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

Minutes of the meeting held on Tuesday, 19th of March 2019 in Broadway House Conference Centre, Tothill St, London SW1H 9NQ

Present

Chairman:	Dr Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr René Crevel Prof John Foster Dr Mark Graham Dr Caroline Harris Dr Sarah Judge Prof Brian Lake Ms Juliet Rix Dr John Thompson Dr Mireille Toledano Prof Faith Williams Prof Matthew Wright	
Food Standards Agency (FSA) Secretariat:	Dr D Gott Dr A Cooper Ms H Gbormittah Dr D Hedley Ms F Hill Mr B Maycock Ms C Mulholland Dr O Osborne Ms C Potter Dr J Shavila Ms C Tsoulli Ms F Uy	FSA Scientific Secretary
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Assessors:	Dr Tim Marczylo	PHE

Officials:	Ms Daphne Duval	PHE
	Dr Selwyn Runacres	FSA
	Mr Richard Uchotski	FSA
Other Invited Experts and Contractors:	Prof P Aggett	SMCN
	Dr Sarah Bull	WRc
	Dr Kate Vassaux	WRc
	Mr Nigel Sarginson	ExxonMobil
	Dr John Norman	ExxonMobil
	Mr Perry Walters	CEFIC

Observers:

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Announcements

1. The Chair welcomed Members and other attendees.

2. The Chair informed the Committee that this would be the last meeting for Professor Harrison, Professor Lake and Dr Graham (and possibly Dr Thompson). This was discussed further under Item 12.

Interests

3. 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

4. Apologies were received from COT Member Dr Coulson. Professor Tim Gant and from PHE and Ms Valerie Swaine from HSE also apologised for their absence. Dr Coulson had provided written comments.

Item 2: Minutes from the meeting held on 6th of February 2019 – TOX/2019/01

5. The minutes were accepted subject to minor amendments to the list of attendees and the apologies for absence.

Item 3: Matters arising from the meeting held on 6th February 2019

Item 3: Matters arising from previous meetings:

6. Para 7: The overarching Statement on the potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years and its lay summary had been published.

7. Para 9: The folic acid Statement and its lay summary had been finalised and published.

8. Para 15: The recruitment for the Expert Committees had been finalised and a proposed induction day had been set for the 16th of May.

Item 5: Review of potential risks from fumonisins in the diet of infants aged 0 to 12 months and children aged 1 to 5 years

9. Para 25: Members had reviewed the methodology used in the paper assessed by JECFA and its relevance to the UK population.

10. Para 26: A Member had examined the Zimmer et al. paper. The authors of the Zimmer et al. paper had been contacted for further clarification on the food groups used.

Item 4: Potential future discussion items – horizon scanning – TOX/2019/08

11. The paper presented to Members detailed agenda items for 2019 (mostly ongoing items) and potential discussion topics. The latter included possible public consultations from EFSA, which would require consideration by the COT, items carried forward from the 2018 horizon scanning, and new suggestions for topics. The balance of expertise on the Committee was also presented. Members were asked to comment on the items detailed in the paper, whether there were any additional topics that should be addressed, for any proposals for research that should be funded in order to improve COT risk assessments, and to consider whether there were any important gaps in expertise amongst the current COT membership or in light of possible future developments.

12. The paper contained a proposal for a COT subgroup to consider the approach to risk assessment of endocrine disrupters to human health following the discussion at the last meeting. The Committee wished to form a view on how effects on the various hormonal systems should be assessed. The Committee agreed that a subgroup should be formed to consider this. However, the first stage would be to produce a scoping paper to consider the terms of reference. Members considered that it would be better not to include consideration of environmental risks, as there are important differences from the assessment of human health risks.

13. Members agreed to consider developments in the area of physiologically-based pharmacokinetic modelling. Initially a scoping paper would be produced. The Committee would then consider convening a workshop either individually or together with one or more other committees.

14. The Committee agreed the proposal to form a subgroup to consider the synthesis of epidemiological and toxicological evidence, following on from production of the report on synthesising epidemiological evidence. Members considered there was a need for COT guidance in this area. Initially a scoping paper would be produced and brought to the Committee.

15. A proposal to hold a workshop to discuss ideas for a potency estimation research project was discussed. Members agreed that a workshop would be useful and should incorporate external bodies such as the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). There should also be a separate session incorporated into the workshop for general project ideas. However, the workshop would need to be focussed and Members requested a scoping paper with a proposal be brought to the Committee first.

16. Members discussed the balance of expertise on the Committee. New areas of expertise that should be considered included, new approach methodologies such as organ-on-a-chip models, systems biology (specifically adverse outcomes pathways) and the microbiome. For both dietary and environmental exposures, expertise needed

to be maintained. In relation to the COT's future consideration of microplastics, a Member wondered whether the Committee has the necessary expertise in physical and mathematical knowledge to assess exposures.

Item 5: Phosphate-based flame retardants: Follow-up to scoping paper on phosphate-based flame retardants and the potential for developmental toxicity – TOX/2019/09

17. No interests were declared.

18. This paper presented further information on the structural characteristics of phosphate-based flame retardants (PFRs) to assess their potential to interact with the active site of acetylcholinesterase (AChE), which had been requested at the October 2018 COT meeting. In addition, the paper considered the potential for neurotoxicity of PFRs through action at the neuropathy target esterase (NTE). The paper also provided information on effects on the GABA receptor.

19. With respect to activity on AChE, as seen with organophosphate pesticides (OPs), the Committee agreed that combined with the available evidence, the structural features of PFRs currently in use were such that they would not produce irreversible or potent inhibition of AChE and therefore this mechanism was not of importance for PFRs.

20. The Committee concluded that, based on structural considerations, a non-cholinergic mode of action via NTE was also unlikely for PFRs.

21. It was clarified that while ortho-tricresyl phosphate had potential to cause organophosphate induced delayed neurotoxicity (OPIDN), this was not used as a PFR, though it could be present at low levels (<0.1%) as a contaminant in commercial tricresyl phosphate PFRs.

22. It was noted that GABA receptor inhibition was associated with neurological effects, but it was not clear what role this had in PFR neurotoxicity. The availablestudies had used high doses in vivo or high concentrations in vitro of PFRs, and any effect of on GABA receptors appeared restricted to only some PFRs. Members concluded that based on their low potency, PFRs are unlikely to cause neurotoxicity at human exposure levels via effects on GABA receptors.

23. The Committee agreed that the data presented did not support a plausible mechanism for any neurotoxic effect from PFRs in exposed humans through inhibition of AChE, NTE or GABA receptors. Adequately conducted studies would be needed to exclude potential effects via other mechanisms.

24. It was noted that this was an example of the need to integrate toxicological data with epidemiology data, albeit there was only limited toxicology data available and only a few findings from the epidemiological literature for PFRs to be considered, along with a structure-activity comparison with OPs.

Item 6: First draft Committee view on phosphate-based flame retardants and the potential for developmental toxicity – TOX/2019/10

25. No interests were declared.

26. The Committee agreed the title should emphasise that the Statement considers the potential for neurodevelopmental effects of PFRs.

27. Further clarification on the potential effects of phosphate-based flame retardants on the GABA chloride channel was suggested. In addition, the description of the study in PC12 cells should make clear what endpoints were measured as it is not considered to be a neurotoxicity assay. With respect to the ATSDR assessments, it was noted that comment should also be made about brain lesions associated with TCEP exposure.

28. The Committee requested the Secretariat to add a paragraph on the proportional use of different types of flame retardants, to provide an overall view of the likely extent of exposure to phosphate-based flame retardants.

29. The Committee agreed that the conclusion needed to describe the findings of the epidemiological studies along with the lack of mechanistic information to explain the observed effect. However, in its current form there was a lack of clarity of the Committee's overall opinion on these findings. The paragraph would be revised and circulated for initial comment to a Committee member before the next version was prepared.

30. The Committee highlighted the potential for co-exposure to other flame-retardant compounds and agreed a comment should be added to the statement on this. The Committee further requested whether it would be feasible to have a list of which PFRs are currently in use within the European Union and their proportional market share.

31. Following a question about the need to use flame retardants, the Committee was informed that the regulations require products such as mattresses to pass certain fire tests, and one means of doing so is use of flame retardants. It is for manufacturers to determine how they will ensure their products comply with the Furniture and Furnishings (Fire) (Safety) Regulations.

Item 7: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes), Paper 9: Bystander exposure – TOX/2019/11

32. No further interests were declared in addition to those previous declared at the COT meeting in December 2018.

33. This paper summarised the available literature relating to bystander exposure following E(N)NDS use. The data related to human use of E(N)NDS, and did not

include studies where machines were used to generate E(N)NDS aerosol. A paper would be presented at a later meeting on user exposure.

34. The main constituents assessed in the E(N)NDS aerosol were nicotine, particulate matter (PM), glycerol and polyethylene glycol. Concentrations of glycerol and polyethylene glycol were below the health-based guidance values previously agreed by the Committee. Therefore, discussion focused on the potential risks from nicotine and PM in the air during and following E(N)NDS use.

35. The solubility of the measured PM concentrations was not clear from the available information, but it was noted that the WHO consider it is likely that PM in E(N)NDS aerosol is likely to be soluble and hence its toxicological profile may well differ from that of insoluble particles. There was therefore some reservation over applying the risk coefficients for PM2.5 in ambient air to E(N)NDS aerosol. However, it was noted that ambient air risk coefficients also include soluble constituents of atmospheric pollution, such as ammonium sulphate and ammonium nitrate.

36. There was no information on the lung deposition of PM from E(N)NDS aerosol in animal models. The Committee considered that the PM is likely to be droplets of condensate and if it was primarily the E(N)NDS vehicle then possibly the health-based guidance value for glycerol or propylene glycol could apply. The Committee concluded that there is significant uncertainty in the risk from PM in E(N)NDS aerosol. A further uncertainty was in the short-term nature of PM exposures arising from E(N)NDS use, for which good epidemiological data are not available to aid interpretation.

37. With respect to the nicotine concentrations identified, additional information on nicotine effects were required to determine the potential health concern. It was difficult to identify a LOAEL and NOAEL from the human study EFSA had used to establish an ARfD for nicotine, and access to the original information would be helpful. The Committee agreed that it would be useful to review the risk characterisation of nicotine, updating the EFSA and US EPA reviews, as this was the exposure of concern for bystanders, which would need to be considered in terms of absolute risk, while for users it would be relative risk compared to that from smoking. The data did not support the view that no nicotine is exhaled following E(N)NDS use, and it was important to be clear that nicotine has potential to cause harm, despite the view of many members of the public that it is not harmful.

38. One Member reported on occurrence of an allergic response associated with exposure to E(N)NDS aerosol, with effects including rhinitis which responded to anti-histamines. It was important to highlight that the exhaled aerosol is not water vapour as many users and bystanders think and other chemicals are present, which may be responsible for this type of reaction.

39. Overall, the Committee concluded that bystander exposures were of potential concern based on some of the reported nicotine concentrations.

40. While no specific information had been identified on bystander exposure to flavourings and their thermal breakdown products, this would be covered in upcoming papers.

Item 8: Discussion paper on the public consultation on the EFSA Opinion "Draft update of the risk assessment of dibutylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isonylphthalate (DINP) and di-isodecylphthalate (DIDP) for use in food contact materials" – TOX/2019/12

41. Dr Harris declared a non-personal non-specific interest in that her employer had conducted work on phthalates. Dr Gott declared that he was a member of the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) and its working group on phthalates, which had prepared the draft opinion.

42. EFSA had released for public consultation this draft opinion. The EFSA CEP panel had been asked by the European Commission to update its 2005 risk assessments of dibutylphthlate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isonylphthalate (DINP) and di-isodecylphthalate (DIDP), which are authorised for use in food contact materials, by using the same database as the European Chemicals Agency (ECHA) for its 2017 assessment of certain phthalates.

43. The limitations of this approach were acknowledged by the CEP panel, but due to the limited time for the completion of the opinion and the amount of new evidence available since the 2005 opinion, the panel had considered it unfeasible to perform a comprehensive review of all the data on these phthalates. Therefore the CEP panel had decided to undertake the review of the toxicological data used by ECHA on DBP, BBP and DEHP, mainly dealing with reproductive toxicity; additionally review the toxicological data for reproductive effects of DINP and DIDP (published after EFSA's previous review of phthalates in 2005); analyse the possibility of establishing a group health-based guidance value for these substances; refine the assessment of dietary consumer exposure to these substances, which are all authorised in plastic food contact materials; and carry out a risk characterisation on this basis.

44. The COT was invited to provide comments to be submitted to EFSA.

45. Concerns had been expressed that due to the approach in the mandate, the database on DINP toxicity had been incompletely reviewed by EFSA. Industry experts (Mr Nigel Sarginson and Dr John Norman from ExxonMobil and Mr Perry Walters from the European Chemical Industry Council, CEFIC) had been invited to provide an overview of the entire database to the COT. They noted that there had been a major switch in use from lower molecular weight phthalates, including DEHP, DBP and BBP, to higher molecular weight phthalates, including DINP and DIDP, since 2000 due to the reproductive toxicity of the lower molecular weight phthalates. Consistent with this,

biomonitoring data showed a decrease in exposure to DEHP, DBP and BBP and a small increase in exposure to DINP and DIDP.

46. They did not believe that the lower and higher molecular weight phthalates should be considered together as one group. They noted that ECHA's risk assessment Committee (RAC) had published an opinion on the classification of DINP in March 2018 which concluded that DINP should receive no classification for developmental toxicity, effects on sexual function and fertility or developmental toxicity.

47. They pointed out that EFSA considered DEHP, DBP and BBP to have a common mode of action which was postulated to be decreased fetal testosterone production; however, the WHO framework for mode of action had not been followed. For DINP and DIDP the critical effects were on the liver but EFSA had then grouped DINP with DEHP, DBP and BBP to be prudent due to a reversible decrease in fetal testosterone production. They made the case that even if EFSA's mode of action is correct for DEHP, DBP and BBP this does not apply to DINP as any changes produced by DINP are temporary and occur at a time point that cannot cause permanent organism-level effects. A temporary effect on anogenital distance had been reported at a high dose in one study but was not statistically robust, and epididymal agenesis and testes agenesis/atrophy was observed in two animals in one study but the incidence was well within the historical control range.

48. The Committee noted that a chemical would be classified as an endocrine disruptor if it causes adverse effects via an effect on the endocrine system; accordingly, depending on conclusions on how DINP causes its effects, this compound could be on the border of being classified as an endocrine disrupter. This would have important implications for its use. For risk assessment, DINP could be grouped together with DEHP, DBP and BBP based on all four substances decreasing fetal testosterone, but this should be as part of a tiered approach, in which this is a lower tier. If exposures were not of concern even with the conservative assumption that all of the comopounds act in the same way, the risk characterisation could be concluded there. If there is potential concern, then the risk characterisation should then be refined, looking in more detail at the evidence that the compounds all share a mode of action, to provide a higher tier assessment.

49. Members questioned whether the molecular initiating event was the same for DEHP, DBP, BBP and DINP. The molecular mechanisms were unknown. However, in relation to pesticides, EFSA had concluded that dose addition should be assumed even if the molecular initiating event is not the same, if all the substances affected the same intermediate point on a pathway, e.g. decreased testosterone level.

50. Members noted that EFSA had accepted a mandate which restricted the data it could consider. This does not meet EFSA's best practice guidelines. Hence, the COT considered the approach EFSA has taken to be scientifically valid only in the context of the constraints of this mandate.

51. The EFSA draft stated that the panel had reconfirmed the critical effects derived in 2005 for the individual phthalates considered. However, the panel could not reconfirm the critical effects as it had not considered all of the data.

52. Members observed the precedent taken in including DINP in the group TDI for reproductive effects while using an additional assessment factor to account for DINP's more sensitive liver effects. The TDI established for DINP individually addressed effects on the liver. Members considered it reasonable to conclude that DINP has possible effects on fetal testosterone levels and to group it with DBP, BBP and DEHP for the purposes of a low tier cumulative risk assessment, as in para 48. A Member questioned why the effects on the liver were not considered adaptive rather than adverse, but it appeared this was not considered in detail in the opinion.

53. Members considered the evidence insufficient to conclude that DINP is an anti-androgenic endocrine disruptor. However, they considered it reasonable to group DINP with DEHP, DBP, BBP in a low tier cumulative risk assessment.

54. The Committee considered the group TDI and the relative potency factors to be appropriate for DEHP, DBP and BBP. Members were content that the exposures estimated by EFSA did not indicate a health concern using the group TDI for DEHP, DBP, BBP and DINP.

55. Members considered that the uncertainty assessment in the draft Opinion did not adequately reflect on the conclusions on DINP.

56. A Members observed that EFSA and ECHA had produced guidance on the identification of endocrine disruptors. The process that had been followed in this draft opinion could well lead to contradictory conclusions from those were this guidance to be followed.

57. Members were asked to send in any further comments. COT comments would be compiled and circulated to Members before submitting to EFSA.

Item 9: Risk to human health from the use of certain additives not currently allowed in the EU – TOX/2019/13 (Reserved Business)

58. The FSA was preparing for a future outside the European Union (EU). In anticipation of the UK Government engaging in trade negotiations with various countries, the FSA has identified a number of food production practices and uses of chemicals in the food chain in countries outside the EU, which are currently not permitted in the EU and on which the FSA will need to form a position on the risks to health.

59. As part of the work, the safety of three food additives was considered. This item was discussed as reserved business.

Item 10: Draft 2018 annual report – TOX/2019/14

60. Members were provided with the draft COT section of the Annual Report for 2018. It highlighted the COT statements which had been published in 2018, provided a summary of each of the EFSA public consultations on which the Committee had provided comments/recommendations, work produced or published by COT working groups, and a list of ongoing work which would be continued in 2019. At the end of the section were the declaration of Members' interests for 2018.

61. Members were asked to provide any comments on the text, to check their interests and affiliations were correctly listed, and to consider how the COT had performed during 2018 against the FSA Good Practice Guidelines for scientific advisory committees.

62. Members made editorial suggestions and agreed to send in any additional editorial comments on the text. The Committee discussed how it complied with each of the Good Practice Guidelines.

63. Regarding defining the problem and the approach, the Committee agreed that in general this is adhered to but considered that it could be better involved in defining the problem.

64. With regards to the uncertainty section the Committee agreed that it followed all of the points in this section. With regards to quantifying the degree of uncertainty, Members agreed to wait for the conclusions from EFSA on the application of its recent Guidance on Communication of Uncertainty in Scientific Assessments by the Panels and Units. It was also noted that advice had been taken on this issue from the Social Science Research Committee. The COT would revisit descriptions for uncertainty through the work of the subgroup that would look at synthesis of epidemiological and toxicological evidence.

65. The Committee discussed the "Drawing conclusions" section and agreed that it followed paragraphs 18, 21 and 22; it has not had to deal with differences of opinion (paragraph 20), as this had not arisen. Members noted that, with respect to paragraph 19, whilst under its terms of reference it considered only risks, it did flag the need for risk-benefit comparison where these were considered appropriate or necessary.

66. The Committee agreed that it adhered to all of the points in the sections seeking input, validation and communicating the Committee's conclusions.

Item 11: Paper for Information: FSA Scientific Advisory Committees (SACs) update – TOX/2019/15

67. This paper was provided for information.

Item 12: Any other Business

68. The Chair expressed his gratitude to the departing Members Professor Harrison, Professor Lake and Dr Graham (and possibly Dr Thompson who may be reappointed for one further year) for their contributions to the Committee, noting that the COT had benefited greatly from their areas of knowledge and expertise over the years, which would be difficult to replace.

Date of next meeting

69. The next meeting would be held on Tuesday 7th May 2019 at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ.