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

Minutes of the meeting held on Tuesday, 3rd of December 2019 in the Amba Hotel Charing Cross, The Strand, London, WC2N 5HX

Present

Chairman:	Professor Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr Stella Cochrane Dr René Crevel Prof John Foster Prof Gary Hutchison Dr Sarah Judge Dr Gunther Kuhnle Dr David Lovell Dr Mac Provan Ms Juliet Rix Prof Faith Williams Dr Michael Routledge Dr Cheryl Scudamore Dr Natalie Thatcher (by TC) Dr John Thompson Prof Matthew Wright	
	Prof Ken Ong	SACN Liaison
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland	FSA Scientific Secretary
	Dr A Cooper Dr B Doerr Mr B Maycock Dr D Hedley Ms C Hoppie Dr O Osborne Ms C Potter Mr J Shavila Ms C Thomas Ms S Thomas Ms C Tsoulli Ms F Uy	
Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary

Assessors:	Dr Tim Gant	PHE
	Ms Valerie Swain	HSE
Officials:	Ms Rachel Elsom	PHE
	Dr Daphne Duval	PHE
	Mr Liam Johnstone	BEIS
	Mr Freddie Lachmann	FSA
	Dr Andrea Lorenzoni	FSA
Other Invited Experts and Contractors:	Prof John O'Brien	Science Council
	Dr Sarah Bull	WRc
	Dr Kate Vassaux	WRc
Observers:	Niall O'Brian	VMD
	Callum Harris	VMD

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Announcements

1. The Chair welcomed Members and other attendees. He welcomed in particular Professor John O'Brien from the Science Council, who serves as COT liaison and was attending the Meeting as an observer.

2. The Chair welcomed and introduced Cleanncy Hoppie, a new member of the Secretariat.

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 Members Professor Maged Younes, Dr Caroline Harris and Dr James Coulson, and Mrs Frances Hill of the Secretariat. A Member provided written comments in advance of the meeting.

Item 2: Minutes from the meeting held on 22nd of October 2019.

5. The minutes were accepted as an accurate record. The reserved minutes were also accepted as an accurate record.

Item 3: Matters arising from the meeting held on 22nd October 2019

September 2019 Update from the Working Group on Synthesising Epidemiological and Toxicological Evidence (SETE)

6. Members were informed that following the presentation to, and discussion of, the scoping paper on the synthesis and integration of epidemiological and toxicological evidence in risk assessments, the first joint Working Group (WG) meeting of COT and COC took place on 19th November 2019 as a teleconference.

7. The WG Members had agreed that the output would need to be realistic and applicable and should include case studies. The WG Members further identified areas for which additional expertise was needed and suggested possible experts, who are in the process of being contacted.

8. The next meeting, which will be face-to-face, will be held in February 2020.

Para 10: Update from the COM meeting in October

9. The Committee were updated on the discussions of the COM at their October 2019 meeting on a flavouring additive (reserved business), patulin and cannabidiol. The COM minutes will be available following their February 2020 meeting.

Para 17: EFSA consultation on aflatoxins

10. Comments on the draft aflatoxin opinion were submitted to EFSA and the Chair thanked the Members who provided them.

Para 46: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)

11. It was agreed at the October meeting that a recent paper[1] on the potential carcinogenic effects of E(N)NDS should be referred to COC for consideration, to check if this would result in any change of the COC position from July 2018. Based on the *in vivo* study and a further recent *in vitro* study[2] identified whilst updating the literature search undertaken for COC, the Committee agreed that no change in its previous position was required.

Item 4: Food Standards Agency Scientific Advisory Committees (SACs) and Joint Expert Groups (JEGs) (Reserved Business) - TOX/2019/67

12. In order to expand the capability of the Food Standards Agency's (FSA's) Scientific Advisory Committees (SACs), three new Joint Expert Groups (JEGs) have been created to assess regulated products, in support of the FSA's new Risk Analysis Process. The role of the JEGs is to support the work of the SACs through undertaking risk assessments of regulated products, while raising areas of particular concern to the SACs, as appropriate.

13. This paper had set out the proposed approach to the relationship and working of the JEGs with the SACs. This item was conducted as Reserved Business. The Minutes will be published at the earliest appropriate opportunity.

Item 5: Discussion paper on potential risks from chemicals in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - additional information on DON - TOX/2019/68

14. No interests were declared

15. The COT was asked to review the risks of toxicity from chemicals in the diet of infants and young children aged 1 to 5 years, in support of a review by the Scientific

[1] Tang, M. S., et al. 2019 Electronic-cigarette smoke induces lung adenocarcinoma and bladder urothelial hyperplasia in mice. Proc Natl Acad Sci U S A.

[2] Zahedi, A., et al. 2018 Epithelial-to-mesenchymal transition of A549 lung cancer cells exposed to electronic cigarettes. Lung Cancer 122:224-233.

Advisory Committee on Nutrition (SACN). The reviews would identify new evidence that had emerged since the Government's recommendations were formulated and will appraise that evidence to determine whether the advice should be revised.

16. A scoping paper summarising information on a number of mycotoxins was presented to the Committee in July 2017 and Members requested the amendment of the exposure assessment to include the sum of DON and its three forms. Since a new EFSA opinion had been published prior to the meeting in 2017, Members further asked for an update on the EFSA opinion, especially regarding the derivation of the health-based guidance value (HBGV).

17. At the present meeting the Committee discussed the additional information. Members noted that the 3-DON-glycoside was not included in the exposure assessment and were informed by the Secretariat that the TDS measured only DON, 3-Ac-DON and 15-Ac-DON and therefore no information on the concentration of 3-DON-glycoside was available.

18. Members noted that the exposures to DON and its acetylated/modified forms were lower in the UK than in Europe, when comparing the overall conclusions of the present paper to the EFSA opinion. Members further noted that the exposure assessment was based on the limit of detection (LOD) rather than on measured values, and concluded that the exposure estimates therefore might be conservative.

19. The Committee agreed to include DON and its acetylated/modified forms in the Addendum to the Overarching Statement.

Item 6: Discussion paper on the potential risks from HCH in the diet of infants aged 0 to 12 months and children aged 1 to 5 years - TOX/2019/69

20. As declared previously, it was noted that Dr Sarah Judge had published a paper on lindane 3 years ago but that it was not commercially funded.

21. This paper was presented to the COT as an update to paper TOX/2019/53, with a greater emphasis on the historical decline in levels of HCHs and inclusion of new exposure values/units for γ-HCH.

22. The Committee suggested a number of minor corrections and amendments to be included in the final text.

23. The relevance of the rodent liver tumours to humans was discussed. It was considered that the rodent liver tumours were a consequence of a mode of action (MOA) that was not relevant to humans, as it was via activation of the constitutive androstane receptor (CAR).

24. It was noted that the Avon Longitudinal Study of Parents and Children (ALSPAC) study had a biobank of breast milk samples collected from children born in the 1990's and could be a useful future data source. The Committee's previous

discussions on the Breastmilk, Environment, Early-life and Development (BEED) study, coordinated by Imperial College London, were also noted[3].

25. Members questioned whether the mean level (15 µg/kg) of β-HCH in breast milk, reported in paragraph 55, was used in the exposure assessment as it was much higher in comparison to those for α-HCH and γ-HCH. It was confirmed that this was the value in the published paper and it had been used in estimates of mean exposure.

26. It was agreed that the conclusion should refer to the conservative use of the 97.5th percentile in the exposure assessment.

27. Members agreed that the information should be included in the Addendum and that exposures to α-, β-, γ-HCH were of no toxicological concern to children aged 1-5 years.

Item 7: Environmental, health and safety alternative testing strategies: Development of methods for potency estimation

(Reserved Business) - TOX/2019/70

28. It was noted that most Members had research interests related to this general topic but none of these was considered such that it precluded full participation in the agenda item.

29. The combined advances in discovery and clinical sciences, data science and technology have resulted in toxicity testing reaching a pivotal transformation point, taking advantage of the 4th industrial revolution (4IR). Many different types of *in silico* and *in vitro* methods have been developed to characterize and predict toxic outcomes in humans and the environment. These developments will be particularly important in risk assessment scenarios where limited or no information is available on the toxicity of a chemical.

30. The COT was provided with a concise review of these methods, which included databases, different kinds of quantitative structure activity relationship (QSAR) methods, adverse outcome pathways (AOPs), high throughput screening (HTS), read across models, molecular modelling approaches, machine learning, data mining, network analysis tools, and data analysis tools using artificial intelligence (AI).

31. The COT discussed the planned March 2020 workshop and reviewed potency estimation models.

32. This item has been taken as Reserved Business as it is hoped that a publication will be possible after the March workshop. The minutes from the present meeting will be published in due course.

[3] https://cot.food.gov.uk/sites/default/files/tox2017-38.pdf

Item 8: Discussion paper on soya drink consumption in children aged 6 months to 5 years of age - TOX/2019/71

33. A member provided written comments for this item.

34. No interests were declared.

35. Soya drinks are a popular alternative to dairy products and their use is becoming more widespread. Soya products contain isoflavone, compounds which have phytoestrogenic activity that have been shown to have effects on reproduction and development in animal studies, although the evidence for effects in humans from epidemiological studies is inconclusive.

36. The COT considered the safety of soya phytoestrogens in 2003 and in 2013. In 2013, the Committee concluded that there was no substantive medical need for, nor health benefit arising from, the use of soya-based infant formula and it should be used only in exceptional circumstances in this age group, to ensure adequate nutrition.

37. Levels of phytoestrogens in soya-based infant formula and soya drinks are variable but of the same order of magnitude, with soya drinks generally having higher levels. The Department of Health and Social Care (DHSC), Public Health England (PHE) and the FSA are receiving an increasing number of enquiries regarding the use of plant-based drinks in the diets of infants and young children. The COT is asked to consider the potential health effects of soya drinks in the diets of children aged 6 months to 5 years of age. Since the WHO state that soya-based drinks are unsuitable as a major source of nutrients in non-breastfed children aged 6-24 months of age, the COT is also asked to consider differences between this population group and those aged 2 to 5 years of age.

38. Following comments from members at the meeting in October 2019, the exposure estimates were revised and now included UK specific data.

39. The Committee noted that estimated intakes of phytoestrogens from the consumption of soya drinks in children aged from 6 months to 5 years of age were similar to those in infants receiving soya-based formula. As the Committee was unable to determine, on the basis of the available data, whether sensitivity to phytoestrogens varied among these age groups; it was similarly not possible to determine whether the level of concern differed between the age groups.

40. As for other soya-based products (e.g. cheese, yoghurts) in the diets of children aged 6 months to 5 years of age, the Committee concluded that any potential concern(s) would be dependent on how much they contributed to the overall diet and therefore to exposure to phytoestrogens.

41. The Committee’s current advice for children aged from 0-12 months, that soy formula should be used only in exceptional circumstances still stands and there are also potential concerns for children up to 5 years of age consuming soy drinks.

Item 9: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Follow-up from September 2019 COT meeting: updated risk assessments for nicotine exposure from ENDS – TOX/2019/72

42. Although not present at the meeting, Members were informed that Dr James Coulson declared an interest, stating that he had recently become an investigator and advisor on a contract research organisation-led (Simbec-Orion Plc) a commercial study sponsored by the British American Tobacco Group; this is a Personal specific interest. No other additional interests were declared from those declared in December 2018.

43. Paper TOX/2019/72 presented an updated risk assessment for nicotine exposure from ENDS following discussion of TOX/2019/47 in September 2019; that paper proposed a Health Based Guidance Value (HBGV) for inhalation exposure to nicotine based on the study of Lindgren et al., (1999)[4].

44. The Committee agreed there was a need to consider the risk from exposure to nicotine in the following scenarios: a smoker switching completely to an ENDS device, a non-smoker who has taken up ENDS (i.e. a naïve user), a bystander exposed to exhaled nicotine, and a dual user of cigarettes and ENDS.

45. It was acknowledged that there were continual, fast-paced technological advances in the design of ENDS, and it was noted that these could affect nicotine exposures, with some publications lagging product design. The Secretariat explained that the data presented in the paper (TOX/2019/72) were those available on nicotine concentrations and illustrative of the breadth of devices available. Overall the range of exposure estimates in typical exposure environments were broadly in agreement, but with some extremes, e.g. at vaping conventions. The higher concentrations could impact, for example, on people working in those environments and might be above levels otherwise of low risk to bystanders from nicotine in ENDS.

46. It was noted that in the UK there is an upper limit of 20 mg/mL on nicotine concentrations in e-liquids.

47. The clinical studies presented in Table. 1 of the paper (TOX/2019/72) were discussed. It was concluded that the Ghatan et al., (1998) study[5] provided the most conservative estimate of the relative sensitivity of non-smokers and smokers to nicotine, with non-smokers being around three times as sensitive to acute effects on heart rate. It was agreed that this could be combined with the evidence from the Lindgren et al. (1999) study to help interpret the margins of exposure for bystanders.

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[4] Lindgren, M, Molander L, Verbaan C, Lunell E, Rosen I (1999). Electroencephalographic effects of intravenous nicotine – a dose-response study. Psycopharmacology (Berl), 145, 342-350.

[5] Ghatan, P. H., M. Ingvar, L. Eriksson, S. Stone-Elander, M. Serrander, K. Ekberg & J. Wahren (1998) Cerebral effects of nicotine during cognition in smokers and non- smokers. *Psychopharmacology,* 136**,** 179-189.

48. The Committee agreed that it is appropriate to utilise the Lindgren et al. (1999) study No Adverse Effect Level (NOAEL) of 7 µg/kg bw for effects of nicotine in the electroencephalogram in calculations of risk to regular users of ENDS. For bystanders and naïve users, an increased sensitivity of 3-fold could be assumed, based on Ghatan et al. (1998). For dual users a general comment should be made in the upcoming Committee statement, namely that use of ENDS is unlikely to reduce their risks substantially, as the ongoing risks from smoking would still be present.

Item 10: Physiologically-based pharmacokinetic (PBPK) modelling case studies - TOX/2019/73

49. No interests were declared.

50. Paper TOX/2019/73 follows on from the PBPK scoping paper (TOX/2019/34) that was considered by COT in July 2019. At that meeting, the Committee agreed that it would be useful to have further information in the form of case studies, for example where *in vitro* data had been successfully extrapolated to *in vivo*, or cases where risk assessments considered in retrospect may have benefitted from PBPK modelling.

51. The paper presented a number of PBPK case studies that have been used in risk assessment (PFOS & PFOA, dioxins, bisphenol A, acrylamide & glycidamide, chloroform & carbon tetrachloride, vinyl acetate, methylene chloride, and vinyl chloride), in addition to cases where *in vitro* to *in vivo* extrapolation has been conducted (PFOS, triclosan, pyridaben & fluazinam, estragole, and trichloroethylene). Furthermore, examples such as 2-butoxyethanol, persistent organic pollutants, amphetamine analogues and E(N)NDS devices were presented, where the use of PBPK modelling may facilitate their risk assessment.

52. The Committee noted that PBPK models have predominantly been developed and applied on a case by case basis, for example to assess exposures of chemicals with narrow margins of exposure (MOE) or to fill data gaps from more conventional approaches. Since these bespoke PBPK models are chemical-specific, they are not directly applicable to other chemicals.

53. It was recognised that PBPK modelling is of current interest in the field of chemical risk assessment. However, it is still largely used more in research capacities to refine estimates of risk. PBPK models are not routinely applied or assessed by regulatory bodies because they are generally complex and both labour and data intensive, for example in terms of the data required for model parameterisation. In addition, one Member noted that whilst PBPK modelling may be used to better understand limited datasets, the introduction of modelling uncertainties may ultimately affect the scientific conclusions that are subsequently made.

54. However, despite the multitude of case-specific PBPK models, systems were being developed to enable generic PBPK models to be generated. One Member

noted that such a platform may be used in conjunction with the read-across approach to assess human health risks without the need for animal testing.

55. One Member noted that the US Environmental Protection Agency (EPA) recognises the development and application of PBPK models to be labour intensive. Thus, the EPA's current interests lie in a process through which they are able to generate high throughput data for use in a generic PBPK model, applicable to a large number of chemicals. Whilst less accurate than bespoke models, this may still be sufficient for a number of their risk assessment needs.

Item 11: Draft Statement on the safety of turmeric and curcumin - TOX/2019/38

56. No interests were declared.

57. Turmeric has been widely used for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases, for centuries.

58. Many of the purported pharmacological properties of turmeric which include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities, have been attributed to curcumin, a compound naturally present within turmeric rhizomes.

59. Due to its purported health benefits, the consumption of curcumin/turmeric supplements is becoming increasingly popular. However, in recent months there have been a number of reports of hepatotoxicity linked to the consumption of curcumin supplements.

60. The Food Standards Agency has been monitoring incidents related to consumption of raw and powdered turmeric and its supplements. In light of recent reports and due to the uncertainties surrounding the composition and possible contamination of these commodities, the Committee on Toxicity (COT) has been asked to comment on the risk to human health from turmeric and curcumin in their various forms.

61. A discussion paper (TOX/2019/52) was presented to the Committee in September providing information on the data available on the safety of curcumin in supplements and past raw turmeric contamination issues, particularly in relation to lead. The current statement expanded on exposure to raw and powdered turmeric, both in the diet and as used in higher quantities for their purported health benefits.

62. The Committee discussed the first draft of the statement and agreed that, for clarity, the issue of hepatotoxicity from supplement intake should be discussed separately from the issue of contamination of raw/powdered turmeric with heavy metals, and therefore suggested restructuring the statement to reflect this.

63. Regarding supplement intake, the Committee questioned whether there was information available on the individual cases of hepatotoxicity related to intake of

turmeric supplements and whether or not the cases could have been due to a localised issue with the supplements available in the Italian market. The Secretariat informed Members that at the time of preparing the statement information on the individual cases reported had not been located however should it become available it would be added to the second draft of the statement. It was noted that the Italian authorities had excluded contamination as a cause of the hepatotoxicity.

64. It was agreed that information on the sales and market share of turmeric/curcumin supplements should be included, to put into perspective the incidents of toxicity reported. Furthermore, Members noted that the increase in the incidents reported could be a reflection of the increase in the trend for consuming these supplements. Overall it was agreed that, based on the case studies presented, the effect is consistent with an idiosyncratic reaction, especially in people with underlying conditions such as latent impairment of biliary function. The Committee requested that the European Medicines Agency's conclusions of their review of curcumin be included in the statement and also for the text to reflect that effects in humans appear to occur at appreciably lower doses on a bodyweight basis than in experimental animals, where hepatocellular changes are observed only at high levels.

65. A number of amendments to the text were suggested and a revised draft statement would be brought to the March 2020 meeting.

Item 12: Draft Addendum to 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 - TOX/2019/75

66. No interests were declared.

67. The Committee on Toxicity in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants and young children aged 1 to 5 years, in support of a review by the Scientific Advisory Committee on Nutrition (SACN). The reviews would identify new evidence that has emerged since the Government's recommendations were formulated and will appraise that evidence to determine whether the advice should be revised.

68. In 2015, the COT identified a number of chemicals which might pose a risk to infants and young children and for which advice might be needed or to be amended. In 2019, the COT published an Overarching Statement, reviewing a number of these chemicals. The paper presented at the current meeting was the Draft Addendum to the Overarching Statement, discussing the conclusions of the Committee regarding the remaining chemicals.

69. The Committee discussed the Addendum and a number of editorial suggestions were made; minor clarifications were requested for some of the chemicals and would be addressed in the final version. The Chair also asked for clarification on the origin of the list of chemicals. Members agreed that the history of the establishment of the HBGVs would not be required in the Addendum; it should focus on the most recent and relevant HBGVs.

70. Members discussed the current structure of the Addendum and noted that due to the document's length, an index or table of contents would be beneficial. Several statements by the COT and other bodies were suggested as possible templates for restructuring. Members also suggested a table dividing the chemicals discussed into three groups, namely chemicals of no concern, chemicals of concern and chemicals for which a concern cannot be excluded due to data gaps. This would allow for a clear overview of the main conclusions.

71. Members agreed that the section on aflatoxins required redrafting and suggested broadening the discussion on the exposures and conclusions. The revised section would be circulated to Members for comment.

72. The Committee agreed to finalise the Addendum by Chair's action.

Item 13: Paper for Information: FSA Scientific Advisory Committees (SACs) update - TOX/2019/76

73. The SAC update paper would be circulated after the meeting.

Item 14: Any other Business

74. The Secretariat raised other items of business.

75. Members were informed of the Microsoft Teams site as a means of promoting improved communication and joint working between the scientific advisory committees and their secretariats. This was currently being tested by the ACNFP and if members are willing, it is proposed that their email addresses can be added to the system to grant access and allow collaboration on live documents.

76. The Committee were informed that the publication of EFSA consultations on ochratoxin A (OTA), glycosides and poly-fluoroalkyl substances was expected on 4th December 2019, 12th December 2019 (NB. subsequently postponed) and 27th January 2020, respectively. These would be circulated for comment by correspondence, if the timescales did not allow them to be considered at the 27th January 2020 COT meeting.

77. Members were made aware that the Food Standards Agency (FSA) have been revising areas of research in order to have a more strategic approach to commissioning research. The Committee would be updated on this once more information is available and provided with a chance to comment.

78. The Secretariat concluded that in January 2020, there would be a new round of central recruitment for various Scientific Advisory Committees (SACs). Details would be circulated.

79. No other business was raised by the Committee.

Date of next meeting

80. The next meeting will be held on Tuesday 28th January 2020 at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ.