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

Meeting of the Committee at 10:00 on 27th October via Skype and Teams

Present

Chair:	Prof Alan Boobis	
COT Members:	Dr Phil Botham	
	Dr Caroline Harris	
	Dr René Crevel	
	Prof Gary Hutchison	
	Dr David Lovell	
	Dr Mac Provan	
	Prof Faith Williams	
	Dr Michael Routledge	
	Dr Cheryl Scudamore	
	Dr Natalie Thatcher	
	Prof Matthew Wright	
	Prof Gunter Kuhnle	
	Prof John Foster	
	Dr Stella Cochrane	
	Ms Jane Case	
	Ms Juliet Rix	
	Prof Mireille Toledano	
	Prof John O'Brien	
	Dr James Coulson	
	Prof Maged Younes	
	Prof Philippe Wilson	
	Prof Paul Haggerty	SACN Liaison
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland	FSA Scientific Secretary
	Dr David Gott	
	Ms Jocelyn Frimpong-Manso	
	Dr Alex Cooper	
	Dr Douglas Hedley	
	Dr Barbara Doerr	
	Mr Barry Maycock	
	Ms Cleanncy Hoppie	
	Dr Olivia Osborne	
	Dr Joseph Shavila	
	Ms Chloe Thomas	
	Ms Sabrina Thomas	
	Ms Chara Tsoulli	
	Ms Frederique Uy	
	Ms Aisling Jao	

Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Invited Experts and Contractors:	Dr Ruth Bevan	IEH
Assessors:	Ms Valerie Swaine	Health and Safety Executive
	Prof Tim Gant	PHE
	Ms Gillian McEneff	Department for Business, Energy and Industrial Strategy (BEIS)
	Mr Sam Fletcher	Veterinary Medicines Directorate
	Ms Liz Lawton	Department for Environment Food and Rural Affairs (DEFRA)
	Dr Daphne Duval	PHE
FSA and other Officials:	Mr Vince Greenwood	FSA
	Dr Alan Dowding	FSA
	Dr David Mortimer	FSA
	Ms Bethan Davies	PHE
	Mr Liam Johnstone	BEIS
	Ms Krystle Boss	Food Standards Scotland (FSS)
	Ms Kerry Gribben	FSA NI
	Ms Natalie Coles	FSA
	Mr Richard Annett	FSA NI
	Mr W Munro	FSS
	Dr Ovnair Sepai	PHE

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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 Sarah Judge and Claire Potter of the Secretariat.

Item 2: Minutes from the meeting held on 15th of September 2020

4. On the list of attendees, Professor Philippe Wilson was omitted but had attended. Dr Ovnair Sepai was present for part of the meeting and should also be added to the list. Dr Tim Marczylo was not present and should be removed from the list.

5. For item 6 (TOX/2020/42), Members agreed that the passage in parentheses in paragraph 67 ("although the allergen may not be a chitin/chitosan hapten") should be deleted.

6. All other items were accepted without revision.

7. The reserved Minutes for item 10 (COT Guidelines) were accepted without revision.

Item 3: Matters arising from the meeting held on 15th of September 2020

COT meeting 27th October – paragraph 13

PBPK workshop

8. The planned PBPK workshop would go ahead as an all-day virtual event on Wednesday 2nd December 2020, with email invitations, agenda and handbook being distributed in due course. There would be an optional interactive session after lunch followed by an afternoon presentation.

Exploring Dose Response Workshop

9. As Members had requested, the report of the March 2020 Exploring Dose Response workshop had been revised to expand the discussion panel sections, and these had been cleared with the presenters. The revised report would shortly be

circulated to Members for comment. A summary report of the workshop would also be prepared for potential publication.

Microsoft Teams

10. The majority of Members had been added to the COT Teams site and were able to access shared documents but any Members that had not already done so were asked to check whether they had access to Microsoft Teams. Members were also asked what information would be useful to store in the Teams site in the future. Teams allowed documents to be shared so it would be possible for a single document to be set up on Microsoft Teams for Members to submit comments. This may help to facilitate collaborative working by COT members. It was agreed that this could be tried with the draft EFSA HBCDD opinion (Item 11).

11. The Committee noted that as multiple users were able to use the platform it could cause confusion when working the same document. Concerns were also expressed that the platform worked slowly when there were multiple different users editing the same document.

12. The Secretariat explained that some email addresses could not be added and ways around this were being explored. The FSA might be willing to reimburse Members for purchasing domains that would supply appropriate email addresses to access Teams.

Item 4: Discussion paper on the approach for the review of the dioxin tolerable daily intake (TDI) TOX/2020/49

13. Following discussion of the EFSA Opinion on dioxins and the implications for risk management at the COT meeting in September 2020, the COT concluded it was necessary to reconsider the evidence base and potentially establish its own Tolerable Daily Intake (TDI). The Secretariat had considered the resource implications, approaches for undertaking the review, and the ongoing work by the working group on Synthesising Epidemiological and Toxicological Evidence (SETE) to map an approach and timelines for this task.

14. The draft guidance being prepared by the SETE working group would become available in the first half of 2021 and that, combined with the work on dioxins, would provide a means for testing the application of the SETE framework. Application in a real life scenario would identify any problems in the guidance, and allow these to be addressed and improved in the final version. It would provide a framework for a new assessment of dioxins by combining epidemiological and toxicological information in a justifiable and transparent manner to establish a TDI.

15. Based on these considerations, and with the agreement of the SETE working group, the Secretariat had produced a proposal for taking this work forward and now sought Members' input and comments on the proposal and subsequent agreement on the best way forward.

16. Members noted that the implications of the new EFSA TDI for dioxins were significant, not only for risk management in food safety but also in other areas such as soil remediation. Given the significance of the issue and implications of advice to authorities post EU exit, and the potential deviation from EFSA's conclusions, the Committee repeated the importance of assessing dioxins using a structured approach to evidence. This would help to ensure that any divergence was based on differences in interpretation of the science set out in a transparent way.

17. Members expressed their hope that by applying the SETE guidance, the review of dioxins would establish a future approach where compounds were assessed in a clear and transparent way taking into account the entire scientific evidence base.

18. Members discussed the nature of the literature review that would be required and noted that it was unlikely that the Committee would identify critical endpoints of toxicity different to those already identified by other authorities. Therefore, Members agreed that, rather than performing a systematic review of the entire literature, it would be more pragmatic and feasible to draw on existing work on dioxins and narrow the literature search to the specific endpoints underpinning the TDI. Members agreed that the carcinogenicity of dioxins was established and that this did not occur by a direct genotoxic mechanism; based on the known dose response, Members did not consider this to be one of the critical endpoints that should be further evaluated.

19. Members discussed the exposure pathways of dioxins. They noted that many human studies involve a sharp initial spike in exposure resulting in a long-term body burden rather than chronic high exposure. Whilst previous assessments assessed only chronic exposure, the critical effect for dioxins may not be solely due to chronic exposure but may be reliant on exposure in sensitive windows of time during organismal development. However, Members questioned whether it would be possible to differentiate the effects of this short-term high exposure in a critical window from long term cumulative exposure. The Committee therefore agreed that it would be necessary to consider the mode of action and available toxicokinetic models. The Committee acknowledged that additional external expertise may be required for these aspects.

20. Members stressed the need for a clear formulation of the scientific questions, including consideration of all risk management concerns, and agreed it would be useful to form a small subgroup to discuss the requirements/problem formulation in more detail. The discussion of the subgroup will be presented to Members at the December COT meeting.

21. Members were asked to contact the Secretariat should they wish to participate in this subgroup.

Item 5: Update on alternatives to conventional plastics for food and drinks packaging TOX/2020/50

22. No interests were declared.

23. 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 provide guidance on the potential toxicological hazards associated with the use of biobased food contact materials (BBFCMs), and to advise on which 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.

24. The Secretariat had agreed to identify the most widely used BBFCMs for further review, and subsequently provided a table of enquiries received from the FSA FCM Policy Team in addition to market data.

25. Members were unable to provide any further guidance on the potential hazards of BBFCMs as there was insufficient information concerning potential hazards or other toxicological data. However, Members discussed the potential for BBFCMs to degrade into microparticles. It was agreed that it would be difficult to draw general conclusions on the physiochemical characteristics of BBFCMs and the corresponding toxicological data due to variable product composition and possible size dependent effects in the gut.

26. The Secretariat highlighted some of the challenges and complexities associated with BBFCMs including labelling, composition (including biodegradability) and standardisation. One Member commented on the possible occurrence of pesticide residues in plant-based packaging. The Committee was informed by the Secretariat that this issue would be covered within relevant standardisation protocols (including contaminants) which were currently being developed.

27. The question of safety assessment and legislation covering bamboo coffee cups was raised, owing to an increase in the number of incidents of non-compliant products with respect to formaldehyde/melamine content noted in the paper. It was explained that the presence of bamboo in BBFCMs was not the issue, but rather the migration of constituent plasticisers, notably melamine Additionally, interactions between bamboo and melamine could result in increased migration levels of formaldehyde. Manufacturers often used conventional plastics alongside BBFCMs. The Committee was informed that biobased materials used for food contact were subject to the same requirements as other materials, under The Materials and Article in Contact with Food (England) Regulations 2012 as amended. For use in the material, whatever its source, the product needs to be safe for the use to which it is put. "Safe" as a concept was not restricted by a specific definition within the legislation.

28. It was noted that composite materials, such as bamboo with a melamine binder, were often labelled simply as being of biological origin which was potentially misleading. However, the plastic component of the material was subject to the existing stringent requirements on chemical migration from food contact plastics. The FSA had a working assumption that the plastics legislation was directly applicable if 50% or more of the article was a polymer resin; whilst that legislation should be

referred to for compliance assurances if under 50%, with non-compliance determined under the general rather than specific provisions.

29. The European Commission had indicated it held a different view, implying that it would consider a product to be a plastic if it contained a percentage composition of less than 50%. Bamboo was not an authorised plastic additive, though the FSA was not currently recommending that such products were removed from the market solely on that basis. The same stance was being taken across Europe given that the EU has not put forward its proposals for handling the expected vast number of applications for the authorisation of such materials, with the majority expected to come from those who are already placing articles on the market. Further details about the transitional measures were essential. In the meantime, enforcement action can be taken on misleading labelling, or if migration levels of specific chemicals exceed Specific Migration Limits.

30. The Committee agreed that there were several limitations and knowledge gaps on BBFCMs research and regulation. Specifically, more conclusive results were needed to ensure that the safety of these packaging materials in direct food-contact applications met appropriate standards, and that the labelling was appropriate. Overall and specific migration data of all possible migrating substances (nanofillers, plasticizers, antimicrobial additives, micron and nano sized particles etc.) under appropriate testing conditions were required to obtain estimates of consumer exposure, and to demonstrate that BBFCMs did not pose an unacceptable risk.
Members requested the Secretariat to produce a prioritisation list based on hazard, extent of use (as a surrogate for exposure data where this information was insufficient), and novelty. In addition, the use of nanotechnology and intelligent packaging (including market share and reflection on trends) in food packaging needed to be reviewed as a next step.

Item 6: Herbal supplements used in pregnancy TOX/2020/51

31. No interests were declared.

32. The Scientific Advisory Committee on Nutrition (SACN) last considered maternal diet and nutrition in relation to offspring health in its reports on ‘The influence of maternal, fetal and child nutrition on the development of chronic disease in later life’ (SACN, 2011a) and on ‘Feeding in the first year of life’ (SACN, 2018). In the latter report, the impact of breastfeeding on maternal health was also considered. In 2019, 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.

33. As part of this work, the COT decided it would be useful to consider the use of dietary supplements during pregnancy. These were supplements that were not officially recommended by relevant authorities, but which were promoted by anecdotal evidence and unofficial sources as having various purported health benefits.

34. Herbal food supplements are products claiming to maintain or support a healthy lifestyle. Such supplements may be used by pregnant women who consider them to be a “safer” alternative to pharmaceuticals, which may be believed to cause adverse health effects to the mother and/or child. They are to be distinguished from, medicinal herbs, which can make a specific medical claim to treat or prevent disease in humans and are regulated as medicines by the Medicines and Healthcare Products Regulatory Agency (MHRA).

35. Following a survey of some popular pregnancy and maternity forums, the following supplements were reviewed as being the most commonly recommended during pregnancy: ginger, chamomile, raspberry leaf, echinacea, peppermint oil and leaves, dandelion, and evening primrose oil. Of the supplements reviewed, ginger, peppermint and raspberry leaf were determined to be most regularly recommended.

36. Paper TOX/2020/51 provided a detailed summary of each of the supplements, focusing on studies relevant to pregnancy and maternal outcomes where available. Members were requested to review the available information provided, and to prioritise the supplements requiring a more comprehensive review.

37. The Committee questioned how much of the data were UK specific. Members also commented on current available advice regarding doses and suggested assessing the dosages at which the supplements were being recommended or taken: clarification would be useful for consumers. In the absence of sufficient quantitative human data, the level of consumption of herbal supplements in the UK required further determination. In addition to use levels, it was noted that to determine maternal exposure, information on the levels of the active ingredients in the supplements was also necessary.

38. The intake of certain supplement ingredients in foodstuffs should also be considered. For instance, ginger was noted to be consumed not only as a supplement but also through the diet in foods such as ginger biscuits, ginger tea and ginger beer. Peppermint was also commonly added as a flavouring in foods. As such, aggregate exposures should be considered when addressing the safety of herbal supplements in pregnancy.

39. With regard to all of the supplements reviewed, the main areas of concern highlighted were general toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with drugs.

40. With regards to individual supplements, the Committee questioned if the effects of ginger were seen throughout pregnancy. It was noted that some studies detailed effects on male testes and, though not relevant for females, they were nevertheless regarded as indicating a potential reprotoxic effect from ginger. Studies suggest that ginger affected the viability of pregnancy; however, with no strong conclusive human data, more work was required, especially as these studies suggested a link between first trimester loss and ginger use. Further, the possible fetotoxicity based on evidence from animal data, genotoxicity and possible drug interactions should be further investigated.

41. The Committee suggested investigating more generally the possibility of medicine-supplement interactions, highlighted in the use of ginger.

42. Members suggested ginger required further investigation, noting that both human and animal *in vitro* and *in vivo* data were available.

43. The Committee agreed raspberry leaf should be considered in more detail, due to its potential effect on uterine contractility and possible transgenerational effects.

44. Based on the available information, echinacea was a supplement consumed for general wellbeing, therefore further investigation was required for any potential mechanisms of action that might be specific to pregnancy, along with possible effects on the fetus, particularly on angiogenesis and possible drug interactions.

45. Regarding the rest of the supplements presented in the paper, the Committee noted the lack of available data, especially with regards to pregnancy outcomes.

46. Although a full review would not be possible for some of the supplements, the Committee noted some aspects that might be of relevance. For chamomile these were possible allergenicity and drug interactions, for evening primrose oil these were possible drug interactions and for peppermint the potential effects on the central nervous system (CNS), liver and kidneys; it was noted that it was advised by some unofficial sources not to use peppermint in the first trimester, but no data were available to substantiate this.

47. A SACN representative commented on the different herbal supplements from a nutritional point of view and noted chemicals present in the herbs that might be of relevance. These were caffeic acid in chamomile tea and cadmium in dandelion. For evening primrose oil, the ratio of n3:n6 fatty acids could be involved in induction of labour. In general, pesticide and contaminant levels present in the supplements could require further consideration if data were available.

48. Overall, it was noted there were useful animal data but fewer human data were available. As such, the COT concluded that investigating any supplements other than ginger, raspberry leaf tea and echinacea in detail was unlikely to be very productive, and that information on the remaining supplements could be summarised in an overarching summary.

49. The Secretariat invited Members to inform them of any additional herbal supplements that might be of relevance for the COT to consider, if any.

Item 7: First draft statement combined exposure on mycotoxins TOX/2020/52

50. No interests were declared.

51. The potential risks from combined exposure to mycotoxins have been previously discussed at COT meetings from July – September 2020. The first draft statement, presented in TOX/2020/52 brought together the discussions that took

place and summarised the current state of knowledge, data gaps, and research needs and summarised the conclusions reached to date.

52. The draft statement was reviewed by Members. For background and context, it was agreed that explanatory text on the inclusion of non-consumers in food consumption surveys and issues surrounding left-censored data should be included in both the statement and the lay summary.

53. It was agreed by the Members that the term combined exposures was the most appropriate and should be used consistently across the statement.

54. To conclude, Members were of the view that the grouping of mycotoxins should be based on similarity of their modes of action (e.g. cytotoxicity through inhibition of protein synthesis, genotoxicity). In order to assess the potential combined risks, co-occurrence data should be gathered and, where dose additivity had been observed, a margin of exposure (MoE) should be calculated. If the MoE was below 100, then a more extensive review/risk assessment should be carried out, including possible interactions between different mycotoxin groups.

55. A number of minor editorial comments were raised. A revised version of the statement would be presented to the Committee as a future meeting

Item 8: Presentation from Professor Tim Gant, PHE: NIHR Health Protection Research Units: What they are, what they do, and relevance for COT

56. Health Protection Research Units (HPRU) were established by the former Chief Medical Officer (CMO) Dame Sally Davies in 2014. They are funded by DHSC through the National Institute for Health Research (NIHR).

57. In their first iteration, HPRUs were designed to be 5-year programmes but were extended by one year. As such, the first HPRUs were completed by 31st March 2020, and the second round of the HPRUs started on 1st April 2020.

58. In introducing the HPRUs in March 2014, Dame Sally Davies declared their purpose as “universities working in partnership with PHE, to support excellent health protection research relevant to the needs of PHE”. The HPRUs cover all aspects of public health with five HPRUs in infectious disease, one in vaccines, one in climate change, one in emergency preparedness, one in environmental exposure, one in chemicals and radiation, one in behavioural science, and two HPRUs in modelling, economics and genomics. The total funding over five years is £13 million across all HPRUs equating to about £800,000 per year per HPRU. HPRUs produce new research, show translatable benefit of that research to public health, train new practitioners, undertake knowledge translation and PPE/I (both mandatory budget items), generate new income, support the economy, and facilitate further collaboration.

59. It was noted by the Committee that the FSA was currently reviewing their approach to funding research and suggested that there would be a benefit for FSA and PHE to discuss areas of common interest.

60. Professor Gant agreed to make the presentation slides available to Members following the meeting and also to share the web links for some of the information included in the presentation.

Item 9: Testing the COC guidance on less than lifetime exposure TOX/2020/53

61. The Chair declared that he had participated in a working group of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) which had developed JECFA's approach to considering LTL 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 the implications of less than lifetime (LTL) exposure to genotoxic and non-genotoxic carcinogens. The COT had previously expressed an interest in this topic at the joint COT, COC and COM meeting in October 2017. The COT had been asked to consider the applicability of the principles developed by the COC to LTL exposures for other endpoints, which are considered by the COT. The Committee had discussed the extent to which its work had addressed LTL exposures to date, and concluded that it would be useful to test the COC set of principles using cases from past COT work.

63. TOX/2020/53 included two test cases taken from the COT on the diets of infants and young children in respect of exposures to cadmium and fumonisins. In both cases, exceedances of chronic Health-Based Guidance Values (HBGVs) were identified in infants and/or young children. However, cadmium bioaccumulates, while the fumonisins were rapidly metabolised and excreted. Following the COC principles, a Haber's rule-based approach had been followed for cadmium, while for the fumonisins the establishment of a short-term HBGV had been considered. Members were asked to consider whether the test cases for cadmium and fumonisins had appropriately followed the COC principles on LTL exposure, whether following the COC principles would have changed the conclusions previously drawn by the COT on cadmium and fumonisins in the diets of infants and young children, and whether COT-specific principles on less than lifetime exposure should be produced based on the COC principles.

64. Members considered that that the two test cases were useful. The approach to the fumonisins was appropriate. Taking a Haber's rule-based approach was also considered appropriate in some cases. For cadmium, it was noted that there were probabilistic approaches to averaging exposure over time, which the COT might consider in the longer term. A Member also wondered whether a body burden approach might be even more accurate than averaging dietary exposure over time. In relation to this it was noted that for chemicals that accumulated, such as cadmium, the approach assumes a linear relationship with duration of exposure but the relationship should be exponential. Overall, Members concluded that they wished to consider further how to approach bioaccumulative chemicals.

65. Members considered that the starting point should be the toxicology rather than the exposure period; indeed, the toxicology should inform the exposure window of interest. This was also the view taken by JECFA.

66. The value of establishing short-term HBGVs was discussed by the Committee. It was noted that the comparison in the first instance was to the chronic HBGV and the consideration of a short-term HBGV would only be in cases where there was a need to refine the risk assessment and where it could have practical application in risk management.

67. Members considered that LTL was not exactly the correct term, as such exposures are variable exposure over the lifetimes being considered. The Committee will give further thought to a more appropriate term.

68. Members concluded that the test cases for cadmium and fumonisins had correctly followed the COC principles, but agreed that they needed to further consider the approach taken for bioaccumulative chemicals, particularly in children.

69. Members also concluded that following the COT principles would not have changed the conclusions previously drawn on cadmium and fumonisins in the diets of infants and young children, but would have strengthened the support for the conclusions.

70. Members agreed that COT-specific principles on LTL exposure should be produced based on the COC principles. However, a more accurate descriptive term than “less than lifetime” should be considered.

Item 10: Discussion paper on the potential effects of excess iodine intake may have during preconception, pregnancy and lactation TOX/2020/54

71. A non-specific personal interest was declared by Professor John Foster who had received European Crop Protection Association (ECPA) funding to perform a review of the literature on potential carcinogens that may be present in crop protection products. No other interests were declared.

72. In general, the Committee noted that the paper was well structured and accurately reflected the literature. Members recommended the Secretariat review the data gathered by the World Health Organisation on their work relating to the nutritional aspects of iodine for pregnant and lactating women.

73. The suitability of iodide markers in the blood/urine as an accurate reflection of exposure to iodine was discussed. Healthy people excreted excess iodine in urine so that it was not a good marker for exposure. Deficiency and excess could be identified in a population by looking at the distribution of urinary iodine, but this did not work for individual exposure. Members were of the view that there is not yet an optimised methodology to perform this assessment.

74. The seasonality of iodide concentrations in milk was noted. The contribution of iodine supplements to exposure should also be considered as these would not be captured by the Total Diet Study data used in the exposure assessment.

75. Members agreed that exposure to excess iodine in seaweed consumers (particularly those at the upper percentile) could pose a risk to maternal health, and that a risk benefit exercise should be performed due to the narrow therapeutic window of iodine supplemental intake.

Item 11: Draft EFSA opinion on HBCDD TOX/2020/55

76. Professor Alan Boobis was on the expert Panel for the 2011 EFSA evaluation, however he has not been involved with the current (2020) evaluation. No other interests were declared.

77. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) has launched a public consultation on the update of hexabromocyclododecanes (HBCDDs) in food.

78. While EFSA acknowledged the increasing number of epidemiological studies and human and animal research conducted in relation to HBCDDs since its 2011 assessment, the Panel did not consider that any of the new data were sufficient on which to base their risk assessment. Thus, following their previous assessment, EFSA used the data reported by Eriksson *et al.* (2006) [1], and considered neurodevelopmental effects on behaviour to be the critical effect and subsequently calculated a chronic dietary intake based on the body burden. Contrary to the 2011 evaluation, EFSA did not base their assessment on BMD modelling but applied a NAOEL/LOAEL approach.

79. Members discussed the approach taken by EFSA and noted a general lack of clarity and transparency regarding the decision making process.

80. Although EFSA assessed the relevant toxicological and epidemiological studies, Members agreed that it was not clear from the document on what basis these studies were not further considered. Members noted that EFSA confirmed the critical endpoint from 2011, however it was not substantiated by any new or additional findings. A recent study in rats[2] supported the findings by Eriksson *et al.* (2006) (the study on which the previous and the current assessment was based), albeit at higher doses, however this study was disregarded by EFSA, and COT Members were unclear regarding the justification for this.

81. Given the effect of HBCDDs on the constitutive androstane receptor (CAR) and pregnane-X-receptor (PXR) in the liver of rodents, Members queried the

[1] Eriksson P, Fischer C, Wallin M, Jakobsson E and Fredriksson A, 2006. Impaired behaviour, learning and memory 4115 in adult mice neonatally exposed to hexabromocyclododecane (HBCDD). Environmental Toxicology and 4116 Pharmacology, 21, 317-322.

[2] Zhang X, Wang X, Zhang J, Pan X, Jiang J and Li Y, 2017a. Effects of Taurine on Alterations of Neurobehavior and 4823 Neurodevelopment Key Proteins Expression in Infant Rats by Exposure to Hexabromocyclododecane. 4824 Advances in Experimental Medicine and Biology, 975, 119-130.

conclusions drawn by EFSA on the mode of action for changes in liver weight and noted that more clarification in this regard would be helpful.

82. Members discussed the general problem of comparing different modelling approaches such as BMDS and PROAST without the underlying algorithms. Both modelling software programs as well as different versions of the each program can result in different values, which can be difficult to understand. Members noted that it would be useful if EFSA could provide not only the software version but additional information on parameters underlying the specific model used. Members noted that some of the underlying quality control measures of the current software version may need consideration but given the limited information provided by EFSA, Members found it difficult to follow the approach taken, as well as their decision making process.

83. Members commented that the Eriksson *et al.* (2006) study, while not ideal, may still be the best or only study available on which to base the assessment.

84. Members noted that the reasoning (and/or wording) regarding interspecies effects and derivation of the uncertainty factor for interspecies differences were not clear. However, based on the NOAEL/LOAEL approach, Members agreed with EFSA's additional uncertainty factor of 3 for the extrapolation from a LOAEL to a NOAEL, and that an MOE of 24 would not be of concern. Members did, however, query EFSA's decision to apply the NOAEL/LOAEL approach, and noticed a lack of information provided on the decision making process. This was considered especially pertinent given EFSA's previous efforts to apply BMD modelling and the that the difference in the calculated/estimated chronic human intake was minimal between the previous (BMD) and current (NOAEL/LOAEL) approach.

85. Overall, the Committee agreed with EFSA that exposure from the diet was of not a concern for human health; however, COT Members were unable to conclude on the effect of breastmilk. According to EFSA's calculations and conclusions, breastfed infants are the subgroup with a potential risk to health, however Members were unable to ascertain whether EFSA's assessment/conclusions were conservative, as the derivation of the breastmilk exposures by EFSA was unclear.

86. Members were asked to send any additional comments to the Secretariat by the 18th of November. A document would be set up on the Teams site for Members to add additional comments directly if they wished.

Item 12: Update on the work of other scientific advisory committees and AOB TOX/2020/56

87. This paper was circulated for information.

Item 13: Any Other Business

88. There was no other business.

Date of next meeting

89. The next meeting of the Committee Meeting will be held at 10:00 on 1st December 2020 via Skype and Microsoft Teams, with the virtual workshop on PBPK modelling on 2nd December