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

Meeting of the Committee at 10:00 on Tuesday 1st December via Skype and Teams

Present

Chair:	Prof Alan Boobis	
COT Members:	Dr Phil Botham	
	Dr Caroline Harris	
	Prof Gary Hutchison	
	Dr David Lovell	
	Dr Mac Provan	
	Prof Faith Williams	
	Dr Michael Routledge	
	Dr Cheryl Scudamore	
	Dr Natalie Thatcher	
	Prof Matthew Wright	
	Prof Gunter Kuhnle	
	Dr Sarah Judge	
	Dr Stella Cochrane	
	Ms Jane Case	
	Ms Juliet Rix	
	Dr James Coulson	
	Prof Philippe Wilson	
	Prof Maged Younes	
	Prof Paul Haggarty	Scientific Advisory Committee on Nutrition (SACN) Liaison
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland	FSA Scientific Secretary
	Dr David Gott	
	Dr Alex Cooper	
	Dr Barbara Doerr	
	Mr Barry Maycock	
	Dr Douglas Hedley	
	Ms Cleanncy Hoppie	
	Dr Olivia Osborne	
	Ms Claire Potter	
	Dr Joseph Shavila	
	Ms Chloe Thomas	
	Ms Sabrina Thomas	
	Ms Chara Tsoulli	
	Ms Frederique Uy	
	Ms Jocelyn Frimpong-Manso	

Public Health England (PHE) Secretariat:	Ms Britta Gadeberg	PHE Scientific Secretary
Invited Experts and Contractors:	Dr Ruth Bevan	IEH
	Dr Kate Vassaux	IEH
Assessors	Prof Tim Gant	PHE
	Dr Ian Martin	Environment Agency
	Mr Sam Fletcher	Veterinary Medicines Directorate (VMD)
	Ms Gillian McEneff	Department for Business, Energy and Industrial Strategy (BEIS)
Observers	Prof John O'Brien	Science Council
	Dr Meera Cush	COM
FSA and other Officials:	Ms Aisling Jao	FSA
	Mr Vince Greenwood	FSA
	Dr Alan Dowding	FSA
	Dr David Mortimer	FSA
	Ms Bethan Davies	FSA
	Dr Jo Edge	FSA
	Mr Liam Johnstone	BEIS
	Ms Krystle Boss	Food Standards Scotland (FSS)
	Dr Ovnair Sepai	PHE
	Ms Rachel Elsom	PHE
	Dr Chris Green	Environment Food and Rural Affairs (DEFRA) (Item 7)
	Ms Helena Bird	Medicines and Healthcare Products Regulatory Agency (MHRA) (Items 6 & 9)
	Mr Matthew Birkenshaw	MHRA (Items 6 & 9)
	Mr John Clements	MHRA (Items 6 & 9)

Contents

Announcements

1. The Chair welcomed Members and other attendees.

Interests

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 Dr René Crevel and Professor John Foster and Ms Kerry Gribben from FSA NI.

Item 2: Minutes from the meeting held on 27th of October 2020

4. Members were asked to inform the Secretariat of any errors in the list of attendees.

5. Members asked for some clarification on paragraph 28 (Item 5, TOX/2020/50). The paragraphs were revised as below:

> It was noted that composite materials, such as bamboo with a melamine binder, were often labelled simply as being of biological origin which was potentially misleading. Additionally, the plastic component of the material is subject to the stringent requirements of retained EU Regulation 10/2011 for food contact plastics, such as the need to provide a declaration of compliance.
>
> When considering the scope of retained EU regulations on the import of melamine kitchenware from China and Hong Kong (Regulation 284/2011), the FSA had a working assumption that this legislation was directly applicable if half or more of the article was a polymer resin. If it was less than half, it would fall outside the scope of such controls, but compliance would still need to be determined under the general and plastic food contact requirements.

6. Following the discussion during the October meeting, Members asked for the term “less than lifetime exposure” to be changed to “variable” and/or “intermittent exposure” (Item 9, TOX/2020/53).

7. All other items were accepted with minor editorial revisions and the Minutes were agreed as an accurate record of the meeting.

Item 3: Matters arising from the meeting held on 27th of October 2020

Proposed PBPK Workshop 2nd December 2020

8. Members were reminded of the upcoming PBPK workshop on the 2nd of December 2020. A pre-meeting information pack had been circulated, along with a Teams invite. If these had not been not received, Members were advised to contact the Secretariat urgently.

HBCDD

9. The COT comments on the draft European Food Safety Authority (EFSA) opinion on HBCDD were submitted to EFSA ahead of the deadline.

2019 Annual Report

10. The Secretariat announced that the 2019 Annual report of the COT, COC and COM had now been published online.

Microsoft Teams

11. Members were asked to inform the Secretariat if they were experiencing any issues or problems with the COT Teams site that had not already been notified.

12. Members were asked to inform the Secretariat if they had suggestions on the type of information they would like to see available on the Teams site.

13. Members were unsure if they were unable to see all of the documents on the Teams site as they did not know what should be there. It was explained that there were currently a limited number of documents on the site including the forward work plan, but more documents would be added by the Secretariat when Teams is seen to be working effectively.

14. Members asked if there was a plan for those who are currently unable to access the Teams site. The Secretariat were aware of some general problems, such as those with certain email addresses who were unable to access Teams. The Secretariat asked Members to raise any specific issues with Teams, so that these can be addressed on a case by case basis.

15. A document on HBCDD had been uploaded to the Teams site as a test for Members to add their comments on the draft EFSA opinion. However, no comments were made, but this appears to have been due to the comprehensive discussion held during the October meeting meaning further comments were unnecessary. Further shared documents would be uploaded for additional testing of the site.

SAC Recruitment

16. Recruitment for the FSA Scientific Advisory Committees (SACs) had been ongoing since the 25th of November. New Members were being sought for the FSA SACs (including COT) and the Joint Expert Groups (JEGs); the closing date for

applications is the 4th of January 2021[1]. The COT hoped to appoint new Members with expertise in general toxicology, dermal absorption/toxicology and epidemiology. Members were asked to circulate the advertisement amongst their contacts and networks.

New Ways of Working

17. The Committee had proposed that small groups of Members could be assigned to specific papers to lead the discussion and increase their contributions. This had been tried for several meetings and it was timely to discuss whether COT Members were satisfied with the arrangement, and if there was anything that needed to be done differently. So far Members had been assigned only to EFSA opinions or discussion papers which were at the first stages of consideration. Draft statements were the final output of the Committee and more collective in nature.

18. Members thought the method worked well, particularly for minor comments that might not be brought up during the main discussion of the Committee.

19. Members were asked if they would like to choose papers to work on or be allocated papers by the Secretariat. Some Members had reservations about the possibility of choosing papers of interest as it this could delay the allocation process, and there was the possibility that multiple people might want to work on the same paper. Some Members noted that being allocated a paper whose subject they were less knowledgeable on was beneficial to them, and were thus happy to be allocated such papers. A suggested refinement was for Members to consult the forward work planner on the Teams website and flag any subjects that they may be interested in. These preferences could be taken into account during the allocation of papers to Members.

20. Members found it useful to have the Secretariat lead present at a pre-COT discussion with assigned Members to address any points of clarification, so that they could be resolved before the COT meeting. This setup may help to save time during the COT meeting.

21. The lay Members were not currently assigned to specific papers, and were asked if they would like to take part. However, they were unsure how they could be allocated to papers effectively or if it would be useful to take part in the smaller discussion groups, and they preferred to join the main COT discussion, where they had plenty of opportunity to contribute more generally. It was suggested that lay Members could take a particular interest in draft statements to ensure clarity in the information going out to the public: input from all Members was critical here.

22. The Chair expressed his appreciation of the input received from Members thus far, but noted that Members should read all the papers and should not feel limited to only commenting on papers on which they were leading.

[1] Post meeting note: with the resignation of a member, the list or desirable expertise was expanded and the deadline extended to the 10th January

Item 4: Review of the dioxin tolerable daily intake (TDI): Draft problem formulation statement (TOX/2020/57)

23. Following discussion of the EFSA Opinion on dioxins and the implications for risk management at the September and October 2020 meetings, the COT recommended that a review of the evidence base for dioxins and the derivation of a health-based guidance value (HBGV) based upon it should be undertaken. However, COT acknowledged that a full systematic review of the dioxins database was neither feasible nor practicable.

24. At the October meeting, Members stressed the need for a clear formulation of the scientific questions, including consideration of all risk management challenges, and agreed it would be useful to form a small subgroup to discuss the requirements/problem formulation in more detail. Members agreed the composition of a subgroup for this purpose.

25. Based on these considerations and subsequent discussion by the subgroup, the Secretariat had produced a proposal for the literature search and a draft position statement to be published in the interim setting out the Committee's views and approach.

26. Members acknowledged that a systematic review was more appropriate than a meta-analysis, although the latter would also be useful. Members noted that the inclusion of publications on meta-analysis, without a cut-off date, would ensure that any data/publications missed by EFSA in their search would be captured.

27. Members noted that it was unlikely that the COT would be establishing a TDI. i.e. a tolerable intake based on daily exposure, given the long half-life of these compounds, and asked for the wording to be changed to HBGV.

28. Members noted that the European Commission had not yet utilised EFSA's new Tolerable Weekly Intake (TWI) but was waiting for the review of the TEFs by the WHO to complete the risk assessment. The revision of the TEFs would not be finalised until 2022 at the earliest.

29. The Committee agreed it would be useful to publish the proposed interim position statement. Members were content with the statement but asked for some text to be added to reflect the work and timelines by the WHO and some clarification on the wording in Paragraph 14, especially regarding the reduction of exposure and sensitive populations.

Item 5: Third draft overarching statement on potential risks from exposure to microplastics (TOX/2020/58)

30. Professor Boobis declared that he was involved in discussions with ILSI Europe, JRC, and others in the possible development of a reference bank for microplastic samples. No other interests were declared.

31. The potential risks from exposure to microplastics have previously been discussed at COT meetings from October 2019 – September 2020. The draft overarching statement, presented in Annex A, brought together these discussions, setting out the current state of knowledge, data gaps, and research needs with regard to this topic and summarising the conclusions reached to date. The draft statement had been revised following Members' comments at the September meeting. Following the finalisation of the draft overarching statement, it was intended that additional sub-statements would be drafted to address particular exposure routes or materials.

32. A short update on the recent literature on microplastics was also provided in TOX/2020/58. Members expressed reservations on the reliability of the cited toxicological data presented in the cover paper (Jin et al., 2021[2]; Luo et al., 2019[3]; Li et al., 2020a[4]; Deng et al., 2020[5]), in particular, the small number of animals per dose group, and the low quality of the toxicological data.

33. The Committee discussed the draft statement and requested several changes to its content and structure. It was agreed to add a fourth hazard in the hazard characterisation section; this was the *in vivo* breakdown of the polymers into their constituent monomer units or other constituents (e.g. polyurethane to isocyanates), as well as additional minor editorial comments. Members agreed that the statement could be cleared via Chair's action.

Item 6: A summary of data published to date on the presence and pharmacokinetics of nicotine salts in electronic nicotine delivery systems (ENDS) products (TOX/2020/59)

34. No interests were declared in addition to those previously declared in December 2018 and 2019.

35. The nicotine present in ENDS products, until recently, has predominantly been in the free base form. However, some more recent products contain organic acids in the e-liquid, leading to the presence of a proportion of the nicotine in the

[2] Jin, H., Ma, T., Sha, X., Liu, Z., Zhou, Y., Meng, X., Chen, Y., Han, X. and Ding, J. (2021) Polystyrene microplastics induced male reproductive toxicity in mice. Journal of Hazardous Materials 401, 123430.

[3] Luo, T., Zhang, Y., Wang, C., Wang, X., Zhou, J., Shen, M., Zhao, Y., Fu, Z. and Jin, Y, (2019) Maternal exposure to different sizes of polystyrene microplastics during gestation causes metabolic disorders in their offspring. Environmental Pollution 255, 113122.

[4] Li, Z., Zhu, S., Liu, Q., Wei, J., Jin, Y., Wang, X. and Zhang, L. (2020a) Polystyrene microplastics cause cardiac fibrosis by activating Wnt/β-catenin signalling pathway and promoting cardiomyocyte apoptosis in rats. Environmental Polllution 265, 115025.

[5] Deng, Y., Yan, Z., Shen, R., Wang, M., Huang, Y., Ren, H., Zhang, Y. and Lemos, B. (2020) Microplastics release phthalate esters and cause aggravated adverse effects in the mouse gut. Environmental International 143, 105916.

protonated form, as a salt. Nicotine salts are less volatile than freebase nicotine and are reported to produce a less harsh experience during inhalation.

36. TOX/2020/59 provided a short overview of publicly available information of relevance to the presence of nicotine salts in ENDS products and the pharmacokinetics of nicotine when inhaled in the salt form from ENDS products. Some commentary was also included on the historical development of traditional combustible tobacco products with relation to modulation of smoke pH and nicotine form. Increasing pH by the addition of a base, such as ammonia, will supress the ionisation of nicotine, a weak base. Superficially, this would be expected to increase absorption across lipid membranes in the lung. However, addition of an acid decreases pH, resulting in the form of salts of nicotine which are more palatable. As a result, the nicotine can be inhaled more deeply into the lungs, where it is more readily absorbed than from the upper airways. It was noted that pharmacokinetic studies of inhaled aerosolised nicotine products indicated higher and/or faster delivery of nicotine from nicotine salts than from free base nicotine. Members were asked whether, from the limited evidence available, any conclusions could be drawn on possible differences in nicotine exposure levels or patterns for users of ENDS products that contain nicotine in salt form as compared with products containing free base nicotine, and if this evidence base indicated any additional risks from the use of nicotine salts rather than freebase nicotine in e-liquids.

37. Members noted the lack of information on levels of exposure to the nicotine salts and in particular how the exposure to nicotine might differ from the use of nicotine in the form of salts compared to free base form. If the delivery of nicotine is higher due to greater bioavailability, then consumers might compensate by inhaling less. Self-titration of nicotine had been reported, but it would be useful if this could be independently verified. Nicotine flux had also been suggested as a more reliable basis for investigating nicotine exposure than nicotine concentration.

38. Members also queried whether increased nicotine delivery might increase addictiveness, or if there might be some qualitative difference in the addictiveness of nicotine salts compared to free base nicotine. However, this was outside the remit of the COT. It was also noted that if the delivery of nicotine is increased then the exposure to other, potentially harmful, substances in ENDS may be decreased relative to the nicotine.

39. It was noted that there would be no impact on the bioavailability of nicotine to bystanders as they would not be exposed to the nicotine salt *per se*, but to the free base form via exhaled breath from users.

40. Members were asked whether any conclusions could be drawn on possible differences in nicotine exposure levels or patterns for users of ENDS products that contained nicotine in salt form as compared with products containing freebase nicotine. It was concluded that the use of nicotine salts results in increased bioavailability. However, whether this resulted in increased nicotine levels in the user would depend on user behaviour.

41. Members were also asked whether the database indicated any additional risks from the use of nicotine salts rather than freebase nicotine in e-liquids.

Members noted that they could not draw conclusions as it was unknown whether actual exposure to nicotine would be higher or not. The risks of ENDS also depended on what other substances were being inhaled from the ENDS and whether exposure to these might decrease when nicotine salts were being used compared to free base nicotine. In addition, there might also be risks from the acids used in formation of the salts. One other aspect to consider was the implication for smokers who are trying to switch from conventional cigarettes to ENDS and the possibility that the success in switching might be different for nicotine salts compared to free base nicotine.

Item 7: First Draft Statement on the EFSA Opinion on the risks to human health related to the presence of perfluoroalkyl substances in food. (TOX/2020/60)

42. Professor Boobis declared that he had been involved in the SETAC North America workshop report on exposure to and toxicity of perfluoroalkyl substances (PFAS).

43. EFSA had been asked by the European Commission to prepare an opinion on the risks to human health related to the presence of PFAS in food, and to consider existing hazard assessments and available occurrence data. The draft EFSA opinion was reviewed by the COT at their meeting in March 2020 and also at a subsequent additional meeting in April where the key studies underpinning the proposed tolerable weekly intake (TWI) were discussed. The final EFSA opinion was published in July, and the COT had been requested to review this. The TWI had decreased since the draft opinion was published and was now 4.4 µg/kg bw.

44. Annex A to Paper TOX/2020/ 60 contained a draft statement setting out the background to the topic and the Committee's conclusions. The Secretariat had also provided some additional UK exposure data to assist the COT with their discussions.

45. Members requested that some context be added to the introduction section, by explaining where the chemicals originated from and some context on exposure, particularly during pregnancy.

46. Two studies (Abraham et al., 2020[6] and Grandjean et al., 2012[7]) were used by EFSA for the derivation of a TWI for PFAS. The endpoints used were the indications of a decrease in vaccine response in children. The results from the

[6] Abraham K, Mielke H, Fromme H, Volkel W, Menzel J, Peiser M, Zepp F, Willich SN and Weikert C. (2020). Internal exposure to perfluoroalkyl substances (PFASs) and biological marker in 101 healthy one-year old children: Associations between levels of perfluorooctanoic acid (PFOA) and vaccine response. *Archives of Toxicology*, 94(6): 2131-2147. Available at: https://pubmed.ncbi.nlm.nih.gov/32227269/

[7] Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P and Heilmann C. (2012). Serum Vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA.* **307:** 391-397. doi: 10.1001/jama.2011.2034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22274686

studies were not entirely consistent for the PFAS compounds studied. Members also noted that the cohort in the Abraham et al study was relatively small.

47. The Committee discussed the benchmark dose (BMD) modelling that had been carried out by EFSA. This had originally been carried out by Abraham et al. and then replicated by EFSA. A relatively small set of data was used in the modelling. A number of the fitted models showed no threshold, indicating that there was no 'no effect level'. However, there did not appear to be anything in the EFSA Opinion to explain this. There had also been difficulties with the BMD modelling, for example, model averaging did not provide plausible results and was not further discussed by the EFSA panel although model averaging is their preferred approach in BMD modelling. Instead, the lowest value from an individual model was used. It was presumed that this was for a non-threshold dose response. It was noted that the data set could be very difficult to model.

48. The Committee discussed whether there was a real effect or not. The Grandjean et al cohort had initially been studied to assess the effects of polychlorinated biphenyls (PCBs) and the results had been compared after corrected by confounding by PCBs. However, the Committee questioned how effective this correction would be when the major source of exposure for both groups of chemicals was the same, i.e. seafood. It was noted that the assessment was multi-faceted and that the two groups of chemicals were not necessarily confounders because they were on the same causal pathway. However, it would not be possible to put both PCBs and PFAs in the model at the same time and it would also not be possible to fully adjust one model for the other.

49. It was thought that information on the impact of vaccinating against diphtheria in the UK was available. As most children in the UK are vaccinated, the fact that there were almost no cases of diphtheria (10 cases in England in 2019) would suggest that any effect of PFAs on vaccine response was non-linear. However, as there is no cohort of infected subjects (due in part to the effectiveness of vaccination) any effect on impairment of the vaccine response would not necessarily be seen, as only a small percentage of the population would be at risk. Currently there does not appear to be any discernible impact.

50. The EFSA opinion indicated that when antibody titres are diminished, the level of protection from vaccines might be compromised. However, it was not clear what decrease in antibody levels could cause such an effect. It was noted that there were also natural fluctuations in vaccine titres over time.

51. The Committee requested that the statement made it clear that the exposures to PFAs were all estimates, and that the breast milk exposures were very conservative and were skewed by a data set from Spain.

52. Members agreed that qualitatively the correct health endpoint had been used but quantitatively, questioned the calculations. Overall the Committee had some reservations about the choice of the critical study and the specific effect selected. However, the Committee agreed that the critical study was the best available. It was not unreasonable that this study was selected, and, in the absence of more appropriate studies, its use was acceptable.

53. Members agreed that the use of the sum of the four PFAs was acceptable as a first approximation.

54. Members had significant reservations about the model used. For example, the BMD approach was used, yet model averaging was discarded with little explanation. The values for the BMDL and TWI were low and there was a lot of uncertainty surrounding the data used by EFSA.

55. The Committee had reservations about the TWI which had been established due to the uncertainties and the caveats involved. The Committee's concerns related to both the study and thus the data used in the modelling, and the modelling itself.

56. Members asked to see exposures calculated for air, dust, soil and water, where the necessary data to conduct these calculations were available.

57. The Committee generally agreed with the draft conclusions but wanted more detailed descriptions of the uncertainties regarding hazards, exposure estimates, and the possible impacts.

Item 8: First draft statement on the potential effects of excess iodine intake may have during preconception, pregnancy and lactation (TOX/2020/61)

58. No interests were declared.

59. As part of the Scientific Advisory Committee on Nutrition (SACN) review of the maternal diet, the COT was asked to consider whether exposure to excess intake of iodine would pose a risk to maternal health. This was initially discussed at the October 2020 meeting (TOX/2020/54). The first draft statement setting out the issue and the COT's conclusions was attached at Annex A to paper TOX/2020/61.

60. The Committee noted that thyroid hormones were the only iodine containing components in the body and suggested that further information on this should be provided. It was also suggested that reasoning based on pathological or physiological considerations should be included to better explain why some individuals, other than those with underlying thyroid disorders, were particularly susceptible to the effects of excess iodine. Members suggested that it should also be noted that sensitive individuals were unable to escape the Wolff-Chaikoff effect, where excess iodine down-regulates thyroid hormone production.

61. Members noted that more information was needed on mandatory iodisation schemes. The Secretariat also agreed to provide more detail on the fact that any iodine fortification was voluntary in the UK.

62. Members agreed that further information on whether iodophor disinfectants were still authorised in the UK was needed.

63. It was concluded that as it the currently available data were not sufficient to enable a risk benefit assessment to be performed.

Item 9: Potential adverse effects associated with exposure to cannabidiol (CBD) by inhalation. (TOX/2020/62)

64. No interests were declared.

65. Paper TOX/2020/62 followed on from previous COT evaluations of oral and dermal exposures to CBD and presented a summary of published data of relevance to potential adverse effects of inhaled cannabidiol (CBD). This included a rat study, and a human study investigating the kinetics of CBD in five smokers compared with intravenous application.

66. The Committee was asked to consider whether the pharmacokinetic (PK) profile of CBD when inhaled posed a safety concern or raised any further questions regarding its use in products for inhalation exposure. The Committee agreed that the PK study was done well and showed that CBD had a long half-life with a large volume of distribution. These characteristics, in addition to the lipophilic nature of CBD, indicated that there could be accumulation of CBD with repeat dosing. It was noted that the *in vivo* rat data may be questionable since the rats were exposed multiple times to CBD during different experiments. However, these animal studies appeared to demonstrate that CBD exposure via inhalation induced hypothermia which was partially blocked by a 5-HT1A receptor antagonist. However, conclusions on the dose-effect level could not be made due to uncertainties about the exposure.

67. It was noted that the paper covered different sources of inhalation exposure and had been drafted to complement the previous papers on dermal and oral exposure, rather than being source-specific. Sources of exposure might include smoking CBD-containing plant material, solutions added to electronic nicotine (and non-nicotine) delivery systems (E(N)NDS), or from an aerosolised therapeutic application. The Committee agreed that the source material had implications for risk assessment since, for example the presence or absence of thermal degradation products needed to be considered. Different methods of delivery could affect the bioavailability of CBD, for example the ‘dabbing’ method using oils showed up to potentially 65% CBD bioavailability, whilst smoking plant material showed around 20% CBD bioavailability. The Committee considered that the structure of the document did not allow comparison of the different sources of CBD exposure and their implications.

68. Members noted two additional uncertainties regarding inhalation exposure to CBD. There were insufficient quantitative data on the duration and levels of exposure, which made it difficult to comment on the likelihood of toxicity occurring. In addition, the concentration of CBD stated on some products was sometimes inaccurate, for example, one study identified a product with two-fold the amount of CBD stated. Subsequently, the human data was difficult to interpret due to these uncertainties. However, the Committee recognised that more data were available in respect of oral exposure to CBD, where the bioavailability was often lower compared to inhalation exposure and where there were some health concerns regarding achievable exposure levels. On that basis, the Committee agreed that inhalation exposures posed a potential safety concern, and that adverse effects could be

greater than those from an equivalent oral dose. Furthermore, following absorption across the lung, adverse effects were considered to be independent of route of exposure.

69. A Member noted that because CBD was less stable at lower pH, the delivery of CBD to the lung may be affected by chemical mixtures with lower pH. The Committee agreed that the presence of nicotine salts in e-liquid may alter the pH, and this may need to be considered further.

70. It was noted that in paragraph 33, it was stated that “CBD acts as an antagonist with steroids”, and Members questioned whether CBD should therefore be contraindicated in some scenarios, for example use of budesonide by asthmatic individuals. It was agreed that this could be a concern, though CBD is also used by some consumers for its potential immunomodulating effects. Research was ongoing in this area, and it was not well understood.

71. The Committee agreed there was insufficient information on PK and toxicity of CBD available to generate an adequate risk assessment regarding the safety of its use in products intended for inhalation, but some caution was indicated from the available data. It was noted that the data available on inhalation exposure was even less than for oral exposure.

72. The Committee was asked for any comments relating to the potential for drug interactions arising from inhaled CBD exposure. It was noted that in vitro and in vivo experiments indicated that nicotine enhanced the biological effects of CBD. Furthermore, drug interactions would be expected if systemic concentrations achieved from the inhalation route were similar to those obtained via the oral route. The Committee recommended that, if required, undertaking a wider literature search to provide more data on metabolism that might help to characterise any interactions of inhaled CBD with other drugs. There were currently insufficient data on how inhaled CBD was metabolised to enable a more comprehensive assessment.

73. Since the bioavailability of CBD appeared to be higher across the lung than across the gut, inhibitory drug interactions would be expected at levels comparable to those following oral absorption. Furthermore, CNS effects would also be expected following inhalation, therefore a health warning might be necessary for those driving or using heavy machinery.

74. Considering the toxicity and PK profile of inhaled CBD, and the levels of CBD determined in various products, the Committee agreed that the use of CBD in this way poses a potential safety concern, however more exposure data were needed.

75. The Committee was asked to consider any risks arising from combined exposure from the use of multiple CBD-containing products including, but not limited to, products targeted for inhalation exposure. Members noted that the existing FSA position highlighted that dietary exposure should be kept below 1 mg/kg body weight. The Committee agreed that levels above this, which could be reached through a combination of inhalational and dietary CBD exposures, would pose a potential health concern due to aggregate exposure.

76. It was agreed that an update would be made to the position statement to capture potential concerns from exposure by inhalation.

77. Members agreed that it could be timely for the COT to consider any chemicals, including those used in E(N)NDS devices, deliberately inhaled, particularly those that are heated, which may not be captured within specific regulations. A representative from MHRA noted that e-liquids without a medical licence, or not containing nicotine would not fall within the MHRA remit, and the representative from BEIS noted that if a product containing CBD did not come under any specific regulations, then it would fall under General Product Safety Regulations (GPSR).

Item 10: EU Exit (Reserved)

Update on regulated products (TOX/2020/63)

78. Interests were declared by Professor Maged Younes as he was on the EFSA Panel for regulated products.

79. This paper provided information on how the SACs and JEGs will work together for the risk assessment of regulated products that previously would have been conducted by EFSA and the European Commission.

80. This paper is reserved as it is discussing policy under development. The minutes will be published in due course.

Regulated product dossier assessment template (TOX/2020/64)

81. Members were asked for their comments on the draft regulated product dossier assessment template. This paper is reserved as it is discussing policy under development. The minutes will be published in due course.

Problem formulation statement (TOX/2020/64)

82. Members were asked for their comments on the draft problem formulation template. This paper is reserved as it is discussing policy under development. The minutes will be published in due course.

Presentation on regulated product assessment by the EFSA panels

83. The Secretariat gave the Committee a presentation providing an overview of regulated product risk assessment. The minutes will be published in due course.

Item 11: Update on the work of other scientific advisory committees (TOX/2020/60)

84. This paper was provided for information.

85. COT Members who took part in the joint COM/COM discussion the previous week were thanked for their contributions. The discussion on the joint horizon scanning topics will be written up and brought to the COT in 2021. The discussion on biological relevance and statistical significance will also be brought to the COT in due course.

Item 12: AOB

86. There was no other business.

Date of next meeting

87. The next meeting of the Committee Meeting will be at 10:00 on the 2nd of February 2021 via Skype and Teams.