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

Minutes of the meeting held on Tuesday, 3rd July 2018 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ

Present

Chairman:	Professor Alan Boobis	
COT Members:	Dr Phil Botham	
	Ms Jane Case	
	Dr James Coulson	
	Dr Rene Crevel	
	Prof John Foster	
	Prof Roy Harrison	
	Dr Sarah Judge	
	Prof Brian Lake	
	Dr John Thompson	
	Dr Mireille Toledano	
	Prof Faith Williams	
	Prof Matthew Wright	
Food Standards Agency (FSA) Secretariat:	Dr D Gott	FSA Scientific Secretary
	Mr B Maycock	FSA Scientific Secretary
	Ms C Mulholland	
	Ms F Hill	
	Miss Rufina Acheampong	
	Dr D Hedley	
	Ms C Potter	
	Dr B Dörr	
	Ms C Tsoulli	
Public Health England (PHE) Secretariat	Britta Gadeberg	PHE Scientific Secretary
Assessors:	Dr T Marczylo	PHE
Officials:	Ms Rachel Elsom	PHE
	Ms Daphne Duval	PHE
	Ms Wendy Dixon	FSA
	Mr Carles Orri	FSA

	Ms Firth Piracha	FSA
Other Invited Experts and Contractors:	Dr Sarah Bull	WRc
	Dr Kate Vassaux	WRc
	Prof Peter Aggett	SCMN
	Martyn Hooper	Pernicious Anaemia Society
	Professor Martin Warren	University of Kent
	Chris Alford	UWE
	Debbie Webb	DHSC

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Announcements

1. The Chair welcomed Members and other attendees to the meeting.

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 COT Members Ms Juliet Rix and Dr Mark Graham and PHE assessor Professor Tim Gant; Dr Tim Marczylo was deputising in his absence.

Item 2: Minutes from the meeting held on 8th May 2018.

4. The minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 8th May 2018.

Matters arising from previous meetings

5. Para 10: The draft statement on copper in the infant diet had been revised following suggestions and comments from SMCN and Professor Aggett, and had been sent to the Chair for clearance.

6. Para 11: The statement on T2 and HT2 in the infant diet had been published.

7. Para 12: The Secretariat has been working on the comments received from COT, COC and COM members on the second draft statement of the Committees' joint workshop on the use of epigenetics in chemical risk assessment.

8. Para 14: *Report of the COT-COC Synthesising Epidemiological Evidence Subgroup (SEES).* This was being finalised ahead of being cleared by Chair's action.

Item 7: Draft statement on methylmercury in the infant diet.

9. Para 31: This statement was being finalised and would be sent to the Chair for clearance.

Item 4: Folic acid – scoping paper on setting upper levels of intake – TOX/2018/12

10. No interests were declared.

11. Mr Martyn Hooper, chair of the Pernicious Anaemia Society (PAS) and Professor Martin Warren from the University of Kent (an expert on vitamin B_{12} and the methods of diagnosing pernicious anaemia) were in attendance to assist the Committee with their deliberations.

12. It is well established that supplementation with folic acid can reduce the risk of having a neural tube defect (NTD) affected pregnancy. UK Government advice is 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 has not significantly changed from prior to this advice.

13. Consequently, the Scientific Advisory Committee on Nutrition (SACN) have recommended that wheat flour should be fortified with folic acid to increase the folate status of the population and thereby reduce the risk of having a NTD affected pregnancy. This recommendation came with the proviso that fortification should not increase the number of people who were currently exceeding the Guidance/Tolerable Upper Intake Level (GL/UL) for folic acid, meaning that levels in some supplements or other fortified products would need to be reduced.

14. ULs (or their equivalents) of 1 mg/day have been established by a number of advisory bodies, based on the observation that folic acid can mask or delay the diagnosis of pernicious anaemia by improving haematological status while allowing neurological damage also associated with the condition to progress. The UK Expert Group on Vitamins and Minerals (EVM) established a guidance level of 1 mg/day rather than a UL as the database was insufficient to set a UL. Both the US Institute of Medicine Food and Nutrition Board (IOM) and the EU Scientific Committee on Food (SCF) also considered that it was not possible to rule out the possibility that folic acid could exacerbate neurological damage in pernicious anaemia, although both noted that there was no clear evidence for this in humans.

15. A recent paper by Wald *et al*., 2018[1] argues that the basis of the UL is flawed (see scoping paper TOX/2018/12 for details). The criticisms made in the paper applied to the IOM UL but some will also be relevant to maximum intakes recommended by EVM and SCF, as some of the same endpoints were used to establish the UL.

[1] 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.

16. The Committee on Toxicity agreed that the UL should be reconsidered, firstly by considering the basis on which it was established and then, if necessary, consideration of the rest of the database to determine whether a UL was necessary based on other endpoints.

17. The discussion paper TOX/2018/26 provided details on the case studies used to establish the UL by the various bodies as well as background information on pernicious anaemia itself, including its symptoms and prevalence, and on the linked metabolism of folic acid and vitamin B_{12}. It also provided information on current methods of diagnosis of pernicious anaemia.

18. It was noted that in the initial recommendations from COMA (the Committee on the Medical Aspects of Food Policy - the predecessor to SACN) the advice on an upper level for folic acid intake had been based on the EVM guidance level but that this had not been revisited since then. There had been later concerns about carcinogenicity and SACN had worked with COC on this. The most recent consideration of fortification by SACN in 2016 had been in response to a specific question from Food Standards Scotland.

19. Pernicious anaemia is a disease of autoimmune origin in which there is a reduction in the number of cells that produce the intrinsic factor necessary for the absorption of vitamin B_{12} which in turn is essential for erythropoiesis and myelin synthesis. Pernicious anaemia could affect up to 10% of the population but the interaction with folic acid was well known clinically and it was noted that where there was uncertainty over diagnosis, B_{12} treatment would be started before folic acid treatment. Individuals have variable requirements for both folic acid and vitamin B_{12}.

20. However, there are a number of uncertainties around the diagnosis of pernicious anaemia. The symptoms are non-specific and slow in onset so it often takes some time for it to be accurately diagnosed (one third of PAS members wait for 5 years or more for a diagnosis). Changes in cognitive function can occur before anaemia becomes apparent. The Schilling test for the diagnosis of pernicious anaemia is no longer used and there is currently no routinely-applicable means of testing for functional vitamin B_{12} levels. Patients with pernicious anaemia sometimes have serum vitamin B_{12} levels in the normal range but these are not necessarily functional and it is therefore helpful to measure metabolites such as transcobalamin and methylmalonic acid (MMC).

21. There are no specific NICE guidelines on pernicious anaemia though there are for megaloblastic anaemia, with a proposed range of tests that can distinguish the type of anaemia and its underlying cause if any. The cut-off level for deficiency of vitamin B_{12} of 180 pmol/L was of uncertain relevance and was certainly not “a cliff edge”. It was necessary to understand how individual risk fitted within the normal

range. There are individuals with undiagnosed pernicious anaemia – but estimates vary on how large this group is.

22. It should be possible to screen for the vulnerable population. However, whilst methods are available to assess functional vitamin B_{12} levels, these are not widely and routinely applicable. Hence, it is currently not possible to reliably screen the population for pernicious anaemia, although this should be possible when a reliable, readily-applicable test becomes available.

23. There were some studies on the change in the prevalence of pernicious anaemia before and after fortification with folic acid became mandatory in the US but the results were somewhat conflicting, and the studies were not particularly comparable.

24. There was no convincing evidence that folic acid *per se* causes neurotoxicity directly in humans. It was unclear from the case reports whether the neurotoxicity had been accelerated by folic acid treatment or would have happened anyway. There were some limited data in animals but there were methodological problems with these studies. No additional animal studies or more recent human case studies had been identified.

25. It was agreed that folic acid could mask or delay the diagnosis of pernicious anaemia by improving the anaemia which led to an individual seeking medical advice, while the neurotoxicity proceeded untreated. Should a reliable diagnostic test become available then this end point might no longer be relevant, though the rest of the database would require review to ensure that a GL/UL was not needed to protect against another, albeit less sensitive, endpoint.

26. It was agreed that it was appropriate to use the effect of folic acid on masking diagnosis of pernicious anaemia as an endpoint, but it was not possible to identify a LOAEL or NOAEL from the case studies available. If 1 mg/day was not appropriate it was unclear what was, though it was very likely that this would be greater than 1 mg/day. It was proposed by some authors that the duration of consumption was important as well as the dose.

27. It was agreed that the analysis by Wald and colleagues should be incorporated into the final paper. The level of 1 mg/day was protective against any risk from folic acid and this level could potentially be increased if the uncertainties were reduced.

28. It was unlikely that there was another sub-population more at risk from folic acid than individuals with pernicious anaemia.

29. It was agreed that given the significant Ministerial and public interest in this topic, it would be appropriate to prepare a brief statement or position paper on this issue, to set out the interim COT conclusions

Item 5: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (e-cigarettes):

30. The Chair declared that he was a member of the World Health Organization Study Group on Tobacco Product Regulation (WHO TobReg) and Convenor (Chair) of the International Organization for Standardization (ISO) Technical Committee (TC) 126 Working Group 10 on an "Intense smoking regime". 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. Professor Harrison declared that he had contributed to a paper on the volatile compounds in e-cigarette aerosols.

Item 5a: Follow up to paper 3: additional information on 13-week inhalation studies in rats of propylene glycol aerosol (Suber *et al*., 1989) and glycerol aerosol (Renne *et al*., 1992) (TOX/2018/23)

31. As part of the review of the potential human health effects of electronic nicotine (and non-nicotine) delivery systems (E(N)NDS), information on the toxicity of E(N)NDS constituents was being evaluated. A discussion paper reviewing the toxicity of the major constituents, propylene glycol (PG) and vegetable glycerine (VG, glycerol), with a focus on inhalation as aerosol, was discussed at the May 2018 COT meeting. Two key studies had been highlighted, which had evaluated the toxicological effects of exposure for 13 weeks to aerosols of PG (Suber *et al*. 1989)[2] and glycerol (Renne *et al*., 1992)[3]. Members were provided with further details of these studies, along with proposals for possible calculations of HBGVs for use in evaluation of exposures to PG aerosol and glycerol aerosol from E(N)NDS.

32. The Renne *et al*., paper had reported an increased incidence of minimal squamous metaplasia of the epithelium lining the base of the epiglottis with exposure to VG, which was statistically significant at the top dose. In addition, one rat in this group showed mild squamous metaplasia. Members observed that this area of the larynx was exposed to food particles and was very susceptible to squamous metaplasia. The rats were exposed nasally but no adverse effects were observed in the nasal passages as would be expected for an irritant. It was concluded that if there was an effect it was minimal, not of toxicological significance, and that the top dose could be considered a NOAEL.

[2] Suber *et al*., (1989). Subchronic nose-only inhalation study of propylene glycol in Sprague-Dawley rats. Food Chem. Toxicol., 27, 573-583.
[3] Renne *et al*., (1992). 2 Week and 13 week inhalation studies of aerosolized glycerine in rats. Inhalation Toxicology, 4, 95-111.

33. Nasal haemorrhages were reported in the paper by Suber *et al*., (1989) with PG at all dose levels. The authors had suggested that this effect was caused by local dehydration but Members considered that an irritant effect was also possible. However, it was unusual for haemorrhage to have been reported for up to 13 weeks without any other pathology being observed. Microscopic evaluation of the nasal cavity had shown thickened respiratory epithelium in the posterior portion of the nasal cavity, with increased numbers of goblet cells and goblet cell mucin content, in the medium and high dose groups. Members observed that the Dutch Expert Committee on Occupational Standards had identified the low dose of 16 ppm as a NOAEL on this basis. There were no histological changes in the trachea, lungs or larynx.

34. Members considered that the nasal route of exposure was not directly relevant to use of E(N)NDS, and observed that, given the reported particle diameter in this study of 2 µm, the trachea and larynx would have been exposed and yet no adverse effects were observed in these tissues. However, while the route of exposure was of equivocal relevance, the NOAEL of 16 ppm could be used to protect against potential irritant effects on the larynx as the first site of contact in the respiratory tract from E(N)NDS use.

35. The Committee concluded that the uncertainty factor used to set the HBGV should be lowered from 100 to 10 as the effects of concern for both PG and VG were a local irritant effect at site of contact and thus inter- or intra-species differences in toxicokinetics would not be of concern.

Item 5b: *Paper 4: Toxicological and epidemiological evaluations of E(N)NDS aerosol exposures (TOX/2018/24)*

36. Following on from the discussion paper (TOX/2018/19) presented at the May 2018 COT meeting, which reviewed studies that have evaluated the toxicity of exposure to aerosols of PG and of glycerol as individual exposures, TOX/2018/24 summarised published data relevant to the toxicity of E(N)NDS aerosol mixtures. Human epidemiological and clinical data and experimental studies in animals had been included but studies relating to genotoxicity and carcinogenicity were not reviewed in detail as these would be considered by the COM and COC.

37. Members gave consideration to human and animal studies which focussed on a range of respiratory and cardiovascular endpoints. There were no unexpected findings noted and the case studies presented did not provide evidence for any cause and effect relationships above what would be expected from inhalation of vapour containing nicotine. It was noted that use of E(N)NDS by adolescents prone to asthma resulted in exacerbation of symptoms, though it was not by more than would be expected from CC smoking.

38. Generally, use of E(N)NDS products is associated with fewer risks than conventional cigarettes but Members agreed that the communication of this observation should not be viewed as meaning that these products are risk-free. Members noted that more information on developmental studies, particularly those

focusing on effects independent of nicotine would be of value. There was not, as yet, sufficient information of the consequences of long-term exposure, and such studies would help identify any vulnerable individuals. It was noted that people with respiratory sensitivity could plausibly be susceptible if they were a naïve user use of E(N)NDS products. Consideration should be given on the need for advice to people with COPD, cardiovascular disease and cystic fibrosis as susceptible groups. Licensing these products would be a useful approach for capturing more clinical data in future, as it was noted that device failure or adjustment of power settings could result in high exposures The Committee noted that exposure of bystanders to E(N)NDS aerosol would be considered in a future paper.

Item 5c: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (e-cigarettes). Paper 5: Preliminary overview of nicotine toxicity – TOX/2018/25

39. This paper provided an outline of evidence on the toxicity of nicotine, as the Committee had previously identified that this would be an important aspect to consider as part of the ongoing review of E(N)NDS. This paper provided an overview of data from recently published reviews that have discussed nicotine toxicity in the context of exposure from ENDS. Original publications were not obtained or evaluated.

40. The Committee agreed that the review was helpful and up-to-date. Nicotine in a modern ENDS device has a similar pharmacokinetic profile to that from a conventional cigarette, which may be desirable for their use to stop smoking. However, it was noted that this might also enable addiction to nicotine in naïve users, though it was anticipated that the addiction process may not be the same for E(N)DS as for conventional cigarettes, since factors additional to nicotine are involved in this.

41. The availability of nicotine from ENDS was likely to vary across different products depending on the pH of the liquid. For conventional cigarettes it was noted that ammonia is added to the tobacco to ensure effective absorption. A new device with high popularity on the market in the US was reported to contain the nicotine as a salt rather than in acidic or basic form found in other ENDS devices.

42. The Committee noted that the current advice for pregnant women is to stop smoking completely, or use nicotine replacement therapy to aid in stopping smoking but if that is not possible then to use E(N)NDS. Members agreed that the effects of nicotine on the developing nervous system should be considered further. The COT noted that the animal and human data suggest that nicotine *per se* is not carcinogenic, and the mechanistic argument for an effect of nitrosation of nicotine is not borne out by the evidence.

43. There was a discussion around the levels of nicotine in the ENDS aerosol but it was noted that individuals tend to titrate their nicotine intake to achieve the desired

nicotine effect. This might impact on relative exposure to other chemicals if people use stronger or weaker nicotine solutions, similar to the finding that people smoked more cigarettes if they used 'light' cigarettes when these were introduced.

44. In terms of use, it was noted that it was unknown whether once someone switches to E(N)NDS devices, they continue with it for a lifetime, or over time stop using such devices. In addition, the possibility that *de novo* uptake of E(N)NDS might occur from people who would not otherwise have taken up smoking would be difficult or impossible to put a number on. The Committee were informed that there were data available from the UK on uptake e.g. by former smokers and ongoing use profiles from Action on Smoking and Health.

Item 6: Scoping paper on the potential risks from energy drinks in the diet of children and adolescents – TOX/2018/27

45. The Chair, 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. Nonetheless, he felt that the Chair for this item should pass to Dr John Thompson, although Members agreed that he (AB) should not be excluded from the discussion.

46. The Chair welcomed Professor Chris Alford from the University of the West of England, who was present to provide expert advice as he had previously done for the 2012 COT statement on energy drinks and alcohol. Professor Alford declared that he received funding from Red Bull.

47. The Committee debated the definition of the term "energy drink" since other beverages contained similar concentrations of sugar, some contained caffeine (albeit at lower concentrations) and moreover, there were sugar-free varieties available. The term "stimulant drinks" was proposed but, on advice, members decided that they should refer to these carbonated drinks, with a caffeine content of over 150 mg/litre, as "energy drinks" (always in inverted commas) to indicate that this was the common name for these products. It was noted that such drinks are consumed cold.

48. Members decided that a high sugar content was not unique to "energy drinks" and that there were mechanisms, such as the new "sugar tax", available to deal with sugar in beverages. The Chair pointed out that sugar not only increased palatability of these drinks but might also affect caffeine absorption by osmotic effects and by promoting gastric emptying.

49. The Committee recognised that caffeine was a diuretic at high doses and had effects on heart rate and blood pressure. The response to caffeine appeared to be influenced by the presence of food, and individual's intrinsic metabolism, acquired

tolerance, withdrawal status and by psychological parameters such as consumer expectations and societal drivers of consumption.

50. Members questioned whether the focus on children and adolescents was suitable: a comparison with the effects on adults would determine if the level of concern differed in the younger age groups. Adults also consume high caffeine beverages – coffee and tea – and by the time both these drinks and chilled "energy drinks" reach the small intestine, where caffeine is absorbed, they are all at body temperature, so any purported effects of temperature difference at the time of consumption on absorption should be negated.

51. Professor Alford pointed out that caffeine consumption surveys in the EU, USA and Australia all showed that national caffeine consumption was less than the maximum recommended level set by EFSA of 3 mg/kg bw.

52. The Chair suggested that more detail on the paper of Miles-Chan[4] *et al*. (2015), which appeared to show effects of an "energy drink" that could not be attributed to caffeine alone, should be provided.

53. The Committee did not consider either taurine or D-glucurono-γ-lactone in "energy drinks" to be of toxicological concern.

54. Members pointed out that adolescents experiment and behave in ways that may be seen as harmful (e.g. deliberate sleep deprivation, long computer gaming sessions, binge drinking, experimentation with other substances), but which may be passing fashions that are part of growing up and have no long-lasting adverse effects.

55. Members noted that the studies in Table 1 of the paper, listing the reasons provided by adolescents for consuming "energy drinks", were largely limited to Western countries, and it would be useful if this could be expanded to increase the geographical range. Members agreed that the studies were largely cross-sectional and so it was not possible to establish causality.

56. Members noted that a general conclusion from reviews of the health effects of "energy drinks" on children and adolescents is that such consumption has been and is a growing problem. However, the Committee concluded that from the evidence available in the studies presented it was difficult to determine what was "signal" and what was "noise". Hence, it would be more appropriate to regard this as a growing

[4] Miles-Chan JL, Charrière N, Grasser EK, Montani J-P, Dultoo AG. The thermic effect of sugar-free Red Bull: do the non-caffeine bioactive ingredients in energy drinks play a role? Obesity 2015 **23**(1): 16 – 19.

concern, rather than a growing problem, as stated above and more research would be needed to clarify this.

57. The database on the cardiovascular effects of “energy dinks” must be quite large, as these are amongst the most obvious signs and symptoms of high caffeine intake. Comparisons with adults would be useful here.

58. The earlier COT statement found little convincing evidence for an interaction between alcohol and “energy drink” consumption and this paper did not add any further support for causality to the relationship. However, the Committee emphasised that there are already existing mechanisms to address the sale and use of alcohol by children and younger adolescents.

59. The Committee noted that any beneficial effects of “energy drinks” were short-term and no evidence had been presented for longer term benefits. However, the Committee did not review potential beneficial effects in detail.

60. The conclusions of the paper were generally accepted but it should be emphasised more that much of the evidence is inconclusive and causal relationships have not been established. More information on the potential impact on health of the sugar content of “energy drinks” should be included. Members saw little evidence that the effects of “energy drinks” were due to components other than caffeine (and sugar). However, uncertainties were too great for a robust conclusion to be drawn on whether children and adolescents are more susceptible to caffeine than adults. There was insufficient information on the effects of caffeine per se in these age groups to enable EFSA to derive a safe caffeine intake in such subjects. The Committee suggested that in order to address these uncertainties, comparison should be made with adult usage and effects, the possibility of a contribution to the effects from the different constituents should be investigated and well conducted volunteer studies on the pharmacokinetics/pharmacodynamics of caffeine to compare adults and children should be sought. Longitudinal studies to better ascertain cause and effect and more data on current consumption patterns should be sought. Some members were of the view that whilst there are some data gaps, this was not a topic that merited major investment in research and that there were greater priorities for toxicological research.

61. Members expressed the need for care in concluding there was no risk to adolescents and children from consumption of “energy drinks”, as even if such drinks do not present unique risks, the levels of caffeine may be such that they have untoward effects in such age groups.

Item 7: Review of potential risks from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. TOX/2018/28

62. As part of the review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding, the Committee in Toxicology (COT) was asked to review the toxicity of chemicals in the diets of infants and young children aged 1-5 years. A scoping paper (TOX/2015/32) was reviewed by the committee in 2015.

63. The scoping paper (part I) presented at the meeting was a follow up to the members' request to have a more detailed look at a number of chemicals and provides an overview for tropane alkaloids (TAs), zinc, selenium and phthalates.

64. As discussed at the previous meeting, short overviews for each chemical were provided as Annexes, summarizing the respective HBGVs and conclusions drawn from the exposure assessment and risk characterisation. The aim was for the committee to decide if a full review is required or if the chemicals can we included into the overarching statement.

Item 7a: ANNEX 1 – Tropane alkaloids

65. No interests were declared.

66. Following the approach taken by EFSA in the 2013 opinion on TAs, the paper focused on (-)-hyoscyamine and (-)-scopolamine and the sum of (-)-hyoscyamine and (-)-scopolamine.

67. A brief background and a description of the derivation of the previously established acute reference dose (ARfD) by EFSA for TAs were provided; an Acceptable Daily Intake (ADI) was deemed unnecessary by EFSA due to the quick onset of pharmacological effects and the lack of bioaccumulation, genotoxicity and chronic toxicity of TAs. An exposure assessment using UK dietary data as well as a risk characterisation and conclusions were provided.

68. The Committee agreed with EFAs approach and conclusion, that an ARfD would also be protective against long term exposure. Members concluded it unlikely that repeated exposure would lead to an ADI lower than the ARfD. Members also considered the ARfD to be protective for infants and children, although it is based on adult data; the UF of 10 would cover any potential kinetic differences.

69. The Committee asked for clarification on available breast milk data and requested it to be emphasised, that there is only limited data available, however that the data available reports a negligible transfer of TAs to breast milk.

70. The Committee raised concern about the limited number of food groups reported in the UK data set and the possible underestimation of the risk by only

considering two of the 200 TAs. The limited toxicity and occurrence data were noted by the members; additional information was requested on other TAs reported in the current survey to provide more context for the assessment. A paragraph on this will be presented to the COT at the next meeting.

71. The Committee decided a full review on TAs was unnecessary and therefore a brief summary of TAs should be included only in the overarching statement.

Item 7b: ANNEX 2 – Zinc

72. No interests were declared.

73. A brief background and derivation of a range of maximum intakes recommended by different regulatory bodies were provided. An exposure assessment was provided using UK dietary data, including infant formula. Estimated exposures from breast milk were calculated using zinc concentrations from the literature.

74. Information on average requirements and reference nutrient intakes compared to the exposure estimates as well as a risk characterisation and conclusions were included.

75. The Committee noted that in general, the exposures were at or below the upper level, and were not of toxicological concern. Members deemed it unnecessary to include comparisons of exposure with average requirements (ARs) and reference nutrient intakes (RNIs) in this evaluation as it is not required for the toxicological assessment.

76. It was noted by Members that the units were difficult to follow in places and this should be rectified in the final version.

77. The Committee concluded that a full review on zinc was unnecessary and therefore a brief summary of zinc should be included only in the overarching statement.

Item 7c: ANNEX 3 – Selenium

78. No interests were declared.

79. A brief background on the biological relevance and the toxicokinetics of the compound was presented. Information on the Upper Intake Levels set by the Scientific Committee on Food in 2000, the Expert Group on Vitamins and Minerals in 2003 and the Adequate Intake levels as set by EFSA in 2014 was also provided.

Exposures calculations for breast milk and food had been included, followed by a risk assessment and conclusions.

80. Members agreed that dietary exposure from selenium in infants and young children is not of toxicological concern.

81. The Committee agreed that due to the nature of the element, exposure from soil and dust should also be considered.

82. The Committee agreed that a full review on selenium is not necessary and, provided that soil and dust exposures do not make significant contributions, a brief summary should be included only in the overarching statement.

Item 7d: ANNEX 4 - Phthalates

83. No interests were declared.

84. Members queried whether reported low level endocrine effects of phthalates should be taken into account.

85. The Chair pointed out that there was some controversy about the reported effects, some of which appeared to show non-monotonic dose-response relationships and that the EFSA CEF panel was currently considering the phthalates, so a future paper should consider their findings.

86. Members suggested that relative potency factors should be used to determine the contribution to the risk from each of the phthalates in the FSA dietary survey. The survey dated from 2011 and the Committee wondered if there might be any more recent concentration data available to obtain a more accurate estimate of current exposure.

87. Members raised a concern over the possibility of phthalates causing contact dermatitis and asked if it would be possible to expand the paper to cover dermal exposure, for instance to dust.

88. The Committee concluded that in a second draft they would like to see a cumulative risk assessment using the potency of each phthalate individually instead of one TDI to cover the range and acknowledgement that the paper was provisional on the results of the upcoming EFSA review of the phthalates.

Item 8: FSA Scientific Advisory Committees (SACs) update – TOX/2018/32

89. This paper was provided for information.

Item 9: Any other Business

90. The Members were informed that EFSA have launched a public consultation on draft guidance on harmonised methodology for human health, animal health and ecological assessment to combined exposure to multiple chemicals. The closing date for this is the 15th September.

91. Members were asked to send their comments to the Secretariat by the end of August. These would then be complied and presented to the September meeting for ratification, and submitted to EFSA shortly thereafter.

92. A related consultation has been launched on draft guidance from EFSA on the genotoxicity assessment of chemical mixtures. This had been passed to COM for their comments.

Date of next meeting

93. The next meeting will be held on Tuesday 11 September 2018 at **Broadway House Conference Centre, Tothill St, London, SW1H 9NQ**.