Meeting

Final minutes of the 6th September 2022 meeting

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

Present

Chair:	Prof Alan Boobis

COT Members:

Dr Phil Botham

Ms Jane Case

Dr Stella Cochrane

Professor James Coulson

Professor Gary Hutchison

Professor Thorhallur Ingi Halldórsson

Dr Sarah Judge

Professor 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

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

UK Health Security Agency (HSA) Secretariat:	Ms Britta Gadeberg	UK HSA Scientific Secretary
Invited Experts and Contractors:	Dr Sarah Bull	Institute for Environment and Health (IEH)
Assessors	Mr Brian Roberts	Civil Aviation Authority (CAA) (Item 5)
Assessors	Mark Cairns	CAA (Item 5)
Assessors	Ms Valerie Swaine	Health and Safety Executive (HSE)
Assessors	Ms Frances Hill	Department for Business, Energy and Industrial Strategy (BEIS)
Assessors	Ms Rachel Elsom	Office of Health Income and Disparities (OHID), Department of Health and Social Care (DHSC)
Observers	Dr Stephen Ruckman	TSG consulting
FSA and other Officials:	Dr Amie Adkin	FSA
	Ms Natasha Gladstone	FSA
	Dr Andy Axon	FSA
	Ms Krystle Boss	Food Standards Scotland (FSS)

Contents

Announcements

1. The Chair welcomed Members and other attendees.

Interests

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

Item 1: Apologies for absence

3. Apologies were received from Dr Barbara Doer and Ms Frederique Uy of the Secretariat, Dr John O'Brien from the UK Science Council and Professor Tim Gant from the UK Health Security Agency.

Item 2: Draft Minutes from the meeting held on 12th of July 2022 (TOX/MIN/2022/05)

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

Item 3: Matters arising from the meeting held on 12th of July 2022

Matters arising: 2023 Workshop

5. No interests were declared.

6. Following the recent COT workshop "Opportunities and outlook for UK food and Chemicals regulation post EU exit", a possible topic for the 2023 COT workshop was discussed. The Secretariat proposed that the workshop might be a good opportunity to start work on updating the COT guidelines. Applicants for regulated product authorisation used existing EFSA guidance but as this was evolving it would be useful to consider UK specific guidance which could link to work such as the FSA/COT roadmap on New Approach Methodologies; guidance from elsewhere in the world could also be considered.

7. Members agreed that this would be a suitable topic for a workshop.

8. The Committee considered that existing EU regulations should be built on, but with the aim of also producing UK specific guidelines on topics such as

dose-response modelling, combining exposure assessments, Adverse Outcome Pathways (AOPs) and other new scientific developments as appropriate. Emerging issues, such as intermediate endpoints and what level of uncertainty should apply to such endpoints could also be considered. Some of these points could be further developed and fed into the FSA's research programme. Potential topics and speakers were then discussed. It was agreed by Members that any guidelines should integrate with COC and COM guidelines.

9. Members suggested that a working group similar to that for SETE should be put together to work on some proposals for the workshop.

10. Members were asked to send the Secretariat suggestions for topics and speakers.

JEGs update

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

12. The Joint Expert Group for Additives, Enzymes and other Regulated Products (AEJEG) were continuing their work on steviol glycosides and smoke flavouring reauthorisations.

13. The Food Contact Materials Joint Expert Group (FCMJEG) have discussed an additional 3 dossiers, two of which have been approved and will be presented to the COT in the near future. Information and data on can coatings, which were a potential replacement for BPA, were discussed. This was a non-routine assessment that would be presented to the COT in October.

14. The last meeting of the Joint Expert Group on Animal Feed and Feed Additives (AFFAJEG) took place in July 2022. Its role will be superseded by that of the Advisory Committee on Feedstuffs (ACAF), the terms of reference for which were currently being drafted. The AFFAJEG's opinion on 3-nitrooxypropanol (3-NOP) was in its final draft and would be shared with the COT for information.

Item 4: Position Paper on Chitosan (TOX/2022/45)

15. No Interests were declared.

16. Annex B of paper TOX/2022/45 was treated as reserved as it contained commercial data.

17. In May 2020, a scoping paper entitled “Alternatives to conventional plastics for food & drinks packaging” (TOX/2020/24), which introduced some of the possible toxicological hazards associated with the use of bio-based food contact materials (BBFCMs), was presented to the COT. A proposed list of BBFCMs for health risk assessment was presented to the Committee in February 2021 (TOX/2021/01); this list included BBFCMs containing chitosan. Although the Committee reviewed a draft statement on chitosan, it was agreed that a position paper was more appropriate, since further information, particularly on exposure assessment, was anticipated in the short to medium term.

18. The cover paper provided additional information on life-cycle assessments (LCA) for bio-based materials versus conventional plastics which Members had requested. The Committee had requested clarification on 1) whether the computer software packages assessed degradation and possible formation of particulates, 2) whether there are any agreed inputs and outputs for LCA, and 3) how large a difference in impact the normalised impact values represented. Therefore, additional context on how to interpret LCAs would help the Committee to reach any conclusions on the LCA studies.

19. It was noted that in the position paper additional context, background, and explanation was needed on a) the information received from MHRA on chitosan wound dressings (that the potential hazard is in respect of protein contamination, though composition data are unavailable); b) the allergen reference doses (for example, how the ED01 and ED05 values were derived, their level of acceptance across different regulatory authorities, and recent recommendations made by expert panels such as FAO/WHO on whether the ED01 and/or ED05 values should be used as an adequate protection goal, and their consideration of severity profiles); c) tropomyosin (other allergenic proteins are present in crustacea); and, d) the migration limit of 10 mg/dm^2 in the Plastics Regulation (for example, how it was derived, and clarification on whether it represented a maximum allowable limit).

20. Members noted that, throughout the position paper, it should be clear whether the references to “shells”, “shellfish”, “shellfish allergy”, or “seafood allergy” were to crustacea and/or molluscs. Members also noted that in Table 1, an additional potential hazard arising from the use of sodium alginate derived from seaweed was a reaction in those individuals allergic to fish, as small fish larvae could be a source of contamination.

21. In paragraph 9, it should be clarified that chitosan coatings could be applied to food packaging, as well as to food surfaces.

22. Members noted that the molecular weight of 10 kDa for chitooligosaccharides (COS) given in paragraph 22 appeared to be high, since other study authors noted an average molecular weight of approximately 3.9 kDa or less.

23. In paragraph 23, it was stated that “These reference values are derived from human food challenge data, and represent acute intake levels of crustacean-derived protein that are predicted to provoke an objective reaction in no more than 1 and 5% (respectively) of at-risk individuals, who show a minimal allergic response upon challenge”. One Member queried the phrase “who show a minimal allergic response upon challenge” as the severity of these reactions is variable and reactions can include mild anaphylaxis. There was a need to ensure this wording is consistent with what has been used in other documentation.

24. In paragraph 32 of the position paper, the nature of the specific reaction to the chitosan-based straws was queried. It was noted that the issue of labelling of chitosan drinking straws was risk management and risk communication; data were used to determine the level of protein ingested, leading to a level of risk, where individuals with crustacean allergy may need to be alerted via a label that they are at risk.

25. In paragraph 39, it should be clarified that in the study of Waibel et al. (2011), only 10 of the 19 participants completed the study because only these individuals had met the inclusion criteria, rather than the others having dropped out.

26. In paragraph 45, regarding the evaluation of insect chitin, it should be clarified that this evaluation was on a whole mealworm preparation, not just insect chitin, and therefore that this specific evaluation was a more holistic assessment of allergy.

27. The Committee agreed that during its manufacture, chitosan should have a certain specification with respect to protein content.

28. Members considered the data contained in Annex B which was commercial confidential and currently treated as reserved. A number of minor editorial suggestions were made.

29. The revised position paper would be presented to the Committee at a future meeting, however, the Secretariat confirmed that a statement would be prepared when exposure data became available.

Item 5: Aircraft Cabin Air (TOX/2022/46)

Presentation from the CAA

30. No interests were declared

31. A presentation was given to the Committee by the Civil Aviation Authority (CAA) covering four main areas: data analysis, engine seals, operator actions and future developments and modifications.

32. The CAA receive roughly 32000-35000 reports on smoke, odours, fumes and fire (SOFF) in aircraft per year, with an increase noted between 2013 and 2014 due to the new 376/2014 UK regulations on reporting being established. Illustrative data on types of reports were presented from two different operators (one dealing with short and long haul flights and the other mainly European flights only) with values differing for various factors (e.g. onboard cooking of food).

33. The presentation illustrated two main types of engine seals (carbon and labyrinth), how they function, and the potential for oil leaks entering the aircraft cabin air supply.

34. In terms of actions undertaken by Operators, it was noted that increased awareness and reporting of cabin smells had led to extensive investigations from engineers including with various detectors to find the root cause. A number of possible sources were outlined including food smells, smells from de-icing fluid, and a high proportion relating to the auxiliary power unit (APU), however, the cause of many smell events was unknown.

35. Other actions being taken included investigations and modifications to use of the bleed air from the APU including positioning of the air inlets, which differed between aircraft manufacturers. In addition, HEPA filters were being redesigned using a carbon filter to reduce smells from re-circulated air.

36. A number of potential new developments were highlighted including ozone converters and VOC filtration, to potentially reduce VOCs in the cabin as well as utilising sensors to detect these compounds. Finally there was also

potential for development of engine oils to reduce impact of leaks of oil into the cabin air system.

TOX/2022/46 - Volatile organic compounds in aircraft cabin air: comparison with other modes of transport

37. No interests were declared.

38. This paper presented the available data on volatile organic compounds (VOCs) in aircraft and in other modes of transport to provide an indicative comparison of how exposures in aircraft compare with those from other transport, and where feasible identify any specific VOCs which might be of particular concern in terms of the concentrations measured in aircraft.

39. The Committee considered the searches and data were appropriate and summarised well and the paper presented an interesting collation of data with some caveats. Members considered that the data provided an indication of some of the VOCs to which travellers and crew could be exposed and at what levels.

40. It was noted that the data were from different geographical regions and represented a range of vehicle types, usage patterns, and sample numbers, which affected the comparability of the data across the various modes of transport and even from study to study. Differences in the time generally spent in different vehicle types (e.g. aeroplanes compared to cars) were noted and it was suggested that a time-weighted average may be needed if a more accurate comparison was required.

41. The impact of the outdoor environment on concentrations within vehicles had not been investigated in any of the reported studies. It was flagged that the COT was not aiming to carry out a risk assessment of different modes of transport, but to compare concentrations between aircraft and other forms of transport.

42. It was considered that no candidate VOCs could be chosen or excluded for further consideration, at this stage, due to the limitations discussed.

43. The Committee had been asked whether data on levels of VOCs in submarines would be helpful as both submarines and aircraft are pressurised sealed tubes. It was agreed that the nature of exposures was sufficiently different

between the two that this would not be helpful.

44. The Committee were informed that a paper on levels of VOCs in different building environments would be presented at the next meeting.

45. In reviewing this paper, Members highlighted that consideration should also be given to carbon dioxide levels in aircraft, as there was evidence that this could impact on the integrity of decision making of those in the cockpit. Likewise, an evaluation of carbon monoxide would be prudent considering the health effects reported, namely low level, non-specific neurobehavioural changes. It was agreed that future papers on these would be prepared. Other potential confounders such as radiation exposure in aircraft and shift work undertaken by pilots and air crew were noted, but were outside the COT remit to evaluate, though these should be noted.

Item 6: Second draft statement on the effects of lead on maternal health (TOX/2022/47)

46. No interests were declared.

47. The review of lead in the maternal diet was part of the ongoing programme of work on the maternal diet undertaken with colleagues from the Scientific Advisory Committee on Nutrition (SACN). The Committee had agreed that heavy metals, including lead, should be considered as a priority for assessment.

48. A discussion paper on lead (TOX/2022/05) was considered at the February 2022 meeting and a first draft statement (TOX/2022/32) at the May 2022 meeting. A number of recommendations were made by Members on the content and structure of the statement, which have been incorporated into this second draft.

49. The Committee suggested a number of minor editorial changes to be made to the document; these included clarifying in paragraph 18 that EFSA used the raw data from models of the Lanphear et al (2005) study (Environmental Health Perspectives 2005. 113(7): 894-899) whereas JECFA used the published paper to determine their respective BMDL values. Additionally, Members requested that context be provided to the Margin of Exposure (MOE) values to ensure that it was clear that an MOE value of 1 was an acceptable level and that it was an unlikely scenario as it would require top-end exposure in all situations.

50. A Member raised concerns over the use of 70.3 Kg as an average bodyweight for women. It was explained that this was the value obtained from the National Diet and Nutrition Survey (NDNS) and was used only in scenarios where the actual body weight of respondents was not available, for example, in soil and dust exposure. Where exposure from food was assessed, individual body weights were considered.

51. The Committee noted that there was a lack of information regarding the contribution of soil consumption from pica behaviour to lead exposure in the maternal diet. It was suggested that instead of being focussed solely on lead in the maternal diet, a short discussion paper on pica in general should be considered.

52. It was agreed that this statement could be finalised through Chair's Action.

Item 7: Draft FSA/HSE/VMD report on approaches to chronic dietary exposure assessment for chemicals in food (TOX/2022/49)

53. The Chair, Prof. Boobis declared that he was a member of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), the Joint FAO/WHO Expert Committee on Food Additives (JECFA) meetings on veterinary medicine residues, has participated in FAO/WHO working groups on exposure assessment methodologies and was a partner in the EU-funded EuroMix project. No other interests were declared.

54. At the February 2021 meeting, Members were informed that work had started between the FSA, HSE and Veterinary Medicines Directorate (VMD) to consider the approaches to chronic dietary exposure assessment for chemicals in food, and that the outcome would be a report, the draft of which would be brought to the COT for comment ahead of finalisation.

55. This work had been undertaken because there were differences in the current approaches to chronic dietary exposure assessments undertaken by the HSE's Chemicals Regulation Division (CRD) for pesticides, VMD for veterinary medicines and FSA for chemical contaminants and other chemicals in food. Furthermore, there were differences in how these assessments were conducted internationally for pesticides and emerging differences for veterinary medicines. In addition, following exit from the EU, it was timely for UK regulators to consider

the approaches they might wish to take in the future.

56. The draft report discussed the principles of dietary exposure assessments and described the current approaches to chronic dietary exposure assessments being taken by the FSA and for pesticides and veterinary medicines. It discussed the current differences in approach and the reasons for them, uncertainties in exposure assessments, considered the possibilities for common approaches to be taken in the future and the approaches to substances with multiple uses (e.g. as both pesticides and veterinary medicines). It also included some considerations on cumulative and aggregate exposure assessment and referred to the recent considerations of less than lifetime and variable exposure over a lifetime by the COT and COC.

57. The draft report made a number of recommendations. These included increasing collaboration between FSA, HSE and VMD on topics such as exposure assessments for substances with multiple uses, the setting of common Maximum Residue Levels (MRLs) and Health Based Guidance Values (HBGVs), and on methodologies for cumulative risk assessments; continuing international collaborations; periodically reviewing exposure assessment methodologies for fitness for purpose and considering their uncertainties; and having up-to-date comprehensive food consumption data, which are contained within a central database to which staff from each of the departments/agencies have access and training on their use.

58. Members advised that the recommendations should be separated out from the conclusions and possibly prioritised.

59. A Member had sought comments from a recent Member of the COT who was an exposure assessment expert. He had forwarded their comments to the secretariat and noted a few key points. The FSA’s approach was usually closer to actual consumer exposures whereas regulatory approaches for approval of pesticides and veterinary drugs default to being conservative. If joint exposure assessments were performed, what degree of conservatism should there be? There was a strong desire for more information on cumulative and aggregate exposures but the methods were not fully developed yet and there were still improvements that could and should be made to exposure assessments for single substances first. Probabilistic modelling was included in the report as a high tier model but that was not being conducted to much extent at the moment, though the software was available and it could be used more. There was also agreement with the recommendation of a central database for food consumption data.

60. Members considered that it was a good idea to conduct exposure assessments more consistently across chemical areas; however, for applicants there was also the international consideration and to them it would be preferable for there to not be too many differences in the approaches used between regions internationally, e.g. between the UK and Europe.

61. Members asked whether the HSE model had the food consumption data hard coded into it such that the model needed to be rebuilt if the consumption data changed. It was noted that the HSE model used consumption data provided by the FSA in the early 2000s and could be rebuilt using contemporary consumption data; however, work would be required to transform the data the FSA held to the raw agricultural commodity (RAC) equivalents before it could be used by HSE.

62. Members agreed that the term “cocktail effect” should be avoided in a scientific context, instead the reference should be to risks from combined exposures.

63. It was noted that EFSA had taken one approach to the cumulative risk assessments of pesticides and a different approach to other chemicals. While they have produced guidance it was not clear whether they were currently routinely undertaking cumulative risk assessments for chemicals other than pesticides. Where such cumulative risk assessments have been performed, a constrained approach tends to have been taken, for example, grouping chemicals in the same regulatory area that have similar structures. At present, there does not appear to be have been any move to conder, for example, all chemicals across all sectors that cause hepatic steatosis as a single group, for regulatory purposes. It was suggested that the report should recognise the difficulties as well as the possibilities of performing combined exposure assessments across different regulatory areas.

64. It was observed that there were differences in the ages currently being used to define infants, toddlers and children between HSE and the FSA, and the age range for infants used by the FSA of 4-18 months was quite wide. A Member asked for justification for the 97.5th percentile being used for high consumers to be added, and the Committee asked whether the NDNS was kept under review to ensure it reflected the population, with adequate coverage for example of ethnic groups and groups such as vegans. It was noted that the NDNS reflected the whole population but that focused studies would be needed to reflect the consumption patterns of groups that comprise only small percentages of the entire population, to ensure their adequate statistical characterisation. It was

explained that the FSA was currently using all 11 years of the rolling programme in their assessments, and continuing to add each year's data progressively, in order to increase the number of consumers, particularly for less commonly eaten foods and allow more robust exposure assessments. A Member noted that exposure assessors are constrained by the data that they can obtain, for example, JECFA and JMPR do not have access to consumption data with the level of granularity that the FSA has and hence would have considerable difficulties in performing probabilistic modelling.

65. The draft report was also being taken to the UK Expert Committee on Pesticides (ECP) and the Expert Committee on Pesticide Residues in Food (PRiF) for comment.

Item 8: The potential health effects of raspberry leaf in the maternal diet (TOX/2022/50)

66. No interests were declared.

67. As part of the COT's ongoing programme of work on the maternal diet, a scoping paper (TOX/2020/51) was presented to the Committee, reviewing supplements commonly used by pregnant women. Following this, it was agreed that raspberry leaf supplements required further consideration.

68. Raspberry leaf was most commonly taken during pregnancy for its purported effects in stimulating and facilitating labour and in shortening its duration. Paper TOX/2020/50 presented a review of the available data.

69. Members agreed that the risk associated with raspberry leaf consumption during pregnancy was low but carried a high level of uncertainty. This conclusion was based on the results of the two studies identified in the literature search. These comprised a retrospective cohort study by Parsons et al. (1999) and a double-blind, placebo-controlled, randomised trial by Simpson et al. (2001). Neither study reported adverse effects to mother or child associated with raspberry leaf consumption during pregnancy. In addition, a limited number of reports of raspberry leaf exposure during pregnancy had been received by the UK Teratology Information Service (UKTIS) since its inception in 1983 to the present date, with no evidence of adverse effects at normal consumption levels. However, it was acknowledged that the raspberry leaf dose tested in the Australian study by Simpson et al. (2001) was approximately four times lower than the mean consumption level for raspberry leaf, based on data provided by the FSA's

Exposure and Assessment Team.

70. Members considered that it was not possible to derive a point of departure to be used in the risk assessment of raspberry leaf use during pregnancy, based on the data presented. There were numerous reasons for this. These included: the lack of data available on the active components of raspberry leaf; the potential for contaminants, such as cadmium and pesticides; the potential for the sampling and the preparation method to affect the activity of the supplement; the large variation in the literature as to raspberry leaf's critical effects (smooth muscle relaxation vs. contraction), which appeared to depend on a number of factors, such as the species, preparation and whether it was tested in vitro or in vivo; and the lack of clarity in the literature as to the most appropriate choice of animal model for studying raspberry leaf's effects in humans. It was added that there was limited data available on the pharmacokinetics of raspberry leaf (although there were indications in the literature that it was less toxic when administered orally rather than parenterally). Members also recognised that limited reproductive toxicity data were available on raspberry leaf and that only one study, carried out in mice over a two-week period, appeared to have evaluated it for sub-acute toxicity.

71. The Secretariat asked for the Committee's comments on a study by Hastings-Tolsma et al. (2022). The authors of the study had reported a statistically significant reduction in littler size among mice orally administered aqueous raspberry leaf extracts, compared with mice given a control. Members considered that the results of the study were of low concern, as the mouse strain used (C57BL/6N Tac) was not standard and may not have been the appropriate choice of animal model. It was also unclear as to how much raspberry leaf extract the mice were exposed to, as they were given free access to water bottles containing the extract. It was added that the standard error bars for the different treatment groups in the study overlapped, casting doubt on the significance of the findings.

72. It was commented that many of the studies identified in the literature search did not meet the requirements for reporting on botanicals and that many were published a number of years ago. Therefore, they also did not meet current animal welfare regulations or ethical standards. It was highlighted that while the Committee did not endorse these studies it was acknowledged that they were performed in accordance with the guidelines available at the time they were published. Hence, information from such studies, when they were of adequate design, was considered in the assessment of raspberry leaf.

73. It was considered that one of the reasons why raspberry leaf appeared to be of low concern to human health, based on the safety data available, was low bioavailability. However, concern was expressed that if raspberry leaf extracts were reformulated, such as by micronisation or microencapsulation, as had been done for some other supplements such as cannabidiol (CBD) and turmeric, this might increase bioavailability. Such products may need to be evaluated separately in terms of their safety. Members also commented that according to a source cited in paragraph 7 of the paper from 2013, the prevalence of raspberry leaf use among pregnant women ranged up to 58 %. It was requested that the Secretariat check the literature to see if any more recent data was available on the prevalence of use, as this range seemed relatively high.

74. Members further commented that the 'transgenerational' effects reported in the F1 and F2 offspring by Johnson et al. (2009); Makaji et al. (2011) and Hastings-Tolsma et al. (2022) should instead be referred more properly to as reproductive effects, to reflect the fact that they could have resulted from in utero exposure to raspberry leaf, rather than being transmitted through the germline.

75. It was agreed that a draft statement would be prepared, incorporating Members' comments, to be reviewed at a subsequent meeting. They requested that a paragraph be added to the conclusion within the statement, summarising the results of the animal studies identified. It was suggested that paragraph 141 in the discussion paper, on residues and contaminants, be omitted from the conclusion, as this is a generic issue already addressed by FSA's surveillance programmes. In addition, it was requested that the statement cross-reference the COT's previous work on some of the components of raspberry leaf, such as polyphenols.

Item 9: The safety of green tea catechins – first draft statement (TOX/2022/51)

76. Professors Maged Younes and Matthew Wright declared a personal non-specific interest relating to flavanols as the Chair and a Member, respectively, of the EFSA ANS panel that produced the original opinion, but were able to contribute to the subsequent discussion, to provide clarity as required. No other interests were declared.

77. On behalf of the UK, the Nutrition, Labelling, Composition and Standards (NLCS) group have asked the FSA to evaluate whether the conclusions of the

2018 EFSA opinion on green tea catechins were still applicable taking into account any new data that have become available since its adoption, to enable them to consider the next steps with regard to risk management. This evaluation of the 2018 EFSA opinion related to green tea catechins and the associated cases of probable idiosyncratic hepatotoxicity, rather than being a safety assessment of either green tea catechins or green tea infusions and extracts more generally.

78. The Committee agreed that the title of the draft statement was too general, and needed to be more precise, relating more specifically to idiosyncratic hepatotoxicity.

79. The Committee requested that any updates on the legislative status of green tea catechins should be identified and subsequently added to the draft statement.

80. Members commented that paragraph 8 of the statement required clarification on what preparation was being discussed. In particular, whether it was referring to catechins in the green tea, or in the resulting infusion.

81. Members asked for clarification in paragraph 9 as to why '(L.) Kuntze' is referred to in paragraph 9 after *C. sinesis*. Clarification is needed as to whether other hybrids contained catechins. It was also asked whether caffeine was always removed via aqueous alcohol extraction, as members noted some extracts did contain caffeine.

82. Members commented on the consistency of statements regarding the safety of green tea throughout the draft statement as a whole. Although the conclusion was deemed to be clearer, there were varying degrees of the expression of certainty on the relative safety of green tea, and this should be rectified to be consistent throughout.

83. Members questioned whether the pyrrolizidine alkaloids (PAs) detected in green tea were from Camelia sinensis itself, or from contamination with other plant species. It was agreed this would be clarified.

84. In paragraph 17, Members noted there were differences in metabolism with glutathione between mice, rats and humans and the paragraph should be updated to account for the inter-species differences in metabolites.

85. The Committee requested that the wording in paragraph 25 be re-considered, to note the lack of effects below consumption of 5 cups per day.

86. In paragraph 38, one Member commented on how the EFSA Benchmark Dose model has changed slightly, and now a different figure would be generated. However, it was noted that quoting of the specific number from the EFSA text allowed the information to be cross-referenced more accurately, and this concept had been discussed at prior meetings.

87. The Committee discussed the wording used in paragraph 48, and agreed that it required changing to reflect the function of anti-CTLA-4 as a checkpoint inhibitor; that is, removing the inhibition in the mouse immune system to observe the effects. The use of anti-CTLA-4 as an emerging cancer treatment was noted, and therefore the consequences of green tea consumption in conjunction with its use needs to be assessed.

88. Members requested that the dosage of supplement be added to the case report described in paragraph 53 – half a teaspoon of Vital Stem in pomegranate juice every day. However, the listing of additional ingredients was unnecessary and should be deleted.

89. The Committee requested that the wording of paragraph 60 of the draft statement should be reconsidered, as it could imply that green tea was the sole cause of supplement-related liver injury, which was not the case.

90. Members considered that the statement should note as an uncertainty that it was not possible to differentiate between direct effects from green tea and those indirectly from contamination.

91. The Committee requested that throughout the draft statement, it be clarified whether the values stated are in reference to catechins as a whole, or specifically EGCG, which appears to be the compound of most significant concern.

92. The Committee agreed that the value of 800 mg/day EGCG identified by EFSA is probably safe, and that there were no new data to challenge this. However, no NOAEL can be identified. Furthermore, it was emphasised that 800 mg/day lies close to the dosage at which deleterious effects begin to occur. Therefore, although this value may be protective of the majority of the population, susceptible subgroups may not be protected.

93. Members made a number of other minor editorial comments.

94. It was noted that a revised version of the statement would be presented to the Committee at a future meeting.

Item 10: Paper for information: Update on the work of other scientific advisory committees (TOX/2022/52)

95. This paper was circulated for information.

Item 11: Any other business

96. There was no other business.

Date of next meeting

97. The next meeting of the Committee Meeting will be at 10:00 on the 25th of October 2022 at Broadway House, London and on Microsoft Teams.