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

## Minutes of the meeting held on Tuesday, 4th December 2018 in Broadway House Conference Centre, Tothill St, London SW1H 9NQ

Present

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| Chairman: | Dr Phil Botham (deputising) | |
| COT Members: | Ms Jane Case<br>Dr James Coulson<br>Dr René Crevel<br>Prof John Foster<br>Dr Mark Graham<br>Dr Sarah Judge<br>Prof Brian Lake<br>Dr Mireille Toledano<br>Prof Faith Williams | |
| Food Standards Agency (FSA) Secretariat: | Mr B Maycock<br>Ms R Acheampong<br>Dr A Cooper<br>Dr B Doerr<br>Ms F Uy<br>Ms C Mulholland<br>Ms F Hill<br>Dr D Hedley<br>Dr O Osborne<br>Ms C Potter<br>Mr J Shavila<br>Ms C Tsoulli | FSA Scientific Secretary |
| Public Health England (PHE) Secretariat: | Britta Gadeberg | PHE Scientific Secretary |
| Assessors: | Prof T Gant | PHE |
| Officials: | Ms Harriet Robson<br>Ms Rachel Elsom<br>Ms Daphne Duval | DHSC<br>PHE<br>PHE |

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| | Dr Amie Adkin | FSA |
| | Dr Selwyn Runacres | FSA |
| Other Invited Experts and Contractors: | Prof P Aggett | SMCN |
| | Dr Sarah Bull | WRc |
| | Dr Kate Vassaux | WRc |
| Observers: | Mr M Hartwig | Energy Drinks Europe |

**Contents**

## Announcements

1. The Chair welcomed Members and other attendees.

2. The Chair also welcomed a new member of the FSA COT Secretariat, Frederique Uy.

## 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 had been received from COT Chair Prof Alan Boobis and COT Members Prof Roy Harrison, Prof Matthew Wright, Dr John Thompson, Dr Caroline Harris and Ms Juliet Rix. Dr Botham was deputising as Chair. Ms Michaela Benton from HSE and Mr Ian Martin from the Environment Agency had also sent apologies.

5. Prof. Boobis had submitted written comments.

## Item 2: Minutes from the meeting held on 23rd of October 2018.

6. The minutes were accepted subject to minor editorial amendments and the following changes:

7. Two observers had been missed from the list of attendees and would be added.

8. Para 21, lines 6-7: Delete “and acetylcholine receptors (ACh)”

9. Para 21, lines 7-9: Delete “The mechanism of action (MoA) of PFRs for any neurotoxic effect may not be the same as for OPs and may potentially occur as a more generalised effect through inhibition of neuropathy target esterase.”

10. Para 24, line 8: Add “The Committee noted that the mode of action for any potential neurotoxic effect is unlikely to be the same as for OP pesticides.”

## Item 3: Matters arising from the meeting held on 23rd October 2018

*Item 3: Matters arising from previous meetings:*

11. Para 6: The Statement on copper had now been published.

12. Para 8: The Statement on methylmercury had now been published.

*Item 9: Discussion paper on the EFSA opinion "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food"*

13. Para 51: The draft COT minutes of this discussion had been submitted to EFSA to inform them of the COT's views. The EFSA opinion has now been published. Some Member States had disagreed with the opinion and EFSA had published these Member States' comments. The FSA would need to finalise a UK position on the EFSA opinion. In light of this, it would circulate the other Member States' comments for COT views on whether they would wish to elaborate on any of their views expressed at the October meeting or make any further comments.

14. In particular, the FSA would like to know if the reservations identified by the COT in these comments would form a basis for challenging the new TWI.

*Item 11: Any other business*

15. Para 53: Members were updated on the recruitment process for the advisory committees and expert working groups. The recruitment campaign had been launched. Members were asked to bring this to the attention of anyone they thought might be interested.

**Item 4: Risks from a veterinary product in the diet (Reserved Business) (TOX/2018/44)**

16. Professor Boobis declared that he was a member of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) when it evaluated ractopamine. No other interests were declared.

17. This item was discussed as reserved business.

**Item 5: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)**

18. Professor Boobis declared that he chaired the International Organization for Standardization (ISO) Technical Committee (TC) 126 Working Group (WG) 10 on an "Intense smoking regime"; the WG does not address electronic nicotine delivery systems (ENDS). He was also a member of the World Health Organization Study Group on Tobacco Product Regulation (WHO TobReg), which had discussed ENDS. Professor Williams declared a personal non-specific interest in that her brother-in-law was a retired senior manager from British American Tobacco (BAT), one manufacturer of e-cigarettes, and in receipt of a pension from BAT.

19. The COT was reviewing the potential toxicity of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS).

**Item 5a: A review of data relating to developmental toxicity in offspring following parental exposure to nicotine (TOX/2018/45)**

20. No additional interests were declared.

21. At the July 2018 COT meeting an overview paper was presented on the toxicity of the electronic nicotine delivery system (ENDS) constituent, nicotine, (TOX/2018/25). Members requested further information on developmental toxicity of nicotine. TOX/2018/45 provides more information on this topic, comprising a general review of the literature of relevance to developmental toxicity to offspring from parental exposure to nicotine in humans. Data relating to developmental effects of exposure in adolescence were not included. Literature searches identified a very large data set, mostly of relevance to maternal exposure, with a very small number of publications relating to paternal exposure.

22. Data from studies in humans were reviewed including an overview of developmental effects in offspring following maternal or paternal exposure to tobacco products, and a detailed review of studies that have investigated effects of nicotine replacement therapy (NRT) use in pregnancy were also presented.

23. The Committee agreed that, regarding the human data, it was difficult to determine the contribution of nicotine specifically, thus reducing confidence that the effects observed were nicotine-specific. This was because the available studies on NRT showed only low levels of abstinence from smoking, and thus the source of nicotine (NRT or tobacco) could not be determined, though it was noted that this would reflect the real world. In addition, the studies had not been designed to investigate the health effects of nicotine.

24. Taking into consideration the effects, particularly on the developing lungs, observed in animal studies, the Committee concluded that there was biological plausibility for an effect of nicotine on development.

25. The Committee agreed that using ENDS to replace smoking could potentially lower risks related to traditional smoking, however the risk to health, and potential for addiction, from nicotine intake still remains. There was also concern that depending on use of ENDS devices by a smoker, the nicotine exposure could potentially increase compared to that from conventional cigarettes.

26. The Committee also concluded that, in the absence of information on actual nicotine exposures from use of ENDS, and taking into account the data presented in the review, it is possible that nicotine-related health effects could occur in long term use of these products.

**Item 5b: Additional information on developmental toxicity studies of E(N)NDS aerosols (TOX/2018/46)**

27. No additional interests were declared.

28. As part of this COT review, at the July 2018 COT meeting a paper reviewing studies that have evaluated the potential toxicity of E(N)NDS aerosols was discussed (TOX/2018/24). Members had requested further information on the studies relating to potential developmental toxicity that could occur in offspring as a result of maternal exposure to E(N)NDS aerosols. This paper provided more information on these studies, plus an update of subsequently published literature relating to this topic.

29. The Committee commented that it would be helpful if some quantitative indication were provided of what the comparable exposures for the various metrics would be in humans. It was also pointed out that when using cotinine as a proxy for nicotine exposure in animal studies, species differences in metabolism might be important when interpreting the results.

30. The data on global methylation were not very convincing. There were large errors on some of the measurements and very few of the methyltransferases show significant changes. The Members were surprised by some of the statements in the paper by Zelikoff *et al*. (2018)[1] as similar results were obtained with and without aerosols. There was also a query about the sample control, all of which brought the reliability of the paper into question.

31. Some indicative neurological and lung development effects and metabolic effects had been identified in the offspring following maternal exposure to E(N)NDS aerosols. There were numerous inconsistencies, between ENDS with and without nicotine, between males and females, between adults and offspring and some between studies (e.g. pup weight). These may be real differences, but further evidence is needed to substantiate the effects. Most were multi-parametric studies, and even with correction for false discovery rates, there needed to be replication of the findings, particularly in the absence of dose-response data.

32. In consideration of whether conclusions could be drawn on the risks relative to smoking conventional cigarettes, Members considered that there may be a relatively reduced risk compared to conventional cigarettes, but the risks described earlier cannot be excluded, especially relating to nicotine.

33. More generally, Members questioned the claim, often used to publicise E(N)NDS, that they were 95% safer than conventional cigarettes. The Committee considered that the reduction in risk would depend on the endpoint considered. A

[1] Zelikoff, J. T., N. L. Parmalee, K. Corbett, T. Gordon, C. B. Klein & M. Aschner (2018) Microglia Activation and Gene Expression Alteration of Neurotrophins in the Hippocampus Following Early-Life Exposure to E-Cigarette Aerosols in a Murine Model. Toxicol Sci, 162, 276-286.

considerable reduction in risk of lung cancer was anticipated due to lower exposure to tobacco-related carcinogens, but this would not necessarily be the case for all endpoints. It was also noted that the flavours used in these products have been given GRAS classification for the oral route, but they are inhaled in E(N)NDS products. It would also be useful to know how user exposure to nicotine compared between E(N)NDS products and conventional cigarettes.

34. The appropriate kind of investigative studies needed to be performed, and the correct data accumulated in order for the Committee to comment on the relative risk of E(N)NDS products compared with conventional cigarettes.

**Item 5c: Paper for information on COM and COC consideration of genotoxicity and carcinogenicity risks (TOX/2018/47)**

35. No additional interests were declared.

36. The COT was currently reviewing the possible human health effects of electronic nicotine (and non-nicotine) delivery systems (E(N)NDS, 'e-cigarettes'). In spring 2018, it was agreed that advice should be sought from COM and COC on the absolute and relative genotoxicity and carcinogenicity risks of E(N)NDS compared to conventional cigarettes, and if possible heated tobacco products. The COM and COC discussed papers on these topics at their June and July 2018 meetings, respectively. The COT reviewed the minutes from COC and COM.

37. It was noted that the Committee on Carcinogenicity (COC) considered tobacco to be carcinogenic without being heated, and that nicotine is not a carcinogen. The Committee on Mutagenicity (COM) conclusions indicated a lack of consistency in the evidence base depending on the type of study (OECD Test guideline study or other study type).

**Item 5d: Recent paper hypothesising role of nicotine in schizophrenia spectrum disorders (TOX/2018/52)**

38. No additional interests were declared.

39. This paper provided a recent review paper by Scott et al., 2018[2]. The review, of eight longitudinal studies, found evidence of a potential causal association between tobacco smoking and schizophrenia spectrum disorders, which the authors hypothesised was due to nicotine and therefore also a potential concern for E(N)NDS.

[2] Scott, J.G., Matuschka, L., Niemelä, S., Miettunen, J., Emerson, B., Mustonen, A. (2018) Evidence of a Causal Relationship Between Smoking Tobacco and Schizophrenia Spectrum Disorders. Frontiers in Psychiatry, 9: 607

40. Members considered that there should be caution in placing too much emphasis on a single paper, particularly since the findings were for tobacco smoking and did not directly relate to E(N)NDS. Although the paper included data from long term observational studies, the authors could not separate nicotine from tobacco smoke exposure. It was noted that it could be difficult to obtain good longitudinal exposure data specifically for nicotine.

41. The relationship between smoking and schizophrenia was interesting since smoking was very prevalent in this group.

42. It was important to consider exposure to nicotine in adolescence since cognitive development was still happening and therefore adverse neurodevelopmental effects could occur. It was noted that pre-effects of schizophrenia were apparent in adolescence before schizophrenia itself manifested at age 20-30.

43. Overall the Committee considered that the authors' conclusion that the risks associated with smoking could be extrapolated to E(N)NDS was premature since the role of nicotine was not fully understood; while nicotine could be involved there were other possible explanations.

44. As it was not legal to sell E(N)NDS products to under 18s, the COT had to date considered that effects in this group would not be assessed. However, the Members considered it would be helpful to bring together the available evidence on any health effects of E(N)NDS use on adolescents. Given the database was likely to be large, it was agreed that an overview of the topic would be provided. It was likely to be difficult to distinguish the effects of nicotine from those of tobacco smoke in the available studies. Where only data on tobacco smoking were available, the review could consider the studies where cotinine was used as a marker of nicotine exposure . It was suggested that recent reports by the US Surgeon General and the Royal College of Pathologists might be helpful as they covered adolescents.

45. Future activity on the E(N)NDS topic included the effects of bystander exposure, an update on the toxicity of the aerosol itself, and an assessment of the flavourings used in these products.

**Item 6: Draft overarching statement on the potential risk from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years (TOX/2018/48)**

46. No interests were declared.

47. The COT had been asked to review the risk of toxicity of chemicals in the diets of infants and young children aged 1-5 years, in support of a review by the

Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding.

48. Members had requested more detailed considerations of a number of chemicals, which were reviewed in previous scoping papers (TOX/2018/28, TOX/2018/31, TOX/2018/36). The subsequent draft overarching Statement presented at this meeting discussed the conclusions of the COT regarding a number of these chemicals. It provided an overview of the chemical characteristics yet focused mainly on the exposure assessment (where applicable) and the risk characterisation and conclusions.

49. The Committee asked for the heading of legacy pesticides to be changed to legacy chemicals to allow other chemicals that had been phased out to be included in this section.

50. It was noted that PHE were not currently consulting on draft recommendations for saturated fat, as stated; PHE agreed to provide text to reflect the work they were currently undertaking and also to update some of the background information regarding SACN's work on the diet of infants and young children.

51. The Committee agreed to finalise the overarching statement by Chair's action.

**Item 7: Folic acid – Statement on the tolerable upper level (TUL) (TOX/2018/49)**

52. No interests were declared.

53. It was well established that supplementation with folic acid can reduce the risk of having a neural tube defect (NTD) affected pregnancy. Current UK Government advice was that women should take a folic acid supplement prior to conception and up to the third month of pregnancy. However, as many women do not take supplements and many pregnancies are unplanned, the rate of NTD-affected pregnancies had not significantly changed since this advice had been introduced.

54. Consequently, SACN had recommended that wheat flour should be fortified with folic acid. This recommendation had been with the proviso that fortification should not increase the number of people who were currently exceeding the Tolerable Upper Level (TUL) for folic acid, meaning that levels in some supplements or other fortified products would need to be reduced.

55. TULs (or equivalent) of 1 mg/day had been set by a number of risk assessment bodies based on the development of neurological damage in patients with pernicious anaemia treated with folic acid. Whereas the IOM considered the main concern was the possible folic-acid induced precipitation or exacerbation of neuropathy in individuals with pernicious anaemia, the SCF and the EVM based their TUL/GL on the ability of folic acid to mask the diagnosis of pernicious anaemia. Whilst this would improve haematological status, it would not prevent the neurological effects associated with the condition. The SCF noted that they could not

rule out the possibility that folic acid could increase the progression of neurological signs, and that this should be considered the most serious adverse effect.

56. A recent paper by Wald et al. (2018)[3] argued that the basis of the TUL was flawed (see scoping paper TOX/2018/12 for details). The criticisms made in the paper applied to the IOM TUL but some would also be relevant to the Guidance Level established by the UK Expert Group on Vitamins and Minerals (EVM) and the Upper Level (UL) established by the SCF, since very similar databases were used to set the TUL. Wald et al.'s main criticism of the IOM related to them using the possibility of folic acid having a direct neurotoxic effect in the establishment of the TUL. The UK EVM did not use this possibility in in setting the GL. Wald et al. had analysed the data on direct neurotoxicity for a dose-response relationship but had not analysed the masking of B12 deficiency in the same way.

57. The Committee had discussed the basis of the TUL at their meetings in July and October 2018 and agreed that the data on which the TUL is based should be reanalysed to see if any dose-response relationship could be determined. The Committee's comments and views were included in a draft statement which was discussed at the current meeting.

58. Members requested a number of minor editorial amendments be made to the draft Statement and agreed that it could be then cleared by Chair's action.

## Item 8: First statement on the potential risks from energy drinks in the diet of children and adolescents (TOX/2018/50)

59. Professor Alan Boobis declared that he had consulted for Coca Cola until 2014, and in 2014 he had signed a consultancy contract with Red Bull but had not taken up the post and received no payment.

60. No other interests were declared.

61. Recent media interest had led to a voluntary restriction on the sale of so-called energy drinks to adolescents under 16 years of age by the major retailers. The Committee thought it appropriate, after the subject was introduced at the May meeting (TOX/2018/17), to consider in more detail the evidence for possible adverse effects from the consumption of these products by young people.

62. Discussion papers (TOX/2018/27 and TOX/2018/41) had previously been put before the Committee, in July and October, respectively. The comments of the Committee were acted upon to produce this first draft Statement.

63. The table in Annex 1 of the caffeine and sugar content of various commercially available caffeinated beverages, including "energy drinks" had been amended. The table of drivers for consumption of "energy drinks" had been amended for ease of comparison between studies. A précis had been made of the

[3] Wald, N.J., Morris, J.K., Blakemore, C., 2018. Public health failure in the prevention of neural tube defects; time to abandon the tolerable upper intake level of folate. Public Health Reviews, 39:2

information on the reported cardiovascular effects of “energy drinks”. The Committee did not ask for further section summaries to be made.

64. Professor Boobis had suggested various amendments to the text of the paper, with which the Committee agreed. A Member offered to provide information on the involvement of baroreceptors in the cardiovascular responses to caffeine reported in the paper.

65. Overall, the Committee found that there was little current scientific evidence that “energy drinks” posed a specific risk to the health of children and adolescents, especially when considered in the context of confounding factors. Although not in the remit of the COT, Members acknowledged that societal effects, such as behavioural changes in school-age children following excess caffeine consumption, could not be ruled out. This finding was in line with the conclusions of Parliamentary Select Committee report on “energy drinks”.

66. It was agreed that, following revision, the draft Statement would be cleared by Chair’s action.

**Item 9: Review of potential risks from 4, 15-diacetoxyscirpenol in the diet of infants aged 0 to 12 months and children aged 1 to 5 years (TOX/2018/51)**

67. No interests were declared.

68. A scoping paper (TOX/2015/32) “COT contribution to SACN review of complementary and young child feeding; proposed scope of work for 1-5 year old children” had been reviewed by the COT in 2015. A further scoping paper for mycotoxins had been presented to the COT in 2017. When the COT discussed this in July 2017, JECFA had recently published their evaluation but EFSA were still working on theirs.

69. This paper was a review of the new EFSA acute reference dose (ARfD) and tolerable daily intake (TDI) values established for 4,15 DAS, the latter of which was >10-fold higher than the provisional maximum tolerable daily intake (PMTDI) established by JECFA. Included in this paper were data on the toxicity and toxicokinetics and the derivations of the health-based guidance values (HBGVs), as well as exposure assessments.

70. The Committee requested that the terminology “vulnerable groups” used for the cancer patients be replaced with “atypical”, which was the terminology used by Cancer Research UK.

71. The toxicokinetics of 4,15-DAS were discussed after the Committee queried the bioavailability of 4,15 DAS and conjugate materials. Some clarity was sought on certain papers, specifically Wang et al.[4] (1990).

[4] Wang, J.S., Busby Jr, W.F. and Wogan, G.N., 1990. Comparative tissue distribution and excretion of orally administered [3H] diacetoxyscirpenol (anguidine) in rats and mice. Toxicology and applied pharmacology, 103(3): 430-440.

72. The Committee noted the limited toxicity data available in experimental animals, using intravenous (i.v.), intraperitoneal (i.p.) and oral routes. The Committee agreed that it was appropriate to use the human studies with DAS (anguidine) administered i.v. as a cytostatic anticancer drug in the hazard characterisation.

73. The Committee discussed the toxicity data comparing i.v. vs oral exposure in relation to gastrointestinal (GI) toxicity. It was noted that very little data were available using the oral route. The only direct oral/i.v. comparison was for the rat, where there was a 5-fold difference in $LD_{50}$. Hence, this suggested that the use of a no observed adverse effect level (NOAEL) after i.v. dosing would likely over-estimate risk and should reasonably be expected to protect against oral exposure. Taking all this into consideration, the Committee agreed with the use of i.v. data to establish the health-based guidance values (HBGVs).

74. The Committee agreed with the establishment of an ARfD for DAS, the use of the clinical trial data, and the application of an uncertainty factor (UF) of 10 to account for differences in toxicokinetics and toxicodynamics in humans. Furthermore, the application of the UF of 10 to the reference point would make it conservative and precautionary.

75. The Committee agreed with the establishment of the TDI for DAS, based on the NOAEL for haematotoxicity and myelotoxicity from the clinical trial data.

76. The Committee then discussed the establishment of the PMTDI by JECFA and pointed out that inclusion of DAS in the group PMTDI for T2 and HT2 was quite conservative, given that the JECFA group PTMDI was 0.06 µg/kg bw, whilst the EFSA TDI for DAS was 0.65 µg/kg bw. Establishment of the JECFA PMTDI was not based on DAS-specific information.

77. The Committee agreed that this discussion should be included in the overarching Statement rather than a separate document.

78. Based on the current HBGVs, the Committee recommended the use of the EFSA ARfD and TDI values, rather than the PMTDI established by JECFA, for future risk assessments for 4,15-DAS.

**Item 10: paper for Information: FSA Scientific Advisory Committees (SACs) update (TOX/2018/52)**

79. This paper was provided for information.

**Item 11: Any other Business**

80. Members were informed that EFSA had launched a public consultation on draft guidance on the threshold of toxicological concern (TTC) approach, produced

by its Scientific Committee. Members were asked to send any comments to the Secretariat by 3rd January 2019.

81. Members were informed that EFSA had also launched a public consultation on the draft "Scientific Opinion on evaluation of the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels". Members were asked to send any comments to the Secretariat by 11th January 2019.

82. Any comments would then be compiled and submitted to EFSA before the deadlines.

**Date of next meeting**

83. The next meeting would be held on Wednesday 6th February 2019. The venue would be announced at a later stage.