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

Meeting of the Committee at 10:00 on 6th of July 2021 on Microsoft Teams

Present		
Chair:	Prof 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 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 Professor Mireille Toledano Dr Simon Wilkinson Professor Philippe Wilson Professor Matthew Wright Professor Maged Younes Prof Paul Haggarty Prof John O'Brien	 SACN Liaison Science Council Liaison
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland Mr Barry Maycock Ms Claire Potter Dr Barbara Doerr Dr Douglas Hedley Dr Joseph Shavila Dr Alex Cooper Dr Olivia Osborne Ms Sabrina Thomas Ms Chara Tsoulli Ms Gail Drummond Ms Frederique Uy Ms Cleanncy Hoppie Ms Emma French Ms Jocelyn Frimpong-Manso	FSA Scientific Secretary

Public Health England (PHE) Secretariat:	Dr David Gott Ms Sophy Wells Ms Britta Gadeberg	 PHE Scientific Secretary
Invited Experts and Contractors: Assessors	Dr Sarah Bull Ms Emma Bradley Prof Tim Gant Ms Frances Hill Ms Susannah Brown Ms Valerie Swaine Ms Rachel Elsom Dr Sam Fletcher Mr Ian Martin Ms Estella Hung	IEH FERA and FCMJEG (Items 3 and 5) PHE BEIS PHE PHE PHE VMD EA PHE
Observers	Ms Caroline Rainsford Dr Steve Ruckman	Cosmetic, Toiletries and Perfumery Association (CTPA) TSG consulting
FSA and other Officials:	Dr Ovnair Sepai Mr Will Munro Ms Marianne James Dr Ovnair Sepai Ms Krystle Boss Ms Akosua Adjei Ms Sharon Gilmore Ms Kerry Gribben Ms Natasha Gladstone Ms Wendy Dixon Ms Firth Piracha Mr Timothy Chandler Mr Vincent Greenwood Ms Azhar Kabli	PHE FSS FSS PHE FSS MHRA FSA NI FSA NI FSA FSA FSA FSA (Items 3 and 5) FSA (Items 3 and 5) FSA

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	Date of the next meeting	7th September 2021

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. No apologies were received.

Item 2: Draft Minutes from the meeting held on 4th of May 2021 (TOX/MIN/2021/03)

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

Item 3: Matters arising from the meeting held on 4th of May 2021

Plant based drinks: Proposed Joint COT and SACN Working Group (Reserved) (TOX/2021/28)

5. The COT recently published a Statement on the consumption of plant-based drinks by young children. The review was undertaken at the request of Public Health England (PHE) and the Department of Health and Social Care (DHSC) as a result of the increasing popularity of these drinks for individuals wishing to avoid dairy products. In addition, the Scientific Advisory Committee on Nutrition (SACN) Subgroup on Maternal and Child Nutrition (SMCN) had considered the nutritional implications of plant-based drink consumption by children under 5 years of age.

6. Members discussed the possibility of establishing a joint working group with SACN to bring together the toxicological and nutritional aspects of this topic. The minutes of this discussion are currently reserved as they refer to SACN minutes which are not yet in the public domain. They will be published in due course.

Conclusions of the Overarching Statement and Addendum on the potential risks from contaminants in the diet of infants aged 12 to 60 months – Summary tables for SACN; and editorial update on the conclusions on arsenic (TOX/2021/29)

7. Following discussions at the SACN meeting on the 17th of May 2021, SACN Members noted that the phrase “commercial infant foods could cause concern” and queried whether the wording could be amended to specifically identify the key source.

8. The COT agreed the editorial update for arsenic, but asked for clarification to be added on which forms of milk the FSA advice on substitution by rice milk referred to[1].

Addendum to the statement on potential risks from ochratoxin A (OTA) in the diet of infants aged 0 to 12 months and children aged 1 to 5 years (TOX/2021/30)

9. Over the past few years, SACN have undertaken a review of scientific evidence to inform the UK Government's dietary recommendations for infants and young children. The COT were asked to review the risks of toxicity from chemicals in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. The assessment of ochratoxin A (OTA) was part of the COT's review and the statement on OTA was published in 2019.

10. In 2020, the European Food Safety Authority (EFSA) updated their 2006 assessment on OTA in food and concluded that due to the uncertainties surrounding the genotoxic/carcinogenic mode of action, it would not be appropriate to establish a health-based guidance value (HBGV) and applied a margin of exposure (MOE) approach instead.

11. Following the update by EFSA, the imminent publication of the SACN report and the ongoing work on plant-based drinks (which includes consideration of OTA), the MOE approach had been applied to the 2019 exposure assessment, which utilised the BMDL10s for non-neoplastic and neoplastic effects calculated by EFSA.

12. Members noted some inconstancies in the results of the benchmark dose (BMD) modelling of non-neoplastic effects by EFSA. While this might be due to the change of approach, from single models to model averaging, the derivation of the confidence intervals lacked transparency. Hence the COT agreed it would be useful to obtain a second opinion on the BMD modelling for non-neoplastic effects.

13. Members noted that EFSA's conclusions were based on a conservative assessment of the data. The negative findings of mass spectrometer data on DNA binding would suggest that the evidence of DNA reactivity is minimal to zero, and an MOE of > 10,000 for neoplastic effects may therefore be overly conservative, given the potential threshold mechanism of OTA. The Committee concluded it would be useful to obtain the views of COC and COM on the uncertainties surrounding the carcinogenicity and possible genotoxic mechanism of OTA.

Update on SMCN

14. SMCN held a meeting on the 30th of June, where the outcome of the discussions on the prioritisation of components in the maternal diet at the May COT meeting was reported.

[1] Post meeting note. The text has been updated to read "Consumption of infant or "adult" rice cakes did not indicate an increased risk, while the COT concluded that the current FSA advice not to use rice drink as substitute for breast milk, infant formula or cow's milk should remain in place".

15. SMCN were largely content with the COT's stance on alcohol, although noting that there was some literature on the effect of alcohol on nutrition. The WG decided that alcohol should not be a priority.

16. The possibility of reviewing whole foods was mentioned; a SMCN Member had noted that this had been raised but said COT's remit was looking at constituents separately. Tea was mentioned as a possible priority since there was some literature on its effects on hypertension and it might be heavily consumed by some ethnic minority groups. It was questioned whether there were any differences between raspberry leaf tea and black tea that needed to be considered. The COT Chair noted that assessment of the toxicological risks of whole foods was within the remit of COT, despite the complexities involved. However, COT would need to consider each major constituent of potential concern and furthermore examine aggregate exposure from different food sources. This could be illustrated by large oily fish, where the COT would need to consider contaminants such dioxins and methylmercury separately. Regarding raspberry leaf and tea - the nature of these products was somewhat different. Here, the chemical constituents will vary, and this requires appropriate assessment of respective major components.

17. The SMCN WG agreed that oily fish should be considered - not as an entity in itself, but in the context of dietary contaminants (i.e. within the dioxins and mercury sections as appropriate).

18. The SMCN WG agreed that phthalates should probably be considered, and PFASs should also be considered if this was the view of the COT.

19. No timeline for the maternal diet work has been published by SACN.

20. The SMCN WG thanked the COT and the Secretariat for their continuing work on this project.

UK New Approach Methodologies Roadmap (TOX/2021/31)

21. The future of the safety assessment of chemicals in food depends on adaptability and flexibility in using the best scientific methodologies and strategies available to respond to the accelerating developments in science and technology.

22. In order to achieve this, the FSA and COT have developed a UK New Approach Methodologies (NAMs) roadmap towards acceptance and integration of NAMs including predictive toxicology methods using computer modelling into safety and risk assessments for regulatory decision making. The latest draft of the UK roadmap was presented in TOX/2021/31

23. Building on the March 2019 COT workshop where NAMs were discussed, Members were informed that the FSA were planning to organise a further workshop sometime later this year.

24. The Committee endorsed the roadmap and the proposed workshop, and furthermore congratulated the FSA for taking the lead in this area. The Secretariat

noted that the roadmap would involve engaging with other government departments and regulatory bodies.

25. COT Members highlighted some organisations and projects which also have an interest in this area and could be involved.

PBPK workshop

26. The Secretariat reported to the Committee that an academic journal has been selected to which to submit the report of the 'PBPK for Regulators Workshop' that was held in March 2020. The Secretariat was expecting to submit this report to the journal in the summer.

Update on JEGs and Regulated products

27. The Secretariat provided the Committee with an update on the activities of the Joint Expert Groups (JEGs). Members were informed that most of the regulatory product applications received to date were novel food authorisations for cannabidiol (CBD).

28. The Animal Feed and Feed Additives Joint Expert Group (AFFAJEG) had been working on feed authorisations but there was nothing for COT to discuss at present.

29. The Joint Expert Group on Additives, Enzymes and other regulated products (AEJEG) were expecting to receive additive applications shortly as applications had been received by FSA. There were also some risk assessment requests related to supplements which were likely to be presented to COT in the Autumn.

30. The Joint Expert Group for Food Contact Materials (FCM JEG) reviewed two applications relating to recycling processes at their last meeting. Further information has been requested so there was nothing for COT to review at present. The FCM JEG's position paper on ocean bound plastic was on the agenda later in the COT meeting.

FCM JEG Interim Position Paper on ocean bound plastic (Reserved) (TOX/2021/32)

31. The Committee discussed the potential use of ocean bound plastics in food packaging. As this item relates to developing policy, these minutes are currently reserved and will be published in due course.

Item 4: Position paper on the alternatives to conventional plastics for food & drinks packaging (TOX/2021/33)

32. No interests were declared

33. Recent years have seen a major global increase in the development and use of alternative biobased materials to conventional plastics for food & drinks packaging. Risk assessment advice on biobased food contact materials (BBFCMs)

has been increasingly requested from the FSA so it was therefore considered timely for COT to review the available toxicological information on BBFCMs.

34. To date, the Committee have discussed the prioritisation of the different materials that could be reviewed and have started to review chitosan. It was thus considered appropriate for a position paper to be published on the COT's work on the alternatives to conventional plastics.

35. The position paper summarises the preliminary discussions of the COT and their planned future work, including the reasons for prioritising individual BBFCMs that are recommended for further review.

36. Members agreed with the overall structure and scientific content of the draft position paper. Members agreed that minor editorial changes could be cleared by Chair's action.

Item 5: The potential human health risks of bamboo bio-composites in food contact materials (TOX/2021/34)

37. No interests were declared.

38. Bamboo and bamboo filler are not currently authorised for use as additives within Annex I of EU Regulation 10/2011 on plastic food contact materials. However, coffee mugs, kitchenware, and utensils derived from bamboo composites are currently sold to both the EU and UK, where they are marketed as sustainable, recyclable, natural, and eco-friendly. Although they contain variable proportions of synthetic plastics, several companies appear to have mislabelled these items as either 'eco-friendly' '100% natural', '100% bamboo' or 'fully compostable' (EU Commission Regulation 10/2011). Recently, the safety assessment and legislation covering bamboo-plastic composite coffee cups was raised, owing to an increasing number of incidents of non-compliant products with respect to formaldehyde/melamine content. Additionally, interactions between bamboo and melamine could result in increased migration levels of formaldehyde and melamine monomers.

39. Following the issued EFSA Opinion and the European Commission's Position on bamboo plastic composite FCMs not being covered by a current authorisation in the EU, the COT was asked to examine the toxicological risks arising from the use of bamboo in composite plastic FCMs.

40. Members noted that they would like to know of any expected changes to the relevant UK policy. Members of the FSA FCM Policy team informed COT Members that bamboo composites were bought to the attention of the European Commission (EC) 2-3 years ago. The EFSA panel on FCMs was asked by the European Commission to assess whether the authorisation of untreated wood flour and fibres (FCM no. 96) was still in accordance with EC Regulation 1935/2004, and also to consider whether bamboo could be considered under the scope of this authorisation. EFSA concluded that wood and bamboo should be considered distinct and each material regarded on a case-by-case basis. Also, the food safety authorities of

Belgium, Luxembourg and the Netherlands (Benelux) published a joint letter calling for the market withdrawal of bamboo-melamine plastics. In April, the EC recommended that Member States should take stringent action on bamboo FCMs and set out a coordinated control plan. The UK FSA is aware of the stance by the EC and of the individual Member States and is considering an appropriate course of action based on emerging evidence.

41. Members discussed the migration and leaching behaviours of bamboo plastic composite food contact materials and considered to what extent this was time-dependant, and whether the amount of leaching increased or decreased over time.

42. Members commented on the potential confusion in reporting of formaldehyde blood levels. The concentration of 0.1 µM formaldehyde in blood measured in humans, rats, and monkeys exposed to formaldehyde in several studies was the (non-significant) incremental increase after exposure to formaldehyde (Cassonova *et al*., (1988); Heck *et al*., (1982); Heck *et al.*, 1985). In another study the levels of formaldehyde in human blood stated, of around 2.6 mg/L (87 µM), was the baseline level, consistent with the baseline values found in the other studies.

43. The Netherlands Food and Consumer Product Safety Authority (NVWA) concluded that plastic FCMs such as coffee cups and children's tableware should not be placed on the market. The Committee understood that the NVWA Opinion was emphasising the EU regulation and was not based on a specific health risk assessment.

44. The Committee was informed that a study[2] assessing the health risks associated with bamboo-based packaging and other biobased materials is currently in progress. This study aims to assess migration levels of formaldehyde and melamine and other risks associated with bamboo such as accumulation of heavy metals and pesticides. The Committee agreed that it would be more appropriate to conduct a risk assessment once these data were available.

45. Members asked for the exposure data from the German Federal Institute for Risk Assessment (BfR) and the Netherlands Food and Consumer Product Safety Authority (NVWA) reports to be assessed separately and more critically.

46. Members were asked whether there was a need to increase consumer awareness of the compounds present in bamboo composites. The Committee agreed that consumers need to be aware that there is a potential health risk to bamboo composite FCMs.

Item 6: Second draft statement on PFASs (TOX/2021/35)

47. Professor Alan Boobis declared that he had been involved in the Society of Environmental Toxicology and Chemistry (SETAC) North America workshop report on exposure to and toxicity of perfluoroalkyl substances (PFASs). This did not

[2] The study is not in the public domain so further details have not been provided at this time.

preclude full participation in this item. Professor Thorhallur Ingi Halldórsson had been a Member of the EFSA CONTAM Panel for the Opinion on PFASs (2020); it was agreed that he would be able to contribute to the discussion of this item but not to the conclusions.

48. EFSA had been asked by the EC to prepare an opinion on the risks to human health related to the presence of PFASs in food, and to consider existing hazard assessments and available occurrence data. The COT is reviewing this opinion and will publish a statement in due course.

49. The draft EFSA opinion was put out for public consultation in March 2020 and was discussed by the COT at their meeting in March 2020 and at a subsequent meeting in April 2020 when the research papers used in establishing the EFSA recommendations were published. Following these meetings, a first draft statement was presented to the COT in December 2020.

50. Following the COT's discussions, a second draft statement was presented to Members for discussion as paper TOX/2021/35, which included changes requested by the Committee. These included addition of contextual information on PFASs, estimates of exposures from dust, air and drinking water, and more detailed descriptions of the uncertainties regarding the hazards and the exposure estimates.

51. The COT discussed the toxicity and epidemiology studies reviewed by EFSA and requested that the conclusions in the draft statement be revised to better reflect the outcomes of the studies and the weight of evidence for each endpoint.

52. One Member mentioned that additional immunotoxicity studies had been published and considered whether these should also be included in the draft statement to reflect the uncertainty surrounding the mechanism of action of PFASs. However, it was agreed that the COT were focussing on the EFSA opinion and were not reviewing the database for PFASs.

53. There was also a request to consider more carefully the way the conclusions regarding birth weight were worded. Some populations were already at risk of low birth weight. The additional exposures from PFASs could potentially result in a clinical outcome of low birth weight, which would not have been the case without these exposures.

54. When presenting the exposures for dust and air, it was agreed that averages for exposures for the four PFASs could be added together to provide a reasonable estimation of combined PFASs exposure for comparison to the TWI.

55. Additional minor editorial changes were requested for inclusion in the draft statement.

56. It was agreed that the draft Statement could be finalised by Chair's action.

Item 7: Review of EFSA opinion on TiO2 (TOX/2021/36)

57. 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, 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.

58. Dr Stella Cochrane and Dr Natalie Thatcher declared personal non-specific interests as they work for companies that use titanium dioxide in their products; it was agreed that they could contribute to the discussion of this item. Professor Matthew Wright and Professor Maged Younes were Members of the EFSA Scientific Panels that reviewed the safety of titanium dioxide for the 2021 Opinion. They were available to answer COT Member's questions and offer clarifications on the EFSA Opinion, however they did not participate in the COT's discussion or conclusions.

59. Titanium dioxide is an authorised Food Additive (E171) in the EU and 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. In 2016, EFSA evaluated the safety of E171 and determined that it consisted mainly of micro-sized titanium dioxide particles, with a nano-sized (< 100 nm) fraction less than 3.2% by mass. Uncertainties around the identity and characterisation of E171 were highlighted, noting that no limits for the particle size of E171 were set in the EU specifications. Similarly, with regard to toxicity, uncertainties around the identity and characterisation of E171 were also highlighted.

60. In 2019, the specifications of E171 titanium dioxide were reviewed. Based on the fraction of nanoparticles present in E171, the food additive fell under the scope of the EFSA guidance on nanotechnology for "a material that is not engineered as nanomaterial but contains a fraction of particles, less than 50% in the number–size distribution, with one or more external dimensions in the size range 1–100 nm" and a recommendation for re-assessment of the safety of titanium dioxide was proposed and as a result a new EFSA Opinion was published in May 2021.

61. In the opinion, the available lines of evidence from the genotoxicity studies were combined and the Panel concluded that titanium dioxide particles have the potential to induce DNA strand breaks and chromosomal damage, but not to cause gene mutations. No clear correlation was observed between the physico-chemical properties of titanium dioxide particles – such as crystalline form, size of constituent particles, shape and agglomeration state – and the outcome of *in vitro* or *in vivo* genotoxicity assays (i.e. a cut-off value for titanium dioxide particle size with respect to genotoxicity could not be identified). The Panel concluded that several modes of action (MOA) may operate in parallel and the relative contributions of the different molecular mechanisms resulting in the genotoxicity of titanium dioxide particles are unknown. Based on the available data, no conclusion could be drawn as to whether the genotoxicity of titanium dioxide particles was mediated by a mode (s) of action with a threshold(s). On the other studies, they considered that some findings regarding immunotoxicity and inflammation with E171 as well as neurotoxicity with TiO2 nanoparticles may be indicative of adverse effects. They also considered that

there are indications of the induction of aberrant crypt foci with E171 and that no studies appropriately designed and conducted to investigate the potential carcinogenicity of TiO_2 nanoparticles were available. Overall, on the basis of the currently available evidence along with all the uncertainties, in particular the fact that the concern regarding genotoxicity could not be resolved, the EFSA Panel concluded that E171 can no longer be considered as safe when used as a food additive.

62. In June 2021, a paper discussing the EFSA Opinion was presented to the Committee on Mutagenicity (COM), focusing on the genotoxicity studies. The preliminary notes of the discussions and conclusions of the COM were included in paper TOX/2021/36 for consideration.

63. The COT highlighted the COM's preliminary comments. In particular that the COM had questioned the quality of the data and noted the difficulties in evaluating it adequately from the description given in the opinion. The COM raised questions over the robustness of the data, the use of data from labs not proficient in genotoxicity studies in a regulatory context and the weight given to studies with low reliability scores. The lack of a good dataset and a well-defined test compound (due to the poorly defined specifications) were also considered as severe limitations. The COM considered the mechanism of genotoxicity appeared to be indirect and probably had a threshold. The COM considered that the positive effects could be attributed to the nano-fraction, which accounts for only a small fraction of E171 titanium dioxide by weight. Overall the COM considered that based on the quality and equivocality of the dataset, further evaluation was needed before a conclusion on the safety of TiO2 with regards to genotoxicity could be confidently made. They did not find EFSA's wording of the conclusion helpful, due to the lack of good database that would allow firm conclusions.

64. The COT agreed with the COM and noted the large discrepancy between the underlying dataset and the conclusions drawn by EFSA. On the genotoxicity of nanoparticles, it was noted that this could either be a concentration effect leading to oxidative damage or a stress effect, however, it was unclear as the results in different cell lines were equivocal and inconsistent. It was also noted that in some tests titanium dioxide had shown less reactivity. Members were informed that EFSA considered that genotoxicity was most likely due to an indirect mode of action however it was difficult to determine a threshold due to the multiple pathways that might act in parallel and that the conclusion erred on the side of caution. It was also acknowledged that the greater the nanoparticle content present in the test material, the more likely that the outcome of the study was to be positive.

65. The COT noted that in several parts of the Opinion, published papers were presented at face value, however there was no discussion of the results nor the Weight of Evidence to support the conclusions being made. They furthermore noted discrepancies and conflicts between the results of the studies reported and the overall conclusions. For example, in certain parts whilst the results were inconsistent between studies, the conclusions reported that clear effects were observed. For example, there were discrepancies in the conclusion of the effects of E171 on the immune system. Additionally when acetylcholine inhibition was being evaluated, no discussion was presented on the sensitivity of inhibition. In one study there was a flat curve of response, a second study claimed marked effects in the histopathology with

response at the high level of dosing whilst a third study dosed at higher levels reported no effects. However there was no discussion of these results nor their weighing in the evaluation was presented. Overall, the COT considered that there was a lack of internal consistency and objective weighing of the evidence. While some of this might have been due to differences in the nature of the TiO_2 tested, this was not clear in the Opinion.

66. For example, with regards to nanoparticulate TiO_2, it was noted that the compound comes in two forms - the anatase and rutile forms, and some of the toxicity could be driven by the form tested. It was noted that the majority of the material was in anatase form and there was evidence that a high amount of residual contaminants could exist in this, which had not been considered. It was therefore difficult to draw any conclusions from the studies and a closer look in terms of material characterisation was needed in order to understand some of the effects reported. Members also considered that follow up was needed on the reproductive toxicity study as only the presence or absence of an effect was measured.

67. Members noted that in Appendix W of the Opinion, which presented the reported data on the analysis of pristine E171, it appeared that in the samples collected, more than 50% of the constituents were in the nano-range so more clarification was needed on the actual composition of E171. In another part of the discussion, it was also acknowledged that EFSA considered that the E171 specifications allowed for a large number of nanoparticles to be present and a completely new database on the current specifications was needed. It was noted that the EFSA definition of nanomaterials lacked clarity with regard to materials that were not engineered as nanomaterials but contained particles in the nano range. The possibility and plausibility of removing the nano fraction from E171 in order to mitigate the risk was also discussed by the COT.

68. With regard to absorption, it was noted that there was no reason to believe that titanium dioxide particles behaved differently to other particles in the gastrointestinal tract. It was also observed that the percentage of absorption was reported to be higher in the 2021 opinion, based on the same dataset considered previously. It was clarified to Members that newer studies used in the previous evaluation were re-considered (evidence from deceased humans and indications that titanium dioxide could cross the placenta). The duration of the animal studies was not sufficient to evaluate at which levels steady state would be reached and therefore it was considered that absorption had previously been underestimated. Finally, the extended one generation reproductive toxicity (EOGRT) study provided indirect evidence for systemic exposure following administration of titanium dioxide.

69. Members were informed that EFSA had indications that when used by industry E171 was dispersed into nanoparticles by sonication and therefore also considered data on materials made solely of nanoparticles for the assessment. However, this was questioned by Members as it was noted that pure nano-titanium dioxide would lose its technical function in the food (as it would not provide colour) and would therefore not be of use. It was also noted that in the only study in which aberrant crypt foci were reported, the material tested was sonicated, whilst the other studies used undispersed material and, as EFSA considered that sonification/dispersion could happen, only the one study was used for evaluation.

70. The findings of the studies on neurotoxicity were considered inconsistent by the COT. It was noted that the EOGRT study did not report any effects and that most of the other studies on this endpoint were of nanomaterials. It was clarified to Members that in the EFSA evaluation, the issue of the test material in the EOGRT not being dispersed was taken into consideration with regards to the conclusions on this endpoint, as they considered that had it been dispersed and stabilised in the nano form some effects could possibly have been observed. The COT, as previously, questioned the relevance of such dispersion to real world use. Members noted that the histopathology tests performed for the EOGRT study were standard and were not sensitive enough in comparison to other studies on this endpoint that performed specific neuro-histopathology testing.

71. On balance, the Committee considered that the weight of evidence did not support the conclusions drawn by EFSA. The COT also agreed with the comments of the COM with regards to risk communication that “As it stands the conclusion is highly risk adverse based on the weak evidence available, and it might create unnecessary concern to the public.” They considered that care should be taken when expressing the conclusions as they might cause unnecessary concern and they were uncomfortable with EFSA’s binary communication on a dataset with a lot of uncertainties. They highlighted that the COT does not follow the precautionary approach and reiterated that there is a lot of uncertainty on genotoxicity. The COT suggested that the COM should independently review the database on genotoxicity and apply the COM’s Guidance on determining thresholds. When considering whether they agreed with EFSA’s conclusion that no differentiation could be made with regards to size/form of titanium dioxide and different aspects of toxicity, the COT erred towards the view that nanoparticles were driving the toxicity. It was decided that an interim position paper, capturing the COT’s view and the proposed next steps should be published.

Item 8: Draft report on the synthesis and integration of epidemiological and toxicological evidence in risk assessments (SETE) (TOX/2021/37)

72. Following the publication of the SEES report, the Synthesis and Integration of Epidemiological and Toxicological Evidence (SETE) subgroup was formed to report, in a transparent fashion, the approaches taken by the Committees for assessing epidemiological and toxicological evidence and furthermore to provide practical guidance on how to integrate the two evidence streams.

73. The second draft report presented in paper TOX/2021/37 contained some minor editorial updates to the considerations and deliberations of the SETE subgroup, and following the discussion of the first draft of the report by COC and COT in March 2021, along with practical examples applying the procedures for the integration of evidence and SETE guidance.

74. Members agreed that the report would benefit from additional text highlighting that the visualisation of causation moves away from a probabilistic/ numerical approach. Instead, it represented the influence of the different lines of evidence on causation, assessed by debate and agreement of scientific experts. The section on

methods of epidemiological assessment currently discusses binary outcomes only, and thus text will be added to include continuous outcomes.

75. The COT endorsed the report and guidance of the SETE WG and stated that they were excellent documents and presented a more pragmatic approach compared to other similar approaches.

76. Going forward, the COT recommended that the guidance on integration be tested by the Committees on upcoming assessments and to publish a shorter paper in a peer-reviewed journal.

77. Members were informed by the Secretariat that the SETE report had been accepted for poster presentation at EUROTOX 2021.

Item 9: Sub-Statement on the potential risks from exposure to microplastics: oral route (first draft) TOX/2021/38

78. Due to time constraints, COT Members agreed that this Item could be postponed to the next COT meeting.

Item 10: Draft EFSA Scientific Committee Opinion on scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals (TOX/2021/39)

79. No interests were declared.

80. EFSA has released draft guidance, prepared by its Scientific Committee, on the grouping of chemicals for risk assessments of combined exposure, to which an assumption of dose addition would apply. The consultation closes on the 10th of July 2021 and Members comments would be submitted. The Secretariat thanked Members who had submitted comments in advance of the meeting.

81. The Committee agreed that the proposed guidance provides a pragmatic and scientifically sound approach for grouping chemicals for a combined risk assessment.

82. Members noted that there were several reviews on combined risk assessment for chemicals, for example considerations by the OECD in 2018. One aspect detailed in the OECD paper was the principle of response addition (also known as independent action), for chemicals which do not have the same mode of action (MOA) (or follow the same adverse outcome pathway (AOP)). Such chemicals are treated separately for risk assessment, as there was no scientific case for doing a combined risk assessment. Although the scientific criteria for dose addition were provided in the draft EFSA guidance, the underlying assumption of dose addition is not clearly stated. If the criteria for dose addition are met, and there is sufficient information on MOA, the MOA may not necessarily be relevant to humans.

Moreover, if the criteria for dose addition are not met, is the reader left to assume that the principle of response addition should be used instead? There does not appear to be any consideration of antagonism or synergy in the text, though "antagonism" is covered in the Glossary. It would be useful to consider the relevance, or otherwise, of these somewhere in the text as different types of interactions.

83. The Committee clarified that if information on key events is not available, then the guidance is to group chemicals based on a common adverse outcome. Computational tools, such as those developed under the EuroMix project and the OECD toolbox, can be used to predict adverse outcomes for data-poor chemicals; however, chemical grouping done with such information is associated with greater uncertainty. The potential application of these computational tools could be better reflected in the EFSA guidance.

84. In respect of hazard-driven criteria, the Committee agreed with the sorting of different chemicals into assessment groups on the basis of common key events. However, the Committee noted that for data-poor chemicals, this may result in the formation of very large chemical assessment groups (CAGs), particularly if grouping is done on the basis of adverse effects, such as potential liver effects.

85. The Committee agreed that *in vitro* and *in silico* methodologies may be used to identify not just key events but wider AOPs. For example, if there are different AOPs at play, this may be helpful for managing and breaking down large CAGs. The weight of evidence approach is particularly important here, for example two chemicals may act on the same key event *in vitro* (or *in silico*) but may not share the same adverse outcome, because of very different target tissue exposures.

86. The Committee recognised that key event responses must reach a certain magnitude before an AOP is propagated. For example, a receptor must be activated to a certain level before a cellular response is triggered. Different implications seem to arise when this process is considered in the context of a biologically-based dose response approach, or a population-based dose response approach. Additionally, the Committee anticipated that with the proliferation of AOP networks (as opposed to individual AOPs), the likelihood of multiple chemicals hitting different key events within the AOP network will increase dramatically. Subsequently, it may become more difficult to exclude a chemical from a grouping when using this approach without additional considerations.

87. With regards to the prioritisation methods for grouping chemicals into assessment groups, the Committee noted that the default threshold values appeared to be rather arbitrary, and not entirely supported by scientific data. However, they provide a starting point, and the guidance provides some caveats to move away from these values in certain situations. The Committee recommended that the threshold values are tested, and re-evaluated after some time. For example, does the use of these values result in very large CAGs, which are not practical or feasible to assess?

88. The Committee recognised that the exposure-based prioritisation approach is particularly useful in instances where occurrence or consumption data are unavailable. In the guidance document, EFSA notes that the exposure-based

approach has a drawback since potent compounds with a low probability of co-exposure might be excluded from grouping. The Committee considered whether, in the absence of hazard information of the chemicals involved, there is any way to gauge the potency of such chemicals. The Committee noted that there are some possibilities such as the read-across approach. The read-across approach, however, is not always well accepted within the regulatory community. The Committee also recognised that there comes a point when the exposure is so low that potency does not matter. Indeed, this is the basis of the threshold of toxicological concern (TTC). Although the TTC is arguably not relevant to attribution of chemicals to assessment groups (and indeed, is not referred to in the EFSA guidance), perhaps the TTC could nevertheless be used as a point of departure in low-tier assessments.

89. The Committee noted that whilst the breast milk example in appendix E is a good example of co-exposure, it is not assessing the same type of key events or effects. Furthermore, the exposure-based approach for prioritisation for risk assessment needs to be a more iterative (rather than linear) process, where the inputs need to be revisited throughout the entire process.

90. Regarding appendix C (statistical methods to study the probability of combined risk or combined exposure), the Committee noted that this appendix is not directly referred to in the guidance document. It would be useful to have some examples where these statistical methods are used, such as use of correlation matrices for multivariate pattern analysis. Furthermore, the Committee noted that it may be possible to obtain a high probability of co-exposure ('r' value) from assessment of a low number of chemicals.

Item 11: Paper for information: Update on the work of other scientific advisory committees (TOX/2021/40)

91. This paper was circulated for information.

Item 12: Any other business

Impact of updated BMD modelling methods on perchlorate and chlorate assessments of human health hazard – Haber et al. 2021 (TOX/2021/41)

92. A recent publication by Haber *et al*. (2021) entitled "Impact of updated BMD modelling methods on perchlorate and chlorate assessments of human health hazard" had been brought to the Secretariat's attention by HSE (informally) via a Member of the Expert Committee on Pesticide Residues in Food (PRiF).

93. Two COT Members provided comments on the paper in advance of the meeting, which were circulated to the COT.

94. The Committee noted that the authors criticised the standard method, however the new approach requires specialist knowledge as well as justification for applying different parameters. The main differences between the approach presented by Haber *et al.* and previous modelling approaches (e.g. PROST) does

not lie in the modelling itself but in the definition of the benchmark response (BMR). It did, however, highlight a more general discussion on how different modelling assumptions on the same data set can lead to different results.

95. Members noted the method had not been formally approved yet. Members also queried whether other research groups (using the same modelling approach, but with different underlying assumptions) could reach different outcomes. The main question was therefore whether there is sufficient evidence in the approach to merit further investigation, considering the conservatism in the EFSA approach.

96. Due to the residues of chlorate on fruit and vegetables after washing, there may be potential exceedances of the current HBGVs, hence why the paper came to PRiF's attention in the first place. The COT noted that the current advice is conservative, and agreed that consideration is required on how concerns regarding exceedances will be addressed.

97. Members agreed that it would be useful to obtain some guidance from FSA policy colleagues as to whether there is a concern about the adequacy of the advice given by the FSA. Previously, the COT had agreed that the basis for EFSA's HBGV was adequate for risk assessment, but had noted the associated uncertainties and acknowledged that if there were potential safety concerns about the exposures this would warrant considering the dose-response again and a closer assessment of the modelling approaches.

98. There was no additional AOB.

Date of next meeting

99. The next meeting of the Committee will be at 10:00 on the 7th of September 2021 via Skype and Teams.