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

Meeting of the Committee at 10:00 on 2nd February 2021 via Skype and Teams

Present

Chair:	Prof Alan Boobis	
COT Members:	Dr Phil Botham Dr James Coulson Prof Gary Hutchison Dr David Lovell Dr Mac Provan Prof Faith Williams Dr Michael Routledge Dr Cheryl Scudamore Dr Natalie Thatcher Dr Stella Cochrane Ms Jane Case Dr Sarah Judge Ms Juliet Rix Prof Mireille Toledano Prof Philippe Wilson Prof Maged Younes Dr Rene Crevel Prof Gunter Kuhnle	
	Prof Paul Haggarty Prof John O'Brien	SACN Liaison Science Council Liaison
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland Dr David Gott Dr Alex Cooper Ms Jocelyn Frimpong-Manso Dr Douglas Hedley Ms Cleanncy Hoppie Mr Barry Maycock Dr Olivia Osborne Ms Claire Potter Dr Joseph Shavila Ms Chloe Thomas Ms Sabrina Thomas Ms Chara Tsoulli Ms Frederique Uy	FSA Scientific Secretary
Public Health England (PHE) Secretariat:	Ms Britta Gadeberg	PHE Scientific Secretary

Invited Experts and Contractors:	Dr Sarah Bull	IEH
Assessors	Prof Tim Gant	PHE
	Ms Rachel Elsom	PHE
	Mr Ian Martin	Environment Agency
	Dr Sam Fletcher	Veterinary Medicines Directorate (VMD)
	Ms Gillian McEneff	Department for Business, Energy and Industrial Strategy (BEIS)
Observers	Dr Mindy Dulai	OPSS at BEIS
	Dr Emma Bradley	FCM JEG Member
FSA and other Officials:	Ms Aisling Jao	FSA
	Dr David Mortimer	FSA
	Mr Vince Greenwood	FSA
	Mr Will Munro	Food Standards Scotland) FSS
	Ms Krystle Boss	FSS
	Mr Liam Johnstone	BEIS
	Ms Sophy Wells	FSA
	Ms Susannah Brown	PHE

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Announcements

1. The Chair welcomed Members and other attendees.

2. Members were informed that Professor John Foster had resigned from the Committee as he is re-balancing his priorities. The Chair and Members expressed their appreciation for his valuable contribution to the Committee over the years.

3. It was announced that Dr Sarah Judge has agreed to take up the role of Deputy COT Chair.

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 Dr Caroline Harris and Professor Mathew Wright of the Committee, Dr Barbara Doerr and Ms Claire Potter of the Secretariat, and Ms Kerry Gribben of the FSA NI.

Item 2: Draft Minutes from the meeting held on 1st of December 2020 (TOX/MIN/2021/01)

6. Ms Juliet Rix had been omitted from the list of attendees but was present at the December meeting. There were no other amendments and the minutes were accepted as an accurate record. The reserved minutes were also accepted as an accurate record.

Item 3: Matters arising from the meeting held on 1st of December 2020

Proposed list of BBFCMs for health risk assessment (TOX/2021/01)

7. No additional interests were declared to those noted in May 2020.

8. In May 2020, a paper entitled “Scoping paper: alternatives to conventional plastics for food & drinks packaging (TOX/2020/24)” was presented to the Committee. The Committee was asked to advise on which biobased food contact materials (BBFCMs) should be the priorities for consideration in further detail. Due to the diversity of the available BBFCMs for industrial use, the Committee agreed that in addition to policy priorities, it would be helpful to focus on the BBFCMs that were most, or most likely, to be used in the UK, either directly or through import.

9. The Secretariat provided a table of proposed priority BBFCMs for health risk assessment based on potential health hazards, usage, and priorities from the FSA’s

Food Contact Materials (FCM) Policy Team. These were polylactic acid (PLA), starches, bamboo bio composites and polyhydroxyalkanoates (PHAs).

10. The Chair noted that since this list was not fixed, other priority BBFCMs could be added as necessary. A Member suggested that any BBFCMs that contained common food allergens such as wheat could be assessed as a priority material. A Member of the FCM Policy team explained that many of the materials described in paragraph 7 of the paper (including wheat-based packaging) were at a developmental stage and therefore not yet commercially available. Furthermore, there was no legal requirement to have labelling on packaging to state if it was biobased, or whether it contained allergens.

11. The Committee agreed that health risk assessments of the prioritised BBFCMs would need to be considered within the context of life cycle assessment studies, which included environmental hazards to address indirect impacts on human health, not all of which was within the remit of the COT. It was noted that the Department for Environment, Food and Rural Affairs (DEFRA) (and its expert scientific committee, the Hazardous Substances Advisory Committee, HSAC), the Organisation for Economic Co-operation and Development (OECD), and the Environment Agency were also assessing the wider environmental impacts.

12. It was noted that PLA was on the priority list not because of any inherent safety issues, but due to the nanoparticles it could be blended with in some BBFCMs. The Secretariat clarified that many BBFCMs and not just PLA were blended with nanoparticles.

13. Members enquired about future assessments of nanomaterials and "intelligent" materials used for food packaging. Members were reminded that this will be reviewed in the future as part of this work on BBFCMs, and will include consideration of several aspects:

- issues with shelf-life to facilitate risk/benefit analyses;
- potential for migration into food they are protecting, in addition to migration across the packaging from one food to another, for example during transportation or storage; and,
- nano-coatings which are currently in development.

14. Members were content with the proposed list.

Additional data on MYTOX research group (TOX/2021/02)

15. No interests were declared.

16. The COT had previously reviewed the potential risks from combined exposure to mycotoxins with the first draft of the statement (Annex A of TOX/2020/52) being presented to the COT in October 2020. Following the discussion of the draft statement, COT Members requested clarification on the ongoing projects of the Mycotoxin and Toxigenic Moulds (MYTOX) research group in order to confirm whether the impact of multi-mycotoxin exposure is within the scope of their research.

17. Table 1 of TOX/2021/02 presented the ongoing/or about to start MYTOX projects that evaluated the impact of multi-mycotoxin exposure.

18. Members had no specific comments on the projects being carried out by the MYTOX research group and looked forward to seeing the data produced from these in the future. It was noted that the MYTOX work, to date, does not affect current COT conclusions on the potential risks from combined exposure to mycotoxins.

Update on the Joint Expert Groups (JEGs)

19. Members were informed, that following EU exit, the FSA had received a number of applications for approval of regulated products covering a number of different product categories.

20. The Secretariat noted that Members would receive regular updates regarding the work being carried out by the JEGs.

Item 4: Additional information requested by the Committee on allergenicity of chitin and chitosan based BBFCMs (TOX/2021/03)

21. No interests were declared in addition to those noted in May 2020.

22. In September 2020, a discussion paper entitled “Allergenicity of chitin and chitosan based BBFCMs (TOX/2020/42)” was presented to the COT. This paper described the commercial manufacture of chitin and chitosan from the shells of crustaceans. It explained that incomplete deproteinisation of chitin may lead to the presence of allergenic proteins, such as tropomyosin (Tm) in the final material. Tm is the main allergenic protein in sea food, which can cause allergic reactions in sensitised individuals.

23. Members had considered that the risk of allergenicity from chitin- or chitosan-based BBFCMs based on the potential presence of allergenic proteins appeared to be low. However, to confirm this, more information was needed. In particular, additional data characterising the proteins in chitosan and the final BBFCMs would be useful, together with data on migration from and consumption of BBFCMs.

24. Paper TOX/2021/03 presented additional information on the potential for allergenicity of BBFCMs that contain chitin and/or chitosan, based on the presence of shellfish protein. No measurements of the amount of shellfish protein in BBFCMs were found in the literature. Therefore, to assess the risk of allergenicity with respect to shrimp protein, a preliminary estimation of the possible quantity of shellfish protein was conducted for both edible and inedible BBFCMs. No consumption or public usage data for chitin or chitosan based BBFCMs were identified in the literature or the National Diet and Nutrition Survey (NDNS) database.

25. Overall Members agreed the paper provided the initial data requested and set out a valid initial approach to estimating exposure. However, there were several points on which further clarification or additional information was needed.

26. More information was needed on chitin derived from fungi, particularly if the use of species such as *Aspergillus niger* was being explored as it could contain allergens which would be relevant to the risk assessment. More generally, it would be useful to know the taxonomy of the fungi of interest.

27. Under market uses, background information was needed on potential risk management elements such as warning labels or contraindications for the products described.

28. Paragraph 9 noted that a shrimp-derived chitosan product developed by Primex Ingredients ASA (ChitoClear®) had self-affirmed GRAS (generally recognised as safe) status in the US market. However, this GRAS status was not one which the U.S. Food and Drug Administration (FDA) had evaluated. Members identified a separate submission by Primex to the FDA in 2012 (GRAS Notice No. 443) which was a comprehensive dossier and could be helpful. It included some approaches to protein measurement that were not described elsewhere, and considerable analytical data. The chitosan used is produced by highly controlled production methods, and whilst its specification may be unlike that of other chitosan products, it nevertheless provided a useful standard.

29. In paragraph 10, the basis of the recommendation from the review of Ylitalo *et al.* (2002) from the text provided was unclear: “chitosan has caused no clinically significant adverse effects, and it has been freely available in health stores for decades…we cannot recommend chitosan products to subjects allergic to crustaceans”. Members agreed this paragraph should therefore be better contextualised, or deleted.

30. In paragraphs 12 and 13, two case reports arising from dermal exposure were described, which were considered to be manifestations of allergic contact dermatitis type 4. Members noted that this type of hypersensitivity very rarely, if ever, occurred in the context of food ingestion.

31. Paragraph 15 stated that the Medicines & Healthcare products Regulatory Agency (MHRA) was “not aware of a safety issue investigated by the MHRA related to this material that has come to light since receiving market authorisation”. It was unclear whether this is due to the risk assessment and risk management measures MHRA require for product approval.

32. Paragraph 25 mentions use of the Bradford assay to measure shrimp protein for derivation of the Eliciting Dose (ED)01; however, the ED01 is based on dose distribution modelling, which is not immediately related to analytical measurements using the Bradford, or indeed any, assay.

33. One Member questioned whether the ED01 was an adequate protection goal, given the potential for increased human exposure to the allergen if it were to be present in food packaging. The ED01 is the amount of allergenic protein

predicted to provoke an objective reaction in no more than 1 % of at-risk individuals, who actually show a minimal allergic response upon challenge. Since approximately 1% of the world population is estimated to be allergic to shrimp, the probability of a reaction in the population is therefore 1% of 1%. Despite this low percentage, widespread usage may affect a significant number of people, thus appropriate risk management measures, such as labelling, and consumer awareness were important. For edible packaging, these aspects should be covered by existing legislation. Due to the large amount of data used for dose distribution modelling, accurate estimates below ED01 were not feasible. It was noted that the choice of benchmark (e.g. ED01) was a risk management decision.

34. Members considered whether, in practice, allergenic FCMs would pose no risk if consumption was below the ED01 level. This might depend on the effects of processing on the levels of allergens in the final material, which could then migrate into food. Migration was relevant to FCMs that were removed before eating, but not for edible FCMs.

35. It was agreed that the estimates concerning the ED01 set out in Tables 1 and 2 were difficult to assess regarding their potential risk to human health and it would be useful to have an indication of total exposures. For example, the upper bound levels of ingestion, or range of amounts of BBFCMs in contact with different foods would be helpful. An appropriate surrogate of exposure could also be used. For example, estimates based on the migration of other allergens into foods could be useful, such as those for latex in gloves worn by food handlers. It was clarified that the estimations in Table 1 assumed that all shellfish protein present would be consumed due to 100 % migration.

36. Whilst paragraph 36 stated that “there are no specific migration limits for BBFCMs”, it was clarified that the Plastics Directive stipulated a generic migration limit of 10 mg/dm^2 surface area of the material, which would be applicable. The applicability of FCM legislation depended on the BBFCM’s intended use and how it was marketed. If the BBFCM is intended purely for containment purposes and was inedible, it was not food and was subject to FCM legislation.

37. It was noted that paragraph 39, stated that “adverse reactions after eating insects are scarce”, but it is the number of reports that are scarce. Two surveys were reported but the clinical measurements of allergy presented did not seem to have been verified. The relevant work of Broekman *et al.* (2017)[1] on mealworm allergens, which showed the possibility of de *novo* sensitisation, was referred to.

38. In summary, the Committee agreed with the approach taken for estimation of shrimp protein in BBFCMs that contained crustacean-derived chitin and/or chitosan. Members agreed that these estimations represented a worst case

[1] Broekman H., et al. (2017) Primary respiratory and food allergy to mealworm. J Allergy Clin Immunol
140(2):600-603.e7.

estimate since the chemical treatments used to derive chitin and chitosan result in low protein levels, thus the levels used for the estimation were conservative. However, Members agreed that additional information was required for the exposure estimates relating to the ED01 in Tables 1 and 2, before the potential risks to human health can be assessed.

Item 5: Second draft statement on potential risks from mycotoxins (TOX/2021/04)

39. No interests were declared.

40. The potential risks from combined exposure to mycotoxins have been previously discussed at COT meetings starting in July 2020. The first draft of the statement was presented to the COT in October 2020. The Committee had requested several changes to the draft, which included further clarification of left-censored data and the separation of *in vitro* and *in vivo* studies. The second draft of the overarching statement was presented in Annex A to TOX/2021/04.

41. Members made a number of minor suggestions regarding the structure and content of the draft statement.

42. It was agreed that the significance of the reviewed *in vitro* and *in vivo* toxicological data to human health should be made more explicit and should relate to the document overall. This would ensure transparent communication of the science.

43. Members agreed that the statement could be finalised by Chair's action.

Item 6: Prioritisation of dietary components and xenobiotics for future papers on their effects on maternal health – Part 1 (TOX/2021/05)

44. No interests were declared.

45. In 2019, the Scientific Advisory Committee on Nutrition (SACN) agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery; this would include the effects of chemical contaminants and excess nutrients in the diet.

46. 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 of an initial list of dietary components and xenobiotics at the COT meeting in September 2020, it was agreed that papers on a number of the components should be prioritised and to this end, papers on iodine, vitamin D and dietary supplements are in the process of being discussed by the Committee. The remaining compounds would then be prioritised on the basis of toxicity and exposure. Paper TOX/2021/04 presented summary information to aid this process. The list of chemical and food entities for consideration in this paper is:

mycotoxins, phytoestrogens, resveratrol, vitamins A, C and E, and caffeine. These are either endogenous substances or substances of biological origin.

47. It was noted that the Committee could refer back to previous statements on some of the substances included in the paper as these could have information that might apply to the demographic group in the current project.

48. The Committee considered each chemical to decide which would require an individual review and which could be grouped together into a combined statement. It was noted that the lists could change depending on the available information. Members suggested that for future papers, a summary table setting out, for example, exposure, HBGVs and endpoints would assist with their discussions.

49. Based on the information in the paper, Members requested separate papers to be written on ochratoxin A, fumonisins, zearalenone, citrinin, ergot alkaloids, phytoestrogens, vitamin A (possibly including β-carotene), and caffeine.

50. The following components will be included in a combined paper: aflatoxins, nivalenol, deoxynivalenol, fusarenon-X, T-2 and HT-2, patulin, vitamin E, vitamin C, and resveratrol. Polyphenols might also be included as a group.

51. Members asked whether alcohol was within their remit. It was noted that there had been a recent report from the Chief Medical Officer, noting that there were many uncertainties about the effects of low levels of alcohol consumption during pregnancy, but that it was prudent for pregnant women to avoid alcohol altogether. The Secretariat agreed to provide further details.

52. The second prioritisation paper covering exogenous contaminants in the maternal diet will be presented to the Committee at a future meeting.

Item 7: PBPK for Regulators Workshop Report: First draft (Reserved) (TOX/2021/06)

53. No interests were declared.

54. The Committee discussed the conclusions and potential outputs of the recent COT workshop entitled “PBPK for Regulators”. The detailed discussion paper has been reserved as it is hoped that a publication in the peer reviewed literature will be possible. This will be made available on the Committee website in due course, as will a fuller version of the minutes.

55. It was, however, agreed that the conclusions should be briefly summarised in the minutes. The overall conclusions from the workshop proceedings were as follows:

- PBPK modelling tools were applicable in the explored areas of use, and that some expertise was available.

- PBPK modelling provides opportunities to address questions that are otherwise not solvable for some compounds.

- Widespread acceptance amongst regulatory bodies appears to be limited by lack of available in-house expertise.

- Familiarisation using real world case studies would help in developing more experts in the field and increasing acceptance.

- In a regulatory context, establishing fitness for purpose for the use of PBPK models requires multi-partite discussion and harmonised guidance.

- Finally, PBPK modelling was part of the wider "new approach methodologies (NAMs)" for risk assessment.

56. Members agreed that the first draft report on the "PBPK for Regulators Workshop" had accurately summarised the meeting; the presenters will now be asked to check the accuracy of their summarised contributions prior to the preparation of the next draft.

57. The possible future use of PBPK modelling by FSA and COT was then discussed.

58. Potential future research on PBPK modelling was also discussed.

59. In addition to the above, the FSA has a Computational Toxicology Fellowship starting early in 2021. This Fellowship is anticipated to run alongside these streams of work, as well as open up potential additional routes of communication and also establishing a hub for these discussions and experts in the field.

60. It was further noted that the Joint COT and Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE) subgroup was currently formulating a pragmatic guidance and transparent reflection of how both Committee's review all available data and apply expert judgement in their assessments.

Item 8: Variable life time exposure and first draft statement (TOX/2021/07)

61. Professor Boobis declared that he had participated in a working group of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in developing an approach to considering less than lifetime exposure. No other interests were declared.

62. At the March 2020 meeting, the COT considered a set of principles produced by the COC on considering less than lifetime exposure to genotoxic and non-genotoxic carcinogens. Subsequently, at the October 2020 meeting, the COT considered a paper which included two test cases from the COT's work on chemicals in the diets of infants and young children, cadmium, and fumonisins. The COT

agreed that COT-specific principles should be produced based on the COC principles. A draft COT Statement was now presented for consideration.

63. At the October meeting, some Members had suggested that the toxicology should be the starting point rather than the exposure scenario, and that the toxicology should inform the exposure window of interest. At present, the draft COT Statement still started with the exposure scenario as it has been drafted to follow the COC principles and further input from the Committee would be needed on how to structure the steps if starting with the toxicology. In addition, risk assessment questions to the COT may start with a particular exposure scenario, e.g. the infant diet or maternal diet, so there may still be some value in starting with an exposure scenario. However, Members were asked to consider this further. At the October meeting the COT had also noted the need to consider further how to approach bioaccumulative chemicals, particularly in children.

64. Members noted that the case for starting with consideration of the toxicology was for evaluations by Committees such as JECFA and JMPR, which review the entire toxicological profile of a chemical and are considering whether there are specific toxicological concerns that might require a separate exposure consideration to the chronic exposure assessment, e.g. where a NOAEL for offspring toxicity is close to the critical No-observed-adverse-effect level (NOAEL) used to establish the chronic HBGV. However, for the COT it depends on the question asked, and either the toxicology or the exposure scenario might be appropriate starting points.

65. The approach starting with the exposure scenario was considered reasonable provided that questions were added under step 2 asking whether there is evidence for progression of toxicity, e.g. a decrease in the NOAEL, with increasing duration of exposure, and how does sensitivity during specific life stages, e.g. offspring, compare with that during chronic exposure. It was observed that these were addressed by the flowchart in Figure 1, so it was just the text that needed to be expanded to include these considerations.

66. Regarding bioaccumulative chemicals, bioaccumulation is not linear with time and a steady state would be reached at some time point, with no further accumulation. It was agreed that the kinetics should be studied carefully, and expert judgement is necessary on a case-by-case basis. A Haber's rule-based approach may be an acceptable approximation in some cases, but not in others. In general, it was considered that if the exposure period is less than the half-life of elimination, then a Haber's rule-based approach would be appropriate, but if it is more than the half-life of elimination this approach would not be appropriate. If the data are available, then the assessment should be based on internal exposure rather than dietary/external exposure.

67. The Committee would consider a revised draft Statement at a future meeting.

Item 9: Discussion paper on the potential effects that excess vitamin D intake may have during preconception, pregnancy and lactation (TOX/2021/08)

68. Personal, non-specific interests were declared by Drs Natalie Thatcher and Stella Cochrane as their employers produced products containing vitamin D. It was agreed they could participate in the discussion.

69. As part of the work being done for the SACN assessment of the maternal diet, a provisional list of chemicals for review had been discussed. As part of the discussion, it was agreed that reviews of a number of components including vitamin D should be prioritised.

70. Paper TOX/2021/08 considered the effects of excess intake of vitamin D and whether current exposures could pose a risk to maternal health

71. Members were content with the exposure assessments presented, but noted that exposure from plant-based drinks fortified with vitamin D should also be considered. The maximum dietary exposures estimated were conservative.

72. The Committee highlighted that vitamin D3 could be of more potential concern than vitamin D2 due to its higher bioavailability and noted that supplements tend to use vitamin D in the form of D3.

73. Members commented that the data provided on loss of function mutations of CYP24A1 (25-hydroxyvitamin D- 24-hydroxylase), an enzyme which is involved in the breakdown of vitamin D, were scarce, and that additional information on the prevalence of this mutation in the population would be beneficial. It was possible that information could be obtained from the OMIM (Online Mendelian Inheritance in Man) database. Polymorphisms in the vitamin D receptor (VDR) should also be considered alongside those in CYP24A1.

74. The Committee suggested that further background data on vitamin D exposure from sunlight, which was a major source of vitamin D, would be helpful.

75. It was proposed that fetal hypercalcemia as a result of excess vitamin D, and the impact of hypercalcemia on fetal morbidity, should be examined.

76. Overall, the Committee had no concerns regarding the potential effects of current vitamin D intakes from food and supplement sources.

Item 10: Draft EFSA Scientific Committee Opinion on biological plausibility of non monotonic dose responses and their impact on the risk assessment (TOX/2021/09)

77. No interests were declared.

78. In 2016, the European Food Safety Authority (EFSA) published the results of a contracted-out report on a systematic review of the existing literature where signs of non-monotonic dose responses (NMDRs) had been observed (Beausoleil *et al*.,

2016[2]). In this Report the scientific evidence for such NMDRs was assessed with a systematic review being performed in line with the EFSA guidance. The Report extracted dose-response datasets from studies having at least 5 dose groups, which were then analysed by the PROAST software package. The strength of the evidence was characterised using visual/statistics-based checkpoints.

79. The EFSA Scientific Committee (SC) was asked to prepare a scientific opinion on the biological relevance, if any, of the apparent non-monotonic dose responses identified in the commissioned report and to address the possible consequences for the human health risk assessments conducted by EFSA. The draft opinion had now been published for public consultation.

80. The Secretariat provided a summary of the draft opinion and the Committee were asked to provide comments, which will be returned to EFSA in time for the submission deadline of the 4th of February 2021.

81. The Committee noted that this was a review of the previous methods used for assessing the presence of non-monotonic dose responses, not of the responses themselves and was somewhat unwieldy.

82. Members made the following specific comments:

83. A critical review of the key studies claiming NMDR would be needed, to compare against, for example, OECD guidelines, and to more fully address randomisation.

84. Some of the evidence supporting the study showing a biphasic effect on heart rate appeared to have been ignored, suggesting that the conclusion regarding NMDR, or otherwise, might have been biased.

85. Consideration had not been given as to whether NMDR might affect the upper and lower confidence limits of the Benchmark dose (BMD), even if the curve was fitted only to those data points before the sign of the dose-response changed.

86. The implications of NDMR of key events at low doses in the context of homeostatic control needed greater consideration.

87. The opinion concluded that if an effect for which NMDR was observed was an apical effect and NMDR was supported by further experimental work, no further investigations were needed. The corollary of this is that when such an observation was not supported by further experimental investigations, more work was needed. This meant that the opinion only provided for two possibilities 1) a conclusion of NMDR or 2) that more work was needed.

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[2] Beausoleil C, Beronius A, Bodin L, Bokkers BGH, Boon PE, Burger M, Cao Y, De Wit L, Fischer A, Hanberg A, Leander K, Litens-Karlsson S, Rousselle C, Slob W, Varret C, Wolterink G and Zilliacus J, 2016. Review of non-monotonic doseresponses of substances for human risk assessment. EFSA Supporting Publications, 13:1027E. doi: 10.2903/sp.efsa.2016.EN-1027.

88. Ethical justification was needed for the increased animal use that would be necessary in order to have sufficient data points to fully explore non-monotonicity. Moreover, possible confounders should be taken into account, and the study design reviewed carefully before committing further resources to investigating possible non-monotonicity.

89. It was unclear whether the Scientific Committee's view was that there were additional data on apical effects suggesting that relevant NDMR do occur; and, if this was the case, then it was unclear why these were not considered in the earlier reports. Conversely, if the data suggested these effects do not occur, then it appears to be unclear why there is emphasis later on the need to consider the possible implications of NMDR at low doses, which should be investigated on a case by case basis (e.g. "in cases where biological considerations or previous results suggest that NMDR may be present"). Hence, the overall message of this opinion could be clearer.

90. It would have been useful to group the recommendations together, rather than have them appear throughout the document.

Item 11: COT annual report (TOX/2021/10)

91. The draft text of the COT section of the "2020 Annual report for the Committees on Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment" was presented to Members.

92. Members were invited to submit minor and editorial comments on the information presented in the annual report to the Secretariat.

93. Members were asked to consider how the Committee had performed during 2020, against the Good Practice Guidelines for committees advising the FSA. The Committee considered that, in general, they had adhered to the Good Practice Guidelines.

94. It was noted that the Committee currently works to a defined problem and series of questions but was working with FSA to further improve problem formulation.

95. Where both risks and benefits needed to be considered, the Committee would address each with equal rigour. However, this has not been needed since benefits are not generally in the remit of the Committee and they had not contributed to formal risk-benefit analyses this year.

96. The Committee agreed that where differences of opinion arise during discussions, they would be explained and documented. However, in practice this has not been necessary to date.

97. The COT seeks to ensure that their interpretation of results, recommended actions or advice will be consistent with the quantitative and/or qualitative evidence and the degree of uncertainty associated with it.

98. The COT agreed, in principle, that it would follow the guideline relevant for any consultation with the FSA Board, but this has not yet been needed.

99. The COT Terms of Reference and Code of Practice were being updated and these had been discussed by the Committee. The most recent version of the draft has now been discussed by COM and will be discussed by COC shortly. Any issues that arise following this will be taken forward by the Secretariats as needed and reported back correctly.

100. Members were asked to check that employment details and interests have been recorded correctly and inform the secretariat of any changes.

101. The glossary had been updated by the Secretariats of all three Committees for the 2019 Annual report, and Members were asked to check that they are content with the updated version. Members noted that the detail included for each entry was very variable and discussed whether there should be a more detailed glossary on the Committee websites, which could explain more complex terms or concepts. The glossary included in the annual report could then be more concise. The Secretariat agreed to consider the issue and bring some proposals to the Committee for future annual reports.

102. It was also highlighted that in 2020 the COT had provided assurance for an FSA risk assessment on soya in wheat, rather than produce its own risk assessment. Members were asked to comment, by e-mail, on whether this had been presented appropriately.

Item 12: Horizon scanning (TOX/2021/11)

103. TOX/2021/11 introduced items scheduled to be on the agenda during 2021, and provided other relevant updates including on the FSA research programme, a proposed workshop on new approach methodologies, and the FSA-funded Computational Toxicology Fellowship.

104. The Committee was asked to comment on the listed items, and for any additional suggestions for future topics either as specific issues to be included as routine agenda items, focused topics for one-day open meetings, or generic issues requiring establishment of a Working Group.

105. A Member asked if the item on developments in dietary risk assessment (Item 15) included risks from combined exposures. It was noted that this would be included.

106. It was recalled that a previously-planned microbiome workshop had to be cancelled, and it was agreed that this should be revisited.

107. It was noted that horizon-scanning and self-tasks by the COT were not specifically mentioned in the COT's terms of reference. Members agreed that these should be amended to make clear that self-tasked items were within the COT's

remit. There was suitable wording in the Code of Practice, and the terms of reference should be in line with this.

108. Members were content with the balance of expertise on the Committee.

109. Members were also asked for any proposals for research that FSA should fund in order to improve future COT risk assessments. It was suggested that dietary exposure data for children should be included.

110. Members were reminded that they may draw particular issues to the attention of the Secretariat at any time.

Item 13: Update on actions taken subsequent to COT advice - for information (TOX/2021/12)

111. This paper was provided largely for information. Members agreed that it was helpful to have this update but did not have any specific questions.

Item 14: Update on the work of other scientific advisory committees and AOB (TOX/2021/13)

112. This paper was circulated for information.

Item 15: Any other business

113. Members were informed that work had started between FSA, the Health and Safety Executive (HSE) and the Veterinary Medicines Directorate (VMD) to consider approaches to chronic dietary exposure assessment for chemicals in food. The planned outcome will be a report, which will be brought to the COT for comment.

114. No other business was mentioned by Members or the Secretariat.

Date of next meeting

115. The next meeting of the Committee Meeting will be at 10:00 on the 23rd of March 2021 via Skype and Teams.