered were soya, oat and almond; rice drinks were not reviewed since there is existing advice that these should not be given to young children due to their arsenic content. The overarching statement on the consumption of plant-based drinks, setting out the views and conclusions of the Committee, was published in January 2021.

75. The Committee had agreed, during their meeting of July 2021, that the main comparator for plant-based drinks should be cows' milk and that a discussion paper should be produced looking at the potential chemical risks from the consumption of this in the population group of interest: children aged 6 months to 5 years.

76. In addition to the chemical contaminants discussed in this paper, the COT noted that it would be worth evaluating per- and poly-fluoroalkyl substances (PFASs) and brominated flame retardants (BFRs) in part 2 to be presented at the next meeting.

77. Members noted that it was not clear in the Veterinary Medicine evaluation what criterion was used to deem a 'positive result.' It was explained that this referred to a sample concentration above the Maximum Residue Limits (MRL) for a veterinary medicine in cows' milk. This would need to be explained more clearly in a subsequent statement.

78. Members discussed the need for a cross-check of all contaminants discussed in this paper against the concentrations presented in the plant-based drinks paper TOX/2020/41 (e.g., for soya). However, it was noted that in many cases data may not be available for concentrations of contaminants in plant-based drinks.

79. The COT discussed the significance of the potential for microplastics in cows' milk and the absence of their consideration in this paper and the forthcoming planned part 2. It was decided that a review of the literature would be undertaken for microplastics in cows' milk, noting that European or UK data may not be available in the public domain.

80. Members queried the use of the terms 'upper bound' and 'lower bound' within the dioxins section and highlighted that a clearer explanation of these terms should be provided.

81. Members concluded that there were no health concerns for any of the contaminant groups in cows' milk based upon the data presented in the paper.

82. A COT statement would be drafted, capturing the COT's suggested changes and incorporating conclusions following the discussion of part 2 which will presented at the next meeting in December 2021.

Item 8: Bamboo composites Discussion paper on the German Federal Institute for Risk Assessment (BfR) and Office for Risk assessment & research (BURO)/ Netherlands Food and Consumer Product Safety Authority (NVWA) opinions on the potential health risks of bamboo food contact materials (FCMs) (TOX/2021/54)

83. No Interests were declared.

84. At the July meeting, the COT were asked to consider whether exposure to bamboo bio-composites in food contact materials posed a risk to human health in discussion paper (TOX-2021-34). Members were informed that a study assessing the health risks associated with bamboo-based packaging and other biobased materials was in progress. The Committee agreed that it would be appropriate to conduct a risk assessment once the data were available. Members also requested that the exposure data from the German Federal Institute for Risk Assessment (BfR)

and the Netherlands Food and Consumer Product Safety Authority (NVWA) reports be assessed separately and more critically. The German and Dutch reports were therefore assessed separately in the discussion paper (TOX/2021/54).

85. Members highlighted that any high migration of constituents into drinks from bamboo-ware articles leading to exceedance of relevant guidance levels was a risk management issue rather than a risk assessment issue. Members discussed the methodologies of the BfR and NVWA opinions. The BfR used a Monte Carlo probabilistic approach for their exposure assessment, but the COT highlighted that there might not be sufficient data to justify this. Also, it was noted that the exposure assessment was applied only to a migration of <50 mg/L, and there was no explanation provided as to why only the third wash was analysed rather than multiple washes. It was further noted that the BfR used their own tolerable daily intake (TDI) of 0.6 mg/kg/day for formaldehyde whereas the NVWA and EFSA used a lower TDI of 0.15 mg/kg/day. Overall, the COT concluded that the exposure assessments were conservative but not necessarily worst-case. It was agreed that although the NVWA and BfR opinions took slightly different approaches, in general the same conclusions were reached.

86. The Committee agreed that it would be appropriate to conduct a risk assessment once UK data were available. The Committee were informed that the study was currently still ongoing. It was concluded that the migration of formaldehyde and melamine from bamboo-ware cups was a potential concern to human health. It was highlighted that Policy will wait for a position paper before contacting the manufacturers of the cups to express the Committee's concerns.

Item 9: Update on the work of other advisory Committees - for information (TOX/2021/55)

87. This paper was circulated for information.

Item 10: Any other business

88. The Secretariat will be holding a workshop at the two-day COT meeting in March 2022, and asked Members for suggestions on what they would like to discuss. Members agreed it would be useful to look at horizon scanning and identify topics that have previously been raised by the Committee, such as the microbiome. Members agreed it would be useful to have a brief discussion at the December 2021 meeting.

89. The format of the workshop has yet to be decided but the Secretariat is hoping for a face to face meeting.

Date of next meeting

90. The next meeting of the Committee will be at 10:00 on the 7th of December 2021, format to be decided.