

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

Meeting of the Committee at 10:00 on 7th July via Skype and TEAMS

Present

Chairman: Prof Alan Boobis

COT Members: Dr Phil Botham
Dr Caroline Harris
Dr René Crevel
Prof Gary Hutchison
Prof David Lovell
Dr Mac Provan
Dr James Coulson
Prof Maged Younes
Prof Faith Williams
Dr Michael Routledge
Dr Cheryl Scudamore
Dr Natalie Thatcher
Prof Matthew Wright
Dr Sarah Judge
Prof John Foster
Dr Stella Cochrane
Ms Jane Case
Ms Juliet Rix
Prof Mireille Toledano
Prof Philippe Wilson
Prof Ken Ong SACN Liaison
Prof Paul Haggerty SACN Liaison
Prof John O'Brien Science Council

Food Standards Agency (FSA) Secretariat: Ms C Mulholland FSA Scientific Secretary
Dr D Gott
Dr A Cooper
Dr B Doerr
Dr D Hedley
Mr B Maycock
Ms C Hoppie
Dr O Osborne
Ms C Potter
Dr J Shavila
Ms C Thomas
Ms S Thomas
Ms C Tsoulli
Ms F Uy
Mr F Lachhman

Public Health England (PHE) Secretariat:	Britta Gadeberg	PHE Scientific Secretary
Invited Experts and Contractors:	Dr K Vassaux Dr R Bevan	WrC IEH
Assessors	Ms V Swaine Prof T Gant Ms G McEneff Ms E Lawton Dr D Duval Mr I Martin Dr S Fletcher	HSE PHE BEIS DEFRA PHE EA VMD
Observers	Mr Joe Brennan Mr Alex Costigliola	NABIM (Item 5) NABIM (Item 5)
FSA and other Officials:	Dr A Lorenzoni Dr E Valanou Dr A Adkin Dr J Edge Mr R Yarham Ms H Rose Ms F Hill Ms A Jao Ms A Aghadiuno Ms B Rendle Ms Bethan Davies Mr R Annett Mr K Gribbin Ms S Gilmore Ms K Boss Ms L Wilson Dr T Marczylo Ms R Elsom Mr L Johnstone Ms S Burnett	EU Fora Fellow EU Fora Fellow FSA FSA (Item 5) FSA (Item 5) FSA (Item 5) FSA FSA FSA FSA FSA FSA FSA FSA NI FSA NI FSA NI FSS FSS PHE PHE BEIS FSS

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Announcements

1. The Chair welcomed Members and other attendees.
2. The Chair welcomed new COT Member Philippe Wilson who is a Professor of animal science and bioinformatics at Nottingham Trent University.

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 Member Professor Gunter Kuhnle.

Item 2: Minutes from the meeting held on 5th of May 2020

5. The minutes of the May meeting were agreed subject to minor amendments to Item 5 on the Potential risks from use of topically applied CBD-containing cosmetic products to ensure the terms “topically applied” and “dermally applied” in paragraphs 27, 31 and 32 were used consistently.
6. Paragraph 31 was extended to note that the extent to which inhalation contributed to total exposure was unknown to better reflect the preceding discussion.
7. Paragraph 32 was revised to include the possibility of local effects occurring in the lung.

Reserved minutes - Item 9 (WRAP study on potatoes and acrylamide (reserved)).

8. The reserved minutes of the May meeting were agreed subject to clarification of the temperature effect addressed in paragraphs 4 and 8.

Item 3: Matters arising from the meeting held on 5th of May 2020

PBPK Workshop in December 2020 (TOX/2020/29)

9. The Secretariat informed the COT members that following the “Exploring Dose Response” workshop delivered in March 2020, the proposed workshop focusing on PBPK modelling was scheduled for the 2nd of December 2020.
10. The learning objectives were shared with the Committee, and their advice was sought for suggestions on potential speakers and other topics of interest that should be covered on the workshop agenda.

11. Suggested topics by the Committee included sessions on; the integration of toxicodynamic modelling development, ensuring the adequacy of models based on validation processes, the shift to use predictive parameters as opposed to obtaining traditional datasets from in vitro/in vivo tests, and a review of the current guidance on application to PBPK models in a regulatory setting, such as those published by the Environmental Protection Agency, World Health Organisation etc. The latter allows the identification of potential oversights and/or other factors that should be included in future iterations of guidance documents.

12. Members were asked to send in any additional comments or suggestions to the Secretariat.

Item 7: Toxicological interactions between xenobiotics and the human microbiota - Second draft statement. TOX/2020/25

13. The draft statement was being revised and would be with the Chair for clearance shortly. The Chair thanked everyone who sent in comments.

Item 10: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes).

14. The draft statement and non-technical summary had been amended with the comments from the May meeting and were now with the Chair for approval.

Item 13. COT website

15. Members were informed that work on the new COT website was progressing and was on schedule for going live in August/September. The Chair thanked everyone who had sent in comments on the proposed branding.

Item 4: Exploring Dose Response Workshop Report (TOX/2020/30) (reserved)

16. No interests were declared.

17. The Committee discussed the conclusions and potential output of the recent COT workshop “Exploring Dose Response”. These minutes have been reserved as it is hoped that a publication in the peer reviewed literature will be possible. The minutes and discussion paper will be made available in due course.

Item 5: Allergen risk assessment for adventitious contamination of soya in wheat flour milled and consumed in the UK. (TOX/2020/31)

18. Dr René Crevel declared that he had been contacted by the National Association of British and Irish Millers (NABIM) about Voluntary Incidental Trace Allergen Labelling (VITAL) 3.0. This was a scientific discussion about the impact of

values used in VITAL. No payment was received. This was deemed to be a personal specific interest but wouldn't preclude participation in discussions.

19. No other interests were declared.

20. Mr Joe Brennan and Mr Alex Costigliola from the National Association of British and Irish Millers (NABIM) were in attendance.

21. Due to the way in which soya beans and other grains, such as wheat, are grown, harvested, stored and transported, adventitious contamination of wheat flour with soya can occur. Soya beans and products thereof are recognised as causing allergies and are included on the Regulation (EU) 1169/2011 annex II list of declarable allergens.

22. In 2014, the FSA recommended an action level of 236 mg/kg be applied by the food industry for soya protein in wheat. This was equivalent to a dose of 7.1 mg soya protein in an average 30 g serving of wheat flour. Since that time, more data have become available on the dose-response relationship for soya protein allergy and approaches to allergen risk assessment have also developed. An Eliciting Dose (ED)01 (where only 1% of the allergic population would be predicted to experience any objective allergic reaction) of 0.5 mg and an ED05 (where only 5% of the allergic population would be predicted to experience any objective allergic reaction) of 10 mg have recently been published (Remington et al., 2020).

23. The FSA is therefore conducting an updated risk assessment to guide risk management actions. In general, the FSA uses ED01 levels, where available, as suitable reference doses for allergenic proteins to determine the risks posed by the allergen levels present in final products. However, there are uncertainties around how industry should best apply the use of reference doses at the raw/bulk ingredient/product level, and specifically for soya in wheat. This is partly due to variation in the level of inclusion of wheat in final products and in consumption amounts as well as the potential effects of processing on the allergenicity and detectability of soya. Therefore, the suitability of suggesting an indicative reference amount and action level for flour in general, in place of tailored calculations for individual products in which the ingredient/flour is used, is unclear and potentially unsuitable.

24. The COT's advice was sought on the risks posed by the current action level of 236 mg/kg soya protein in wheat, and the appropriate consumption values and reference values (e.g. the ED01 or ED05) to use in risk assessment, taking into consideration the effect of processing on the allergenicity and detectability of soya allergens and therefore the potential reduction of risk to the allergic population that final products from these flours may pose.

25. The Committee asked what the aim of setting an action level would be in this context and what the FSA would be looking to achieve with this paper. It was noted that these were mitigation methods; soya contamination was already permitted by

grain standards and that Precautionary Allergen Labelling¹ (PAL) should be introduced earlier in the risk assessment. The action level at the raw material stage needed to be made clear. The risk assessment document was a useful exercise demonstrating that general action limits at the raw ingredient/supply level may not be suitable for industry to use and that instead there was value in understanding the level of contamination in raw product so that the manufacturer of the final products can adequately assess the risk and determine whether PAL needs to be used.

26. In the VITAL 3.0 programme patients were challenged with soya milk and soya flour-based materials. Therefore, the ED01 and ED05 values were not just for soya flour but reported as soya protein. It was noted that the impact of processing on allergenicity and detectability of soya allergens would not necessarily reduce the risk to the allergic population that final products from these flours may pose, as the modified protein may still be allergenic.

27. Wheat flour is widely used, and soya contamination is not an issue if soya-based ingredients have already been declared. The vast majority of bread and other wheat-based products also use soya flour and are therefore out of the scope of this risk assessment. It was agreed it would be difficult to use the risk assessment at the raw material level.

28. Members commented that the risk assessment should provide further detail on the testing done, whether there were trends in the test results, whether the same testing methods were used and the frequency distribution of results. It was noted that the testing data were supplied by NABIM and not all of this information may be available. This type of information had a lot of value and needs to be passed down the supply chain to enable the most accurate risk assessment of the final product.

29. If an action level were set for industry at the early stages of the supply chain, it may then hinder robust sampling and communication of quantitative levels of contamination further along the supply chain. When considering processing there were too many sources of uncertainty to take this into account at this time. Therefore, the limits should not be relaxed to the ED05 or even have a limit set at the raw/bulk ingredient level at all. Sampling data should be communicated down the supply chain by industry with it being more appropriate to introduce limits at the final processing stage.

30. It was agreed that all the scientific factors had been covered in the risk assessment provided in Annex A.

31. NABIM informed Members how the current 236 mg/kg level was being used. Most companies undertook due diligence testing only for the 'high-risk' flours. Most companies who found their sampling results to be below this level, reference the 2014 FSA paper and then recommend to their customers that no PAL is needed.

¹ Precautionary Allergen Labelling (PAL) is used as a control measure to prevent the inadvertent consumption of undeclared allergens by sensitive consumers and enable a variety of safe and nutritious food choices for the allergic consumer.

32. The severity of an allergic reaction to soya is likely to follow the pathway of a generic Ig E-mediated reaction. The risk assessment is performed on the basis of an ED01 or ED05 and the sensitivity varies depending on the allergen. The level of protection provided by the ED01 and ED05 are the same for each allergen (i.e. 1% or 5% of the relevant allergic population) but the concentration of each allergen set for these reference values would vary. It would be useful to provide some context with other allergens e.g. nuts/mustard. However, it was noted that the prevalence data for a large number of allergens is weak.

33. It is not known whether the processing of soya reduced the level of risk or severity of an allergic reaction. There were some validated data for egg and milk in this area but not for soya.

34. NABIM referred to Health Canada's 2013 position that PAL was not needed for soya in flour. Discussions had taken place with allergy groups and it was noted that allergic reactions had not been seen after consumption of wheat flour. Members considered it would be useful to know whether discussions with this type of stakeholder group had taken place in the UK. Currently in the UK there is no systematic way of collecting information on allergic reactions to particular foods and notifications of allergy in this area have not been recorded. It was pointed out that such activity would be risk management and was not in the remit of the COT and would not be captured in the risk assessment.

35. The Committee recommended that the document be reworked without proposing a level to use but noted that risk managers could consider how industry could use sampling information for their raw products to provide information to their customers.

36. It was highlighted that this had been a useful risk assessment exercise and this piece of work could be used to demonstrate that a set level of allergen should not be specified, but that sampling and quantitative information should be communicated by industry, down the supply chain to inform their customers in deciding on whether to apply PAL.

37. The document will be finalised via e-mail correspondence and discussed in matters arising at the next COT meeting.

Item 6: COT Contribution to SACN review of the effects of diet on maternal health: proposed scope of work and timetable. (TOX/2020/32)

38. No interests were declared.

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

agreed to conduct a risk assessment on nutrition and maternal health focusing on maternal outcomes during pregnancy, childbirth and up to 24 months after delivery.

40. The Committee discussed the proposed list of chemicals highlighting several possible omissions. It was agreed that further clarity on the rationale for the selection be provided, before the list of chemicals for review could be finalised. However, the COT focus should be placed on those where the critical effect related to maternal and fetal health.

41. Committee Members then discussed the scope of the work and the endpoints that would need to be considered, requesting further clarity in a number of areas.

42. It was agreed that the immediate priorities should be caffeine, vitamin D and iodine and other items on the list would be discussed in due course once this was finalised. The timetable for this work was not discussed in detail but the Committee agreed that it would, like the earlier infant and child feeding papers, be a body of work that would be addressed over several years.

Item 7: Overarching discussion paper on consumption of plant-based drinks in the diet of children aged 6 months to 5 years of age (TOX/2020/33)

43. No interests were declared.

44. The Department of Health and Social Care (DHSC), Public Health England (PHE) and the FSA were receiving an increasing number of enquiries regarding the use of plant-based drinks in the diets of infants and young children. The COT were therefore asked to consider the potential health effects of soya, oat and almond drinks in the diets of children aged 6 months to 5 years of age.

45. Currently, the UK Government advises that parents should use only infant formula as an alternative to breast milk in the first 12 months of a baby's life. It was also advised that whole cows' milk and unsweetened calcium-fortified milk alternatives, such as soya, almond and oat drinks could be given to children from the age of 1 year as a part of a healthy, balanced diet. The papers considered exposure from these drinks from the age of 6 months as used in cooking and then as part of the diet as a main milk drink for the ages of 1-5 years old.

46. These drinks were previously considered by the COT as separate papers TOX/2019/71 for soya, TOX /2020/16 for almonds and TOX/2020/03 for oats. The main challenge in the assessment of the safety of these drinks had been the lack of information on the dietary intakes of these drinks by children following dairy-free or plant-based diets who were likely to be the highest consumers. At the suggestion of the SACN Secretariat, the exposures had been revised, using information from several sources including the British Nutrition Foundation (2019), the First Steps Nutrition Trust Eating Well: vegan infants and under 5s (2020), Vegan Society Food tips for vegan children (2017) and PHE published Example menus for Early Years Settings in England (EYS) (2017). These sources provided guidance on frequency and portion sizes for children under 5 years and, considering the lack of consumption

information for the groups of interest they were deemed the most representative scenarios for the diet of children following dairy-free or plant-based diets.

Annex A- Follow up discussion paper on the potential risks from soya drink consumption in children aged 6 months to 5 years of age.

47. Soya drinks are a popular alternative to dairy products and their use has become more widespread. They are commonly consumed by all sectors of the population including those wishing to avoid dairy products and by individuals with an intolerance to lactose or another component of milk or those who follow a plant-based diet.

48. Soya products contain phytoestrogens (also known as isoflavones) which have been shown to produce some reproduction and developmental changes in animal studies, although the evidence for effects in humans from epidemiological studies is inconclusive.

49. Soya drinks were considered at the December 2019 meeting (TOX/2019/71). Due to the limited information on the consumption by these age groups, the chronic exposure estimates for isoflavones in children between 6 months and 5 years of age had been calculated assuming that a) milk, yogurt and cheese were replaced with soya-based alternatives; b) all dairy was replaced with soya alternatives and c) meat was replaced with soya alternatives plus isoflavone contribution from tofu, vegetables and bread. However, it was considered that scenarios discussed in TOX/2019/71 might not be representative of the actual exposures to isoflavones in the diets of those wishing to avoid dairy products.

50. Therefore, in the current paper, the exposure calculations were revised based on a number of sources that offered recommendations for the diet of children following a plant-based diet. These recommendations aimed to achieve a well-balanced, nutritious diet and they were used to provide a more realistic assessment of isoflavone exposure. In addition to exposure from soya drinks, the contribution of other soya-based alternatives to dairy products or meat to the diet had also been considered.

51. The Committee agreed that the use of dietary information tailored to children who would be high consumers of these drinks was more appropriate than the previous approach. However, it was noted that there was a high degree of uncertainty with regards to the actual exposures to these drinks in the diets of children following a plant-based diet as these recommendations were designed to ensure that dietary requirements were met, but consumption of the drinks and other soya-based foods might differ in reality.

52. Members concluded that the intakes of phytoestrogens from consumption of soya drinks in children aged 6 months to 5 years of age was less than the previously estimated maximum in infants aged 0 to 6 months, 9.5 mg/kg bw per day, up to which level it was considered that soya-based infant formula could be used to ensure adequate nutrition, if circumstances dictated that this was necessary. Members agreed that exposure to phytoestrogens from other soya-based products in the diets of children aged 6 months to 5 years of age based on the information provided was

lower, and hence there was no potential concern. It was, however noted that when considered aggregately, the exposures were much closer to the level of 9.5 mg/kg bw per day. Members agreed that, in addition to potential toxicological concerns, consideration of nutritional issues would also be required to assess whether it was necessary to issue additional advice on the consumption of soya-based drinks in children aged 6 months to 5 years of age.

53. The need for consumption information for people following plant-based diets more generally was also highlighted by the Committee as the popularity of these diets is increasing and information on realistic dietary intakes would help inform future risk assessments on similar issues.

Annex B- Overarching discussion paper on consumption of plant-based drinks in children aged 6 months to 5 years of age. TOX/2020/33

54. Almond drinks have lower nutritional value compared to soya and oat drinks; however, they have been recommended as an alternative in cases where soya and oat drinks were not tolerated.

55. The mycotoxin, aflatoxin B1 was identified as a common chemical contaminant in almonds which could be potentially transferred to almond drinks. Aflatoxin B1 is a genotoxic carcinogen so the maximum levels set by the EU were based on the as low as reasonably achievable (ALARA) principle.

56. Some varieties of almonds contain cyanogenic glycosides, with levels being very high in bitter almonds. Once macerated, the cyanogenic glycosides in the almonds could interact with β -glucosidase and yield hydrogen cyanide. Exposure to hydrogen cyanide can lead to convulsions, loss of consciousness, dizziness, weakness, mental confusion and heart failure.

57. A discussion paper (TOX/2020/16) was presented to the Committee in March 2020, providing information on the potential health effects of almond drinks in the diets of children aged 6 months to 5 years. The Committee had agreed that more information on the likelihood of bitter almond contamination of almond drinks was needed and the precautions taken by manufacturers to prevent their entry to the supply chain should be investigated. Based on the information supplied by industry, the Committee was satisfied that it was extremely unlikely that bitter almonds would be used in the production of almond drinks. Members agreed that there were no specific concerns for acute toxicity from cyanogenic compounds in almond drinks.

58. When discussing TOX/2020/16, Members had concluded that aflatoxin exposure from almond drinks was a potential concern but there were uncertainties in the exposure assessment, and it was agreed that further work needed to be done to refine it. The current paper addressed the Committee's comments and recommendations.

59. Members suggested that paragraphs 7,8 and 9 should be removed since although the papers discussed presented analytical data on AFB1 from the literature, they were not sufficiently representative to use in the risk assessment.

60. In response to a question from Members, it was noted that the European Union (EU) maximum levels of aflatoxin B1 in Commission Regulation (EC) No 1881/2006 were based on analytical standards.

61. Members questioned if the two columns under each heading in Table 3 were for upper and lower bound concentrations. It was explained that the columns were for minimum and maximum consumption values, but information had been inadvertently lost when simplifying the tables to meet accessibility standards.

62. In the exposure assessment, soya drink consumption data was considered the best surrogate for almond drink exposure. As there was no information on actual AFB1 occurrence levels in almond drinks it was assumed that there was 100% transfer of AFB1 into almond drinks at the maximum permitted level. It was added that manufacturers did not check for AFB1 occurrence levels in the final almond drink product. Members noted that using the maximum levels set by the EU (0.48 and 0.72 µg/kg) did not provide assurance that potential AFB1 contamination in almond drinks was not a concern since margins of exposure (MoEs) were well below 10,000. It was suggested that the derivation of the EU limit values should be re-considered and that better information on actual exposure levels was needed.

63. Members discussed whether the AFB1 MOEs in Table 7 provided any meaningful information, as there was so much uncertainty associated with the exposure data. Members concluded that the MOEs should be removed because they were so uncertain and potentially unnecessarily alarming.

Annex C- Follow up discussion paper on the potential risks from the consumption of oat drinks for children aged 6 months to 5 years of age.

64. A discussion paper on oat drinks (TOX/2020/03) was presented to the COT in January 2020 focussing on the implications of oats being contaminated with the mycotoxins T2 and HT-2. Members considered that the analytical data used for estimating the concentration of HT-2 and T-2 which derived from one sample of oat drink were unlikely to be representative for the UK given the lack of surveillance data and variability of contamination levels in the UK oat harvest. Furthermore, it was noted that there was no indication that mycotoxin concentrations in UK oats would be substantially different to those reported in other European countries by EFSA. The Committee agreed that follow-up work should 1) assess the contribution of mycotoxin exposure from oat drinks in relation to exposure from total oats in the general diet, and 2) estimate the amount of oat drink one would need to consume relative to the rest of the diet to approach the TDI.

65. In paper TOX/2020/33, other mycotoxins (deoxynivalenol, DON and ochratoxin A, OTA) which have been detected in oats and have appeared on the Rapid Alert System for Food and Feed (RASFF) portal were considered in addition to HT-2 and T-2. Therefore, risk assessments have also been conducted for the presence of these mycotoxins in oat drinks. Because these mycotoxins occur in other grains and foodstuffs, background exposure has also been considered in these exposure assessments.

66. In this follow-up discussion paper, exposure assessments have been conducted using consumption assumptions considered to be the most representative scenarios for high consumers of oat drinks. Separately, for the sum of HT-2 and T-2, DON, and OTA, the following exposure assessments have been conducted for 6 to 60-month olds: Exposure from consumption of oat drinks in the UK; Amount of oat drink required to exceed the HBGV in the UK; Dietary exposure from processed oats in the general diet in the UK; Exposure from oat drinks and processed oats in the general diet (combined) in the UK; and, Background dietary exposure in the general diet across Europe.

67. Members noted that the exposure estimates made the best use of the available data, however they included a lot of assumptions.

68. It was concluded there was no health concern in respect of HT-2/T2 exposure, since, as shown in Table 17, intakes were below the TDI other than for 12-24-month olds, in whom exceedance of the TDI was only minor and the exposure estimates used were conservative.

69. It was further concluded that the exposure assessments for DON did not indicate a health concern.

70. In respect of OTA, the Committee were unable to conclude whether the exposure estimates indicated a potential health concern. There were many uncertainties in the cancer endpoint used for risk characterisation, and furthermore, it was unclear whether or not OTA was a genotoxic carcinogen, and thus which MOE threshold value would be applicable. Some age groups had MOEs lower than desirable for non-neoplastic effects while all age groups had MOEs lower than that considered of low concern for a genotoxic carcinogen.

71. It was questioned whether it would be possible to obtain more information on consumption, as young children may be consuming a mixture of different plant-based drinks. However, after discussion, it was agreed that the current approach, which assumed that consumption was exclusively of a single plant-based drink, was most appropriate as young children are likely to develop a preference for one drink. It was noted that there are plans to obtain more consumption data for children who follow a dairy-free diet, as these diets are becoming more popular.

72. Overall, it was noted that in terms of monitoring the levels of relatively potent genotoxic carcinogens, measured levels are often below the LOD resulting in conservative estimations of exposure and preventing any assurance of low concern. Ideally there needed to be studies of at least a few representative samples using a sufficiently reliable analytical method to determine the actual occurrence levels of these contaminants present in the UK diet.

73. Members agreed that although this exposure assessment was for young children, it needed to be extended to adults, as there may be health risks for the general population.

Item 8: Potential risks from aggregated dietary exposure to mycotoxins (TOX/2020/34)

74. The Chair, Professor Alan Boobis declared that he was involved in the EU-funded EuroMix project which considered risk assessments of combined exposures to various chemicals, including but not solely, mycotoxins. Dr Michael Routledge declared that he had previously conducted work on mycotoxins, however, these were not commercially funded.

75. No other interests were declared

76. It was noted that although the title of the paper was 'aggregated dietary exposure', this is a term generally used to cover exposure to a single chemical by multiple routes, whereas the topic addressed was combined exposure to multiple chemicals, sometimes referred to as 'cumulative exposure'.

77. The publications reporting synergistic effects were discussed. The Committee considered that dose response effects were not always properly investigated in these studies, which often used mycotoxin concentrations that were not reflective of realistic exposure scenarios (i.e. where in some studies high concentrations were selected to achieve a positive/synergistic effect).

78. Members discussed Annex B of the paper, which provided an overview of the effects of individual mycotoxins. Members agreed that it would be helpful to add an additional column to include the mode of action (MOA) for each mycotoxin. This would assist in performing a higher tier chemical grouping exercise based on the MOA rather than the toxicological endpoint; however, it was highlighted that consideration should also be given to which real-world mycotoxin combinations occur in practice.

79. The different approaches to assessing cumulative risk were also discussed. If the lowest health-based guidance value for the compounds (in a certain mixture) were utilised, this would result in a very conservative assessment. A further complication would arise should the combination involve one or more mycotoxins that are considered as genotoxic carcinogens. The potential uses of relative potency factors and hazard index approaches were also deliberated.

80. A review of UK specific exposure data to mycotoxin combinations was requested by the Committee, in which biomarker studies would be particularly helpful if available. This would allow the formation of baseline data to inform the level of exposure in the UK population (i.e. low, medium or high).

81. The inclusion of an overview of EuroMix project could be included in future iterations of this paper, as this project considered approaches for both data-rich and data-poor compounds in its case study risk assessments.

82. Members agreed that the discussion paper provided a good summary of the difficulties involved in assessing the risk of combined dietary exposures to mycotoxins and further agreed that based on the current information, it was not possible to perform a risk assessment of such combined exposures. This conclusion

was based on the lack of data on co-exposure and co-effects of mycotoxin combination at human-relevant exposure levels. It was also highlighted that a number of issues needed to be resolved to enable extrapolation from available *in vitro* and *in vivo* data.

Item 9: Draft EFSA opinion on nickel. (TOX/2020/35)

83. No interests were declared.

84. EFSA have recently opened a public consultation on the CONTAM Panel's "Update of the risk assessment of nickel in food and drinking water".

85. In this update, the CONTAM Panel has established a Tolerable Daily Intake (TDI) of 13 µg/kg bw for nickel. Due to the possibility of eczematous flare-up reactions elicited in the skin in nickel-sensitised individuals, an approach for acute assessment was also considered necessary. A LOAEL of 4.3 µg Ni/kg bw was selected as the reference point for acute effects and an MOE of 30 or higher was considered to be indicative of low concern to human health.

86. . The TDI of 2.8 µg/kg bw established by EFSA in 2015 was considered more uncertain than that established in the current update. Whilst it was based on the same studies as in 2015, the modelling approach used differed, which now followed updated guidance published after the 2015 Opinion.

87. EFSA established their TDI on the basis of post-implantation loss as the critical endpoint. However, Members did not consider this endpoint relevant to the infant and young children populations.

88. It was noted that EFSA had not referenced the Haber et al., (2017) paper that the COT had used in its 2018 statement on nickel in the infant diet². The Haber paper had used the same studies as EFSA (2015) but had used a more relevant endpoint as the basis for calculating a toddler toxicity reference value (TRV) for repeat exposures to nickel. The TRV calculated (20 µg/kg bw/day) was similar to the TDI established by EFSA in its recent update (13 µg/kg bw/day).

89. The studies on which EFSA based their reference point for assessing the acute risk from nickel exposure are relatively old, but there were no more reliable studies available. Most recent published articles were on case studies in patients and not dose-response studies. They were therefore not of use for the purpose of dose response modelling.

90. The Committee agreed with the HBGVs established by EFSA

91. In its 2018 statement, the COT had concluded that there was potential concern from acute exposures to nickel in infants and young children, especially those with a sensitivity to the metal. Taking into account the health-based guidance

² COT [statement](#) on the potential risks from nickel in the diet of infants and young children.

values (HBGV) in the EFSA update paper and current exposure estimates, such concern remains for the nickel sensitive population.

92. The Committee discussed whether clinicians were still seeing examples of eczematous flare-up reactions and if not, whether the assessment was overly conservative. It is unlikely that it would be known whether this type of dermal reaction was caused by nickel in any given instance as individuals are often sensitive to more than one chemical. There were no new studies available on oral exposure to nickel and eczematous flare-up reactions for EFSA to consider.

93. With regards to the benchmark dose (BMD) modelling it was highlighted that using different versions of PROAST and BMDS (the two most common software options for BMD modelling) may produce different results. It was noted that small sample sizes may also have an effect. It was considered that UK guidance on BMD modelling was needed to ensure consistency in software use and in interpretation of the outputs.

94. The Committee's comments on the public consultation would be submitted to EFSA. Members were asked to send any additional comments to the Secretariat.

Item 10: Conclusions of the Overarching Statement and Addendum on the potential risks from contaminants in the diet of infants aged 12 to 60 months – Summary tables for SACN. (TOX/2020/36)

95. No interests were declared.

96. The COT was asked to review the risk of toxicity of chemicals in the diets of infants and young children aged 0 to 5 years, in support of a review by SACN of Government recommendations on complementary and young child feeding. The work has been completed and both the Overarching Statement (2019) and Addendum to the Overarching Statement have been published (2020).

97. The SACN Secretariat have asked for a table of conclusions for their report on young children (12 to 60 months) on all chemicals included in the Overarching Statement, Addendum and from separate statements published related to the work on infants and young children.

98. In line with the format of the SACN report, the view of the Committee was sought on the highlighted text in the summary tables and whether Members agree that the text highlighted was the most appropriate in the concluding text.

99. Members enquired about inconsistencies in the wording of the conclusions and if this should be made consistent. The Committee was informed by the Secretariat that the wording has been taken directly from the statements. Given that the work has been ongoing for several years and to allow for conclusions to be related to their respective statements, Members agreed to keep the wording as proposed. However, the Committee stressed that future work, especially with regard to maternal diet, should apply a consistent approach.

100. Overall, the Committee agreed with the highlighted text and only minor amendments were suggested. The document/tables will be finalised by the COT Secretariat and send to the SACN Secretariat upon completion.

101. The Chair of the COT thanked the Committee for its hard work over the years and the COT Secretariat for the support on putting the documents together.

102. The Chair of SACN thanked the Committee for their extensive work, the quality of the outputs produced and the value the work of the Committee has added to the SACN report(s).

Item 11: E-cigarette, or vaping, product use – associated lung injury’ (EVALI): an overview. TOX/2020/37

103. No additional interests were declared to those previously declared in December 2018 and December 2019.

104. Paper TOX/2020/37 provided the Committee with a summary of the EVALI outbreak, within the context of the ongoing watching brief on potential E(N)NDS-related toxicity. The review was based on information provided on the US CDC and FDA websites, plus relevant scientific literature that was identified on this topic; a full systematic search of the scientific literature was not undertaken.

105. The diagnosis of EVALI had similar features to COVID-19 cases and the possibility of a link was raised especially for cases since the start of the pandemic. There was no information on whether any retrospective testing for COVID-19 in EVALI patients was being conducted. The Committee noted the available information on e-cigarette use in general and COVID-19 was contradictory as there is some evidence that covid-19 effects are exacerbated by vaping but there is also some evidence that nicotine protects against covid-19 (<https://www.cebm.net/covid-19/nicotine-replacement-therapy/>). Given that the Committee had not reviewed the diagnosis of covid-19 and did not plan to do so, Members agreed that they were unable to reach any conclusion on this. It was further noted that the diagnosis of EVALI through exclusion could potentially miss other causes that are yet unidentified.

106. The Committee agreed there was evidence for an inflammatory process in EVALI, supporting the potential role of vitamin E acetate. Members noted that while surveillance in the UK population has been substantial there seems to be very little evidence for the occurrence of EVALI in this population, in contrast to the US population.

Item 12: Update on the work of other scientific advisory committees (TOX/2020/38)

107. This paper had been provided for information.

108. Members were informed that the Advisory Committee on the Microbiological Safety of Food (ACMSF) had advised that draft WHO guidelines on microbiological risk assessment of food had been released for public consultation. Although it was assumed that most of this guidance would not have direct implications for the work of the COT, Members would check whether there were any links with the COT's previous work on the microbiome. The COT Secretariat would circulate a link. The consultation was due to close on 15 July 2020.

Item 13: Any Other Business

109. Members were informed that the FSA was proposing to fund two fellowships, one in computational toxicology and one in bioinformatics. The fellows would spend some time in academic departments and some time at the FSA. Members views were sought on the likely interest from academia.

110. Members considered these fellowships to be a good idea, with benefits to both organisations. It would be useful to build a community in the UK which bridges academia and Government Departments. It was suggested that the call be shared with learned organisations such as the British Toxicology Society to ensure a broad reach.

111. There was no other business.

Date of next meeting

112. The next meeting of the Committee Meeting will be at 10:00 on 15th September via Skype and TEAMS.