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

Meeting of the Committee at 10:00 on 7th of September 2021 on Microsoft Teams

Present

Chair:	Professor Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr Stella Cochrane Dr James Coulson Dr Rene Crevel Dr Caroline Harris Professor Gary Hutchison 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 Dr Natalie Thatcher Dr Simon Wilkinson Professor Philippe Wilson Professor Matthew Wright Professor Maged Younes Professor Paul Haggerty Professor John O'Brien	SACN Liaison Science Council Liaison
Food Standards Agency (FSA) Secretariat:	Ms Chara Tsoulli Mr Barry Maycock Dr David Gott 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 Frederique Uy Ms Cleanncy Hoppie	FSA Scientific Secretary

	Ms Jocelyn Frimpong-Manso Ms Sophy Wells Ms Chloe Thompson Dr Gaetana Spedalieri Mr Thomas Hornsby	
Public Health England (PHE) Secretariat:	Ms Britta Gadeberg	PHE Scientific Secretary
Invited Experts and Contractors: Assessors	Dr Sarah Bull Professor Tim Gant Dr Sam Fletcher Mr Ian Martin Ms Frances Hill Ms Susannah Brown Ms Estella Hung Mr Colin Ramsay Ms Martina Brayley	Institute for Environment and Health PHE Veterinary Medicines Directorate Environment Agency Department for Business, Energy and Industrial Strategy (BEIS) PHE PHE Public Health Scotland PHE
Observers	Dr Stephen Ruckman Mr Federico Luppi Ms Catherine Smith Mr Paul Loeven	TSG consulting CuanTec Health Canada Health Canada
FSA and other Officials:	Ms Natasha Gladstone Mr Vincent Greenwood Dr Marianne James Dr Anthony J Wilson Ms Lisa Nelson Dr Ovnair Sepai Mr Tim Marczylo Ms Krystle Boss Ms Louise Dearsley	FSA FSA Food Standards Scotland (FSS) FSA FSA PHE PHE FSS Health and Safety Executive

Contents

Announcements

1. The Chair welcomed Members and other attendees. Dr Stephen Ruckman from TSG consulting attended as an observer for the entire meeting. Other observers who attended for specific Items are noted below.

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 Cath Mulholland of the Secretariat, and Will Munro from FSS.

Item 2: Draft Minutes from the meeting held on 6th of July 2021 (TOX/MIN/2021/04)

4. The Minutes were accepted as an accurate record, subject to some minor amendments. Gareth Thompson from the FSA NI had attended on behalf of Kerry Gribbin. In paragraph 7 of Item 3 (TOX/2021/28), "SACN" should be replaced by "Subgroup on Maternal and Child Nutrition (SMCN)". In paragraphs 14 to 18 (inclusive) "SACN" should be replaced by "MHWG (a subgroup of SACN)". Paragraph 19 on the SACN timelines should be deleted.

Item 3: Matters arising from the meeting held on 6th of July 2021

Terms of Reference of the Scientific Advisory Group on Chemical Safety of Non-Food and Non-Medicinal Consumer Products (SAG-CS) (TOX/2021/42)

5. Following EU exit, regulated product authorisations for non-medical consumer products such as cosmetics, which had previously been conducted at a European level, will now be done at a national level.

6. The Office for Product Safety and Standards (OPSS), a part of the Department of Business, Energy and Industrial Strategy (BEIS), has established a temporary independent expert Scientific Advisory Group (SAG-CS) to advise on the chemical safety of these products.

7. The COT had been provided with a paper for consideration which presented the terms of reference (TOR) for the SAG-CS.

8. Following a question from a Member, the Committee was informed that the SAG-CS had been constituted, all Members had been appointed following an interview, the Membership covers all disciplines of toxicology, and the Membership is

available online. There is some cross-membership of the SAG-CS and other advisory committees, including the COT.

9. The Committee was informed that the SAG-CS had already met on three occasions and discussed a number of issues relating to legislation for cosmetics and toys. The advisory group has a website and will work as transparently as possible. They will also be working closely with other Committees, including the COT, and will aim to communicate to ensure consistency, especially when considering related topics.

10. A question was raised as to what will happen to the SAG-CS after the 9 months for which it was initially set up because there would still be a continuing need for advice on the products looked at specifically by the group. The OPSS will look at this along with other key work that is currently being undertaken. The purpose of the 9-month period was to allow time to review the group. The aim is to have a group going forward but changes may be implemented.

11. A final question was raised regarding BEIS being a named customer for COT advice. There is significant overlap with the SAG-CS TOR and that for COT for non-food advice. It may be difficult for members of the public to know which Committee/advisory group will review particular products. Therefore, greater clarity may be needed in the publicly available TOR. COT Members were advised that this is something that would be discussed in the next meeting of the SAG-CS.

Update on arrangements for the October Meeting

12. The Committee was updated on the arrangements for the next meeting in October. The aim was to trial a hybrid meeting so that some Members and some of the Secretariat could attend in person, while those who were unable or who would prefer not to travel could attend virtually. The venue planned for October is limited in size and so it may be necessary to restrict the numbers of officials and other observers attending in person. The intention was to identify a larger venue in the future. Members noted the need to consider how hybrid meetings might best be arranged such that those not attending in-person can contribute more fully.

Matters arising: Update on the FCM JEG interim position statement on ocean bound plastic (Reserved)

13. Members discussed an update regarding ocean bound plastic. The Minutes of this discussion are currently reserved as they refer to an interim position statement which is not yet in the public domain. This will be published in due course.

Update on JEGs and Regulated products

14. The Committee received an update on the continuing work on regulated products and the current activities of the JEGs.

15. Over 1000 applications for regulated products have now been received by the FSA, the vast majority of these are for novel food authorisations and mainly for cannabidiol (CBD).

16. The Animal Feed and Feed Additives Joint Expert Group (AFFA JEG) has been working on Feed applications which are being treated as pipeline applications. There are no dossiers for consideration by the Committee just yet but the Secretariat is anticipating 3-nitrooxypropanol (3-NOP) to be finished for consideration in the near future.

17. Some additive applications have been received by the policy teams for which further information is required before assessment. The dossiers are for extensions of use and will be presented to the next meeting of the Additives, Enzymes and other Regulated products Joint Expert Group (AER JEG). There are currently no dossiers for the Committee to consider.

18. The Food Contact Materials (FCM) JEG reviewed a dossier on a plastic additive at their July meeting, and additional information has been requested. Two further dossiers will be considered in September. There are currently no dossiers for the COT to consider.

19. Members had no comments on the update.

Item 4: Sub-statement on the potential risks from exposure to microplastics: Oral route (First draft)-postponed from July (TOX/2021/38)

20. Catherine Smith from Health Canada attended as an observer.

21. Professor Alan Boobis had previously declared that he is involved in discussions with the International Life Sciences Institute (ILSI) Europe, Joint Research Centre (JRC), and others on the possible development of a reference bank for microplastic samples. No other interests were declared.

22. The potential risks from exposure to microplastics have previously been discussed at COT meetings from October 2019 to September 2020. In February 2021, the COT published an overarching statement on the potential risks from exposure to microplastics (COT Statement 2021/02). The draft sub-statement, presented in Annex A, considered in detail the potential toxicological risks of exposure from microplastics via the oral route (i.e. resulting from the presence of microplastics in food, drinking water, and bottled drinks).

23. A short update on recent literature was also provided in TOX/2020/58. Members expressed reservations on the reliability of some of the cited toxicological data presented in the cover paper (Deng *et al*., 2021; Hou *et al*., 2021; Xi *et al*., 2020; Amereh *et al*., 2020; Zheng *et al*., 2021; Stock *et al*., 2021), in particular the quality of the toxicological data, which appears to be limited.

24. The Committee discussed the draft statement and requested several changes to its contents and structure. The revised draft will be presented at a future meeting of the Committee.

Item 5: Public Consultation on Code of Practice for Scientific Advisory Committees and Councils (TOX/2021/43)

25. The Committee were informed of a recently published consultation document on a revised version of the 'Code of Practice for Scientific Advisory Committees and Councils' (CoPSAC). The CoPSAC applies to science advisory committees and councils affiliated to the UK government that provide independent expert advice to facilitate decision making. The consultation takes views on the amendments proposed to bring the CoPSAC up to date since it was last revised in 2011. The revised version is based on feedback received from Committee and Council stakeholders, and a wider consultation was now taking place.

26. The consultation is aimed at academics and other experts who provide science advice to the UK government. It seeks views on the independence, transparency, diversity, and inclusion aspects of the CoPSAC in particular.

27. The Committee discussed that in the recruitment section, there needs to be a mention of how to increase diversity through different channels of advertisement.

28. COT Members recommended that section 3.2 needs to be more nuanced. It was advised that there needs to be clarification between declarations of interest and conflicts of interest. Furthermore, more clarity was required on how Members are appointed.

29. It was noted that little was mentioned about lay membership. The document implied that the appointment of lay Members was not mandatory, and there is a need to clarify the expectations of lay Members.

30. The Committee noted that section 5.5 concerning liability might be perceived as unintentionally negative. The penalty section needs to be revised and details on conduct need to be made clearer.

31. There was discussion on section 7.1 on the environmental impact, including attendees' travel. Whilst the environmental impacts are considered to have been lower for virtual meetings, the quality of discussions in virtual versus in-person meetings was raised. It was added that confidentiality may need to be reviewed, as this was considered to be harder to control in a virtual meeting. It was noted though, that virtual meetings may allow for greater diversity, as it may permit access for some individuals who might otherwise be unable to attend in person. For future meetings, hybrid options were discussed.

32. The Chair raised that guidance on retention of both digital and physical documents by Members would be helpful.

Item 6: Discussion paper on the effects of excess Vitamin A on Maternal Health (TOX/2021/44)

33. No interests were declared.

34. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on 'The influence of maternal, fetal and child nutrition on the development of chronic disease in later life' (SACN, 2011) and on 'Feeding in the first year of life' (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered.

35. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments, e.g. in the area of food safety advice. Following a discussion at the COT meeting in September 2020, it was agreed that papers on a number of dietary components should be prioritised and, to this end, papers on iodine, vitamin D and dietary supplements have been or will be presented to the Committee. The remaining list of compounds were to be triaged on the basis of toxicity and exposure.

36. Following discussion of the first prioritisation paper on substances to be considered for risk assessment, the Committee agreed that Vitamin A should be considered in a separate paper.

37. The Committee noted that, for completeness, this discussion paper described all the available publications - including a paper by Mawson and Croft (2019). The Committee expressed a concern that the COT paper appeared to give greater attention than necessary to a contentious hypothesis by Mawson and Croft, parts of which had already been discredited. The Committee wished to point out that the presence of this paper in the evidence base should not be misrepresented as indicative of the COT's views, and that their final statement on the risks of vitamin A to maternal and fetal health would be based entirely on evaluation of the wider evidence base rather than hypotheses and conjecture in any single paper.

38. Members considered that the exposure data provided needed more clarification, especially those data relating to liver consumption, since there were so few consumers recorded and those on butter, since ghee is widely used in some cuisines, but this was not reflected in the data. Arising from the discussion on the consumption of ghee, Members noted that a useful addition to the list of substances for review as part of the Maternal Health project might be heterocyclic aromatic amines and other combustion products from higher-temperature cooking with oils and fats.

39. The Chair questioned why the EFSA upper limit on vitamin A had been used in the risk characterisation but the value established by the Expert Group on Vitamins and Minerals (EVM) had not been discussed and whether there was any known basis for the apparently enhanced adverse effects from retinoid esters, such as the proprietary product "Accutane" compared with dietary vitamin A.

40. A Member asked whether in the UK, as was the practice in the Nordic countries, vitamin A was removed from products such as fish liver oil and liver pate and then was reintroduced at a lower concentration to give the benefits of the vitamin while mitigating its adverse effects.

41. Regarding beta carotene, the Committee decided that the possible increased risks of lung cancer were applicable largely to smokers, and that if women who smoked continued to do so during pregnancy then that was in itself a more substantial health risk than additional exposure to this carotenoid.

42. With regard to other endpoints of possible concern, the Chair suggested the interaction of vitamin A with vitamin D, and the possible ensuing effects on maternal and fetal bone mineral density, could be investigated.

Item 7: The potential effects that excess Vitamin D intake may have during preconception, pregnancy and lactation. Second Draft Statement (TOX/2021/45)

43. A personal, non-specific interest was declared by Dr Stella Cochrane whose employer produced supplements containing vitamin D. It was agreed that she could participate in the discussion.

44. The COT had been asked to consider whether exposure to excess vitamin D would pose a risk to maternal health in a draft statement (TOX/2021/45) as part of the COT's contribution to the SACN review of the maternal diet.

45. A number of comments were provided on the content of the draft statement.

46. The Committee questioned how much 7-dehydroxycholesterol (7-DHC) from the diet contributes to levels in the body, in paragraph 2.

47. The Committee suggested that additional text should be added to paragraph 7 to highlight that the relationship between serum levels and oral intake was not direct.

48. It was also suggested that the possibility of vitamin D toxicity from exposure to ultraviolet (UV) radiation in addition to vitamin D containing supplements should be discussed, noting that UV radiation, even in addition to a high dietary intake of vitamin D, would not result in adverse 25(OH)D levels due to the endogenous regulatory mechanisms in the skin described in paragraph 37.

49. Further suggestions were to define what stoss therapy is, i.e. a high dose treatment for vitamin D deficiency, and to restructure paragraph 18 to separate the studies of high dose vitamin D toxicity from the rest of paragraph. Where possible, the age of patients in the studies should be reported.

50. The Committee recommended the addition of a statement to paragraph 19, to explain that studies of stoss therapy using lower doses did not report adverse effects.

51. Other recommendations were to address the use of vitamin D in early onset osteoporosis in women, and to refer to the potency of vitamin D3 in raising and

maintaining 25(OH)D levels as 1.9 times more potent rather than “87% more potent” discussed in paragraph 23.

52. The Committee asked for adverse effects of vitamin D intake to be referred to as high levels of vitamin D, and to note if the advice presented in paragraph 67 on vitamin D intake and COVID-19 is also the advice given by the UK National Health Service (NHS).

53. Additional requests were to clarify whether 97.5th and mean exposure values presented in the appendix had been summed, and to provide an explanation for the difference in age groups reported in paragraphs 76 and 77.

54. Other requests from the Committee were to add a table comparing the different exposure values from UV radiation, food, vitamin D supplements, to indicate that supplements are the biggest contributor to exposure.

55. In reference to the statement: “doses of 7500 µg at intervals of 3 months or longer would not be expected to cause adverse effects in adults” in paragraphs 78 and 86, the Committee questioned its clarity, and if the doses reported are inclusive of pregnant individuals.

56. The uncertainty of exposure estimates amongst women of child-bearing age was discussed and should be noted in paragraph 81.

57. The Committee concluded that a clear final statement is needed to reflect that the COT does not know the relationships between oral vitamin D intakes, serum 25(OH)D levels, and estimated background vitamin D exposures from UV radiation.

58. The Committee concluded that consumption of vitamin D supplements alone is sufficient to result in exceedance. Further to this, it was agreed that exposure through the diet alone (i.e. without consumption of vitamin D supplements) is unlikely to be a cause of concern, and that consumption of both dietary sources of vitamin D and supplements are likely to result in greater exposure levels.

Item 8: Interim Position paper on Titanium Dioxide (TOX/2021/46)

59. Professor Alan Boobis declared that he is a Member on the External Advisory Committee of the Center for Research on (Food) Ingredient Safety at Michigan State University. One of their research groups have undertaken research on titanium dioxide, which is partly funded by industry. Although there was not a direct interest, it was decided that it would be prudent that Professor Boobis should not Chair this Item. The COT deputy Chair, Dr Sarah Judge, replaced him as Chair for this Item.

60. Dr Stella Cochrane declared a personal non-specific interest as she works for a company that uses titanium dioxide in their products; it was agreed that she could contribute to the discussion of this Item. Professors Matthew Wright and Maged Younes were Members of the EFSA Scientific Panels that reviewed the safety of

titanium dioxide for the 2021 Opinion. Although they were available to answer COT Members' questions and offer clarifications on the EFSA Opinion, they did not participate in the COT's discussion or conclusions.

61. Titanium dioxide is an authorised Food Additive (E171) in the EU. Under UK Food Law it is used in food as a colour to make food more visually appealing, to give colour to food that would otherwise be colourless, or to restore the original appearance of food. Titanium dioxide has been the subject of multiple safety evaluations.

62. Following the recent publication of the EFSA Opinion on titanium dioxide (and subsequent discussions at the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) (MUT/2021/03) in June 2021 and at the COT in July of 2021(TOX/2021/36)), it was agreed that an Interim Position Paper should be made available, capturing the outcomes of the discussions from the two Committees and outlining the next steps.

63. The COT noted that in the draft interim position paper presented, it was not always clear which panels of EFSA the document was referring to. It was agreed there should be some minor alterations in the paper to provide further clarity on references and chronology of past EFSA opinions. The 'food additives and nutrient sources added to food' (ANS) panel should be referenced as an EFSA panel.

64. Members noted that the EFSA definition of a nanotechnology product did not seem to make sense, in that a product with 0% particles (i.e. < 50%) could be classed as a nanomaterial. It was noted that although this was not created as a legal definition, the UK position would nevertheless require greater clarity on a published definition.

65. The draft position paper stated that the 2021 EFSA panel could not conclude as to whether the genotoxicity of titanium dioxide particles is mediated by (a) mode(s) of action with (a) threshold(s). This was inconsistent with the opinion of the Scientific Committee on Consumer Safety (SCCS) which stated that it considered it plausible that there was a practical threshold for this mode of action, and therefore a risk assessment could be carried out for its use in cosmetic products. It was noted that the SCCS focused on inhalation exposure only and less on genotoxicity than the EFSA panel. The position paper needed to highlight the inconsistencies in the conclusions.

66. The COT noted that the conclusion from EFSA's 2021 Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) stating that 'there were no specific studies available designed to assess the safety for the target species' therefore conclusions could not be drawn on the genotoxicity, was confusing. This aspect needs clarity and would be reworded to highlight the FEEDAP panel is referring only to data with which it had been provided.

67. Members noted that clarity is needed regarding the EFSA conclusion that the greater the nanoparticle content present in the test material, the more likely that the

outcome of the study was to be positive, as this contradicts earlier conclusions in the position paper.

68. It was highlighted that the phrase ‘the COT does not follow the precautionary approach’ is not correct. This should be reworded to ‘a precautionary approach’ or ‘a precautionary principle.’

69. A revised version of the interim position paper would be drafted, capturing the COT’s suggested changes, and authorised for publication via deputy Chair’s action.

Item 9: The Safety of Green Tea Catechins (Reserved) (TOX/2021/47)

70. Paul Loeven from Health Canada attended this Item as an observer.

71. Members discussed this Item on the safety of green tea catechins. The minutes of this discussion are currently reserved as they refer to particular details which are not yet in the public domain. These will be published in due course.

Item 10: First draft statement on the potential allergenicity of chitosan in food contact materials (TOX/2021/48)

72. Dr Federico Luppi attended as an observer, in addition to Paul Loeven from Health Canada.

73. The potential allergenicity of chitosan in food contact materials was last discussed by the COT in February 2021, where the Committee noted that it would be useful to have an indication or estimation of total exposures to allergenic proteins from BBFCMs, for example the upper bound levels of ingestion, or range of amounts of BBFCMs in contact with different foods. However, taking into account the available data, it is not currently possible to undertake a reliable exposure assessment due to the uncertainties involved. This exposure assessment is pending further measurement data, studies on which are currently underway.

74. Subsequent to the February COT meeting, the FSA has acquired additional information from a company that is developing food packaging materials comprised of chitosan, as this provides a useful addition to the current state of knowledge for these materials; this information was included in the cover paper which is partially reserved for reasons of commercial confidentiality. Information related to an ongoing PhD project was also provided.

75. Paper TOX/2021/48 contained a draft statement on the potential allergenicity of chitosan in food contact materials. Members made a number of comments on the structure and content of the statement.

76. The Committee noted there needs to be a problem formulation at the beginning of the statement. Furthermore, some structural changes were required to bring together the different sections on hazard, immunogenicity and allergenicity.

The human clinical data that is currently referred to in paragraph 83 needed to be more clearly referenced.

77. In terms of content, it was agreed that fungal sources of chitosan needed to be discussed in further detail. With regards to the PhD project currently being undertaken at Fera, one Member asked whether information on the biological source of the chitosan being investigated there could be included.

78. The information received from the Medicines and Healthcare products Regulatory Agency (MHRA) needed to be further clarified, for example regarding whether their comments related to chitin/chitosan-containing products on the UK market, and if so, whether the MHRA had conducted a risk assessment on these products.

79. For the purpose of context, further information on product types which also carry risk management labels or warning labels was suggested.

80. Regarding the GRAS notices on the FDA website, Members agreed that it would be helpful to clarify the current status of these different notices.

81. The Committee had various questions about the analysis of allergenic protein using the ELISA method, such as the exact target, whether the method would be able to detect larger fragments of tropomyosin (Tm), which might be of allergenic importance, and all necessary controls and matrix checks.

82. In paragraph 57, it would be helpful to refer to the EFSA opinion on mealworm which was published last year.

83. Members agreed that in paragraph 23, the phrase “clinical measurements do not appear to have been verified” should be described as a “limitation” of the data.

84. The estimated prevalence value for shrimp allergy in the population that is currently referenced should be replaced by a more widely accepted prevalence value in Europe, with reference to the relevant 2014 EFSA publication.

85. One Member questioned how representative the levels of chitosan in packaging materials as presented in the annex were, given some products in current development. It was considered that a caveat should be included at the end of annex, noting that "products are being developed which may contain a much higher percentage of chitosan, which would need a separate consideration".

86. In terms of the current paragraphs on immunogenicity, studies which were not relevant to dietary exposure can be removed. Members agreed that the indications were that only a relatively non-specific inflammatory reaction could occur in the gut in response to high levels of chitosan, in common with other insoluble materials.

87. The Committee considered instances of people using crustacea shells in cooking, and whether sensitive individuals have experienced any adverse health effects from consumption of such dishes.

88. Members considered that the risk of allergenicity from residual proteins appeared to be low. However, further information would be necessary before the Committee could conclude on whether there is a health risk posed by residual allergenic proteins to sensitive individuals Further, if these food packaging products are going to be used more widely, consideration should be given to having a specification for levels of protein in the materials used.

89. Members made a number of additional minor editorial suggestions.

Item 11: Update on the work of other advisory committees- for information (TOX/2021/49)

90. This paper was circulated for information.

Item 12: Any other business

91. There was no AOB.

Date of next meeting

92. The next meeting of the Committee Meeting will be at 10:00 on the 26th of October 2021.