TOX/MIN/2019/05

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

Minutes of the meeting held on Tuesday, 17th September 2019 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ

Present

Chairman:	Dr John Thompson (Acting Chair)	
COT Members:	Ms Jane Case Dr James Coulson Professor John Foster Dr Sarah Judge Professor Faith Williams Professor Matthew Wright Dr Cheryl Scudamore Dr Gunter Kuhnle Professor Gary Hutchison Dr Stella Cochrane Dr Mac Provan Dr Natalie Thatcher Dr David Lovell Dr Michael Routledge	(by Skype)
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland Mr B Maycock Ms F Hill Ms C Potter Dr D Hedley Dr B Dörr Ms C Tsoulli Dr A Cooper Dr O Osborne Ms F Uy Dr J Shavila Ms S Thomas Mr D Medlock	FSA Scientific Secretary
Public Health England (PHE) Secretariat	Ms Britta Gadeberg	PHE Scientific Secretary
Assessors:	Tim Marczylo Natalie Hough	PHE HSE

Invited experts and external contractors	Dr Lesley Rushton	COC
	Dr Sarah Bull	WrC
	Dr Kate Vassaux	WrC
Officials	Dr Amie Adkin	FSA
	Dr Selwyn Runacres	FSA (by Skype)
	Ms Daphne Duval	PHE
	Mrs Rachel Elsom	PHE
	Mr Liam Johnstone	BEIS
	Ms Gillian McEneff	BEIS
	Mr Craig Copland	MHRA

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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.

3. The Members were informed that Mr Freddie Lachhman will be covering Ms Henrietta Gbormittah's post as Administrative Secretary for the rest of the year.

4. The Members were reminded that a revised agenda had been circulated earlier that week and that paper TOX/2019/53 had been postponed until the October Meeting.

Item 1: Apologies for absence

5. Apologies were received from the Chair, Professor Alan Boobis, and Members Dr Phil Botham, Dr Rene Crevel, Dr Caroline Harris and Dr Maged Younes. Dr Tim Marczylo from PHE attended in place of Dr Tim Gant and Ms Natalie Hough from HSE attended in place of Ms Valerie Swain.

Item 2: Minutes from the meeting held on 2nd July 2019.

6. The minutes were accepted as accurate record, with minor corrections to the text.

Item 3: Matters arising from the meeting held on 2nd July 2019

Para 20. Review of potential presence of fumonisins in infant formula in the United Kingdom (UK), and differences between the metabolism of fumonisins in infants and adults. TOX/2019/40

7. No interests were declared.

8. As part of the ongoing work on the nutrition of infants and young children aged 0-5, a paper on fumonisins was presented to the Committee in July 2019 where Members had requested some additional information.

9. The Secretariat informed the Committee that the Patel *et al*., (2011) mycotoxin surveillance report, upon further review, did not test for the presence of fumonisins in infant formulae. As such, there were no UK specific data for the presence of fumonisins in this dietetic food, however, this should not affect the exposure estimates presented at the July meeting, which utilised German data.

10. The Committee discussed the additional information provided and concluded that fumonisins were poorly absorbed and metabolised by hydrolysis and acetylation, the metabolites being excreted mainly in the faeces. These metabolic reactions were generally well developed at birth, and the kinetic profile suggested that there should not be marked differences in plasma concentrations between infants and adults, however, the Committee acknowledged that there was a lack of specific information. The Committee agreed that fumonisins could be added to the addendum to the overarching statement.

11. The Committee agreed that it would be helpful if the Secretariat prepared a scoping paper presenting the potential cumulative risks of mycotoxins and, in particular, which mycotoxin groups might be considered together (*i.e.* assessment groups).

July 2018 meeting. Review of potential risk from contaminants in the diet of infants aged 0 to 12 months and children aged 1 to 5 years: Information on TAs (TOX/2019/41)

12. No interests were declared

13. As part of the ongoing work on the nutrition of infants and young children aged 0-5, a paper on the tropane alkaloid mycotoxins was presented to the Committee in July 2018. Further information was requested by Members on some of the Tropane Alkaloids (TAs).

14. The Committee noted that most of the knowledge on TAs was based on pharmacological data and from contamination of crops and that very little was known about TAs other than atropine/(-)-hyoscyamine and scopolamine. The Members expected the effects of a combination of TAs to be different from those of exposure to a single TA, and that agricultural practices and changes in the supply chain could potentially influence concentrations of TAs in food commodities. Information provided by a COT member had been considered for the paper presented.

15. With appropriate information on the effects of structure on the potential effects of other TAs' the Committee agreed to include TAs in the Addendum to the Overarching Statement, including a discussion of uncertainties surrounding the overall exposure to TAs. In addition, the Committee agreed that TAs would be a good case study to be included in the upcoming potency paper/workshop, and to provide further information on the structure and potential risk of all TAs in the future.

Item 7. Review of physiologically based pharmacokinetic (PBPK) modelling used for human health risk assessment

16. No interests were declared

17. At the July COT meeting, Members considered a review of PBPK modelling. Members considered that it might be timely to hold a workshop on this topic. The Secretariat was exploring the possibility of holding a workshop which would also include potency estimation, on the day following the COT meeting on the 10th March. Further information would be presented at the October COT meeting. The Members were asked to contact the Secretariat with any suggestions for speakers or topics.

Item 8. Scoping paper on the synthesis and integration of epidemiological and toxicological evidence in risk assessment (TOX/2019/42)

18. No interests were declared.

19. The Committee agreed to the proposal by the Secretariat to set up a teleconference or skype meeting between Members of the COT and COC to explore

a possible working group on this topic. Members interested in being part of the meeting were asked to contact the Secretariat, two Members of the COT declared their interest at the meeting.

Item 9. Steviol exposures for children aged 1-5 years based on UK consumption data -TOX/2019/43

20. No interests were declared.

21. As part of the ongoing work on the nutrition of infants and young children aged 0-5 years, a summary paper on the safety of commonly used sweeteners was presented to the Committee in July 2019. Amongst the sweeteners presented were steviol glycosides. An Acceptable Daily Intake (ADI) of 4 mg/kg bw/d was established by EFSA in 2010. The EFSA exposures presented were refined in 2015 and for toddlers and children (1-9 years old) they ranged from 0.5 to 4.3 mg/kg bw/d. The Committee requested UK specific exposures to be presented.

22. At the September meeting, exposures to steviols were estimated using recent consumption data from the UK National Diet and Nutrition Survey (NDNS) for the 1.5 -5 year age group. The exposures were calculated assuming that Steviols were present at the Maximum Permitted Level specified for each category by Regulation (EC) No 1333/2008. That allowed the Committee to compare UK specific exposures to the ADI of 4 mg/kg bw/d established by EFSA.

23. The Members noted the conservatism in the exposure assessment and concluded that based on the extreme exposure scenarios presented, steviols were not of toxicological concern. It was agreed that a summary on Steviols would be included in the Addendum to the overarching statement.

Statement on phosphate-based fire retardants.

24. The statement had been finalised by Chairs Action and would be published shortly.

Item 4: Update on the Risk Analysis guidelines (reserved business) TOX/2019/44

25. No interests were declared.

26. The paper updated the COT on the development of the risk analysis guidelines, which were being produced by the Food Standards Agency (FSA) and Food Standards Scotland (FSS) in preparation for the UK's exit from the EU.

27. The risk analysis guidelines will provide context to the future work of the Scientific Advisory Committees. They were intended to provide a high-level overview of the principles that would underpin food and feed safety risk analysis and to introduce the operational procedures that will implement our processes, strengthening our current ways of working by adding further rigour and transparency.

28. This item was discussed as Reserved Business since it was policy being developed. The minutes will be published once the guidelines are finalised and in the public domain.

Item 5: Discussion paper on the EFSA Opinion on "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food." - TOX/2019/44

29. Dr Lesley Rushton, an epidemiologist, was present to help the Committee with their discussions.

30. Dr Sarah Judge declared a personal nonspecific interest as she had published a paper on PCBs four years previously. No commercial funding was received.

31. In November 2018, the European Food Safety Authority's panel on Contaminants in the Food Chain (CONTAM) published their scientific opinion on the risks for animal and human health relating to the presence of dioxins and dioxin-like PCB's in feed and food. The CONTAM panel reviewed the available animal and human epidemiological data and established a TWI of 2 pg TEQ/kg bw which is significantly lower than the TDI previously established by WHO of 1-4 TEQ pg/kg bw. The COT previously commented on the EFSA opinion in October 2018, but subsequently decided that a more in-depth discussion was required on the basis of the TWI.

32. Dr Rushton reviewed the three main epidemiology studies used by the CONTAM panel and offered her conclusions to the Committee. All three epidemiological studies looked at by EFSA were small with significant loss-to-follow up. The three studies looked at different age groups of participants and measured different end points and therefore it was very difficult to compare directly the results. Due to the low number of participants in the Russian Children's study[1], results had to be considered in quartiles to give sufficient power, and pre- and postnatal exposure were not compared. In the Seveso cohort[2], effects on sperm quality were only observed in children exposed before puberty, with boys who had been breastfed by exposed mothers showing a marked decrease in sperm quality compared to boys

[1] Mínguez-Alarcón L, Sergeyev O, Burns JS, Williams PL, Lee MM, Korrick SA, Smigulina L, Revich B, Hauser R. (2017). A Longitudinal Study of Peripubertal Serum Organochlorine Concentrations and Semen Parameters in Young Men: The Russian Children's Study. Environ Health Perspect. 2017 Mar;125(3):460-466.

[2] Mocarelli P, Gerthoux PM, Patterson Jr DG, Milani S, Limonta G, Bertona M, Signorini S, Tramacere P, Colombo L, Crespi C, Brambilla P, Sarto C, Carreri V, Sampson EJ, Turner WE and Needham LL, 2008. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environmental Health Perspectives, 116, 70–77.
Mocarelli P, Gerthoux PM, Needham LL, Patterson DG Jr, Limonta G, Falbo R, Signorini S, Bertona M, Crespi C, Sarto C, Scott PK, Turner WE, Brambilla P. (2011)
Perinatal exposure to low doses of dioxin can permanently impair human semen quality.
Environ Health Perspect;119(5):713-8

from exposed mothers who were formula-fed. In one study from this cohort, sperm parameters were found to improve in the 10-17 year age group, but declined in the 18-26 year age group. All studies appeared to adjust sufficiently for confounders except that mothers smoking habits was not taken in to account in any of these studies. Some of the analysis could be improved in these studies, but generally the studies support each other. Overall, she considered that the authors of each study had done the best with the data they had.

33. Following the summary by Dr Rushton, the Committee discussed their thoughts on the toxicological relevance of the reduced sperm counts observed. They also discussed the animal studies and whether they could be used to support the findings in human studies. The Committee noted that the EFSA CONTAM panel had concluded that the animal studies did support the epidemiological evidence but concluded that the end-points measured were too different between the human and animal studies. Overall the Committee considered that, whilst the data available were limited, it was not possible to dismiss the conclusions of EFSA and therefore were supportive of the TWI established by the CONTAM panel.

Item 6: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes).

34. No additional interests were declared for this item in addition to those previously declared at the meeting in December 2018.

a) Health-based guidance value for nicotine

i. Follow up to Paper 12: An overview of strategies to reduce nicotine addiction using low-nicotine-content products. - TOX/2019/46

35. During discussions of the review of toxicological data on nicotine at the July COT meeting (TOX/2019/38), the question of threshold levels for addiction to nicotine was raised. This topic had not been addressed in TOX/2019/38. It had been noted that reduced nicotine content cigarettes were being developed, with the aim to reduce population levels of addiction to nicotine and thus cigarette smoking, and the Committee requested that further information be provided on this topic. This paper (TOX/2019/46) presented a summary of the initial publication by Benowitz & Henningfield (1994), followed by a brief overview of the development of this field, based on 5 recent articles identified in a PubMed search.

36. The Committee noted the complexity of assessing nicotine addiction due to the psychological aspects of it in addition to the physiological effects. The difference in identified levels between some of the papers was highlighted, and whether the original premise was an indicator of genetic differences between people who become addicted to nicotine and those who can smoke without becoming addicted.

37. There was further uncertainty in extrapolating from cigarette use to E(N)NDS, and whether the timing and delivery of nicotine would be sufficiently similar to allow such extrapolation.

38. The Members considered both user and by-stander exposures in relation to addiction and the suitability of the currently available techniques for measuring exposure (airborne vs chamber measurements) for each scenario.

39. Overall, the Committee considered that data on reduced nicotine content cigarettes may be of use in evaluating threshold levels for effects of addiction in users exposed to nicotine from ENDS, but uncertainty over applicability to bystanders existed.

iii) Follow up to Paper 12: Calculation of a health-based guidance value for inhalation exposure to nicotine based on the study of Lindgren et al. (1999) (TOX/2019/47)

40. The committee had previously identified the Lindgren et al (1999) study as potentially suitable for the derivation of a Health Based Guidance Value (HBGV) for nicotine by inhalation exposure.

41. Paper TOX/2019/47 presented the study and proposed a point of departure using the LOEL for decreased delta and theta power on EEG, indicative of effects of arousal. An opinion was sought from the committee on the suitability of the chosen endpoint, Point of Departure (PoD) and HBGV.

42. The committee considered whether EEG data were a suitable surrogate for clinical outcomes, noting that changes in EEG was a sensitive measure for effect and had been employed in assessments previously, but that it was difficult to extrapolate from. It was noted that the study used smokers who were likely to be addicted to nicotine and had abstained from nicotine for over 12 hours. In contrast, the HBGV proposed would also be applied to bystanders who were assumed to be non-smokers. It was felt this caveat should be highlighted and that a similar study in non-smokers would be valuable.

43. The assessments undertaken by the US EPA and EFSA were considered and it was agreed that i.v. administration was the closest suitable analogue available in the literature to inhalation exposure. EFSA had assessed for oral exposure using i.v. data from the Lindgren study but using cardiovascular effects for the point of departure.

44. The committee agreed that the available data were suitable for assessing nicotine effects in E(N)NDS users but was not presently suitable for assessing effects of bystander exposure. It was suggested that information on differences in receptor status between smokers and non-smokers could be sought, and the literature should be checked to see if any studies had administered nicotine i.v. to non-smokers. The nicotine exposure data for E(N)NDS users and bystanders would be presented again at the next meeting alongside any further information and the POD/HBGV proposed from the Lindgren study.

b) Flavourings

i) Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Paper 10c: Toxicity assessment of flavouring compounds: Menthol (TOX/2019/48)

45. This paper presented the available data on menthol, a common E(N)NDS flavouring compound. It was noted that there was inconsistency in the definition of menthol was across the literature. Therefore, the search was targeted to the most relevant isoforms D-, L-, and the racemic mixture D, L- menthol that are all utilised in E(N)NDS liquids.

46. The recent media reports on the presence of pulegone, a carcinogenic substance which has been found in mentholated e-cigarette liquids according to a US study, were noted. The work had shown that the margin of exposure was lower for users of E(N)NDS when compared to smokers of mentholated cigarettes.

47. It was suggested that *in vitro* data should be included especially those regarding potential immunotoxicological effects of menthol.

48. The Committee recognised that there was a data gap regarding the potential interactions between menthol and nicotine when taken simultaneously, however, the literature suggests that menthol appears to suppress the harshness of nicotine.

49. It was noted that some of the reported effects, namely chronic cough and mucus production, suggested to occur as a result of activation of the TRPM8 receptor, were more likely to be an irritant effect. Additionally, it was acknowledged that there was uncertainty for the potential of menthol to increase the risk of infection or action of irritants in the open airways, and the extent of its effect(s) on lung clearance

50. It was further noted that the TRPM receptor is activated in prostate cancer and is androgen sensitive, and therefore there was a data gap to the potential long-term reproductive effects of menthol in males.

51. A data gap for potential repeat dose and carcinogenic effects was noted especially as some of the more recent studies gave data on cigarettes with and without menthol rather than providing information directly about the potential health effects of menthol. A carcinogenicity study was available, but this had used oral exposure.

52. There continued to be uncertainty about the temperature to which e-liquid may be heated. The possibility was offered of MHRA checking the notification dossiers, accepting that these may reflect a wider range of products than those commonly used by consumers and accepting that some E(N)NDS devices were customable to suit individual use.

53. There was uncertainty with respect to the relevance of the formation of metabolites and breakdown products of menthol at high temperatures. In addition, it wasn't clear whether they are different from menthol degradation products in cooked foods. The Committee acknowledged that there are uncertainties over differences in metabolism following oral exposure to menthol compared to inhalation exposure.

i) Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Follow up to Paper 11: Second draft framework for risk assessment of flavouring compounds in E(N)NDS (TOX/2019/49)

54. At their meeting in May 2019, the COT considered the health effects of two flavouring compounds for use in E(N)NDS products, vanillin (TOX/2019/24) and cinnamaldehyde (TOX/2019/25). During this discussion, the Committee agreed that as a number of flavourings were likely to be considered over time, a decision tree would be a useful tool to aid future assessments.

55. A draft decision tree had been discussed in July 2019, which included a number of end points to be considered including carcinogenicity, mutagenicity, reproductive, acute, and respiratory toxicity, skin sensitisation, respiratory irritation and repeat dose toxicity. Quantitative Structure Activity Relationships (QSAR) and Threshold of Toxicological Concern (TTC) approaches were proposed where data were lacking. This paper presented an updated version of this renamed as a COT framework for risk assessment of flavouring compounds.

56. Members were informed that a survey containing information on flavouring compounds in use in E(N)NDS would be made available in the near future.

57. The paper presented vanillin, cinnamaldehyde and menthol as case studies, which illustrated the different flows through the framework.

58. The Committee made a number of amendments to the framework and agreed the framework could be approved for publication by Chairs action.

59. It was noted that adverse outcome pathways and assessment of respiratory sensitizers in the absence of animal data was an active area of research that should be kept under review.

j) Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Literature update to mid-2019. - TOX/2019/50

60. The COT had been reviewing potential toxicity of electronic nicotine and non-nicotine delivery systems (E(N)NDS). Discussion papers on this topic had been considered by the Committee from November 2017, including studies of constituents of E(N)NDS liquids, the nature of the particulate matter produced on E(N)NDS use, toxicological data on individual constituents and mixtures in E(N)NDS aerosols, and potential user and bystander exposure. This current paper presented the findings from an updated literature search on these aspects, based on paper abstracts.

61. Members noted that exclusion of data from in vitro studies could result in missing information on effects on, in particular, the immune system. It was queried whether any information was available on potential adverse effects on the innate immune system of the lung, such as had been seen for air pollution particles.

62. The Committee recognised that there were data gaps in some of the cited studies and took advice from PHE, MHRA and BEIS regarding the legislation and good practice around of the products on the UK market including prohibited ingredients, guidance on metals in devices and coils and power settings.

63. Members considered that a watching brief should be kept on the effect of E(N)NDS on respiratory diseases, especially considering recent serious and fatal cases of lung disease in the USA that had been linked to E(N)NDS use. Adverse reaction reports, from the UK Yellow Card Scheme and similar schemes elsewhere, were requested including on the exposure of children to E(N)NDS liquids.

64. The Committee discussed the value of the case reports in the paper since although they provided too little data to be used in risk assessment, they could be indicators of possible toxicological events.

65. Members requested more detail on a few papers including Angerer *et al* (2019) (regarding the choice of liquids tested), Osei *et al* (2019) (on the combination of CC and E(N)NDS) and Bayly *et al* (2019) (on second-hand aerosol exposure). Overall the data presented added to the weight of evidence to be discussed in the final Statement on E(N)NDS

66. Members were informed that it was hoped that a draft statement would be discussed at the December or February COT meetings.

Item 7: Scoping paper on endocrine disruptors and risk assessment (TOX/2019/51)

67. Professor Foster declared a personal non-specific interest in that he had received funding by the Crop Protection Association (CPA) to write a review of the hypothalamus-pituitary-thyroid (HPT) axis in 2018. It was concluded that Professor Foster could contribute to the discussion but not to the forming of conclusions. Dr Judge declared that she had published on the hypothalamus-pituitary-adrenocortical (HPA) axis and Dr Hutchinson declared that he had published on the hypothalamus-pituitary-gonadal (HPG) axis; however, these pieces of work were not funded by chemical industry and were not considered to be conflicts of interest.

68. At the February 2019 COT meeting, Members had noted the differing views of different scientists on whether thresholds could be identified for endocrine disruptors. This was further discussed as part of horizon scanning at the April 2019 meeting, at which the Committee agreed to consider approaches to risk assessment for endocrine disruptors. The COT requested that all endocrine systems should be considered. It was proposed that a COT subgroup should be formed to consider this. However, the first stage should be to produce a scoping paper.

69. TOX/2019/51 briefly described the different endocrine systems that have been listed in documents considering endocrine disruptors, and for each endocrine system gave an example of disruption by chemical(s). It briefly touched on the criteria, tests and guidance used to identify endocrine disruptors. It then summarised the

considerations in recent reports and opinions relevant to the risk assessment of endocrine disruptors, i.e. whether thresholds exist for endocrine disruptors, low-dose effects, non-monotonic dose-response relationships and critical windows of susceptibility.

70. The Committee was asked to comment on the paper and consider whether any conclusions could be drawn at this stage, and to consider how it would wish to take this issue forward further.

71. Members did not consider that the peroxisome proliferator-activated receptor (PPAR) signalling pathway should be considered part of the endocrine system as there was no natural hormone. If the PPAR were included then so should be all other nuclear receptors, for example, pregnane X receptor (PXR), constitutive androstane receptor (CAR) and aryl hydrocarbon receptor (AhR).

72. The Committee discussed the cases made for and against the existence of thresholds for endocrine disruptors. A Member noted that a number of well conducted studies across a wide range of doses had demonstrated a marked point of inflection in the dose-response curve, consistent with a threshold. In addition, knowledge of receptor activation, signalling and regulation of hormonal effects through homeostatic feedback provided mechanistic support for a threshold. Members agreed that there would almost certainly be a threshold in most cases. They did not know of any biological systems where a single molecule binding to a single receptor can result in an effect. A Member noted that there is more redundancy in some systems than others.

73. In relation to the “additivity to background” case that some scientists had made, a Member noted that hormone levels vary, there is no constant level, and so while a certain level of increase may cause adverse effects there must be a threshold.

74. Members recognised the lack of agreement amongst scientists internationally. While they considered that thresholds exist, this could had not be proven experimentally, and Members did not consider that consensus could be reached.

75. Regarding low-dose effects and non-monotonic dose-response relationships, Members were not convinced about the existence of claimed low-dose effects, nor of non-monotonic dose response relationships occurring at low doses. Their view could change if they saw consistently reproducible evidence of such effects. A Member commented that if endocrine disrupting chemicals exhibit non-monotonic dose response relationships then it is difficult to understand why mixtures of similarly acting substances show monotonic dose-response relationships over a wide range of doses. For example, dose addition models based on biologically-relevant reductions in fetal testosterone had accurately predicted postnatal reproductive tract alterations by a mixture of phthalates in rats.

76. Members agreed that critical windows of susceptibility to endocrine disruptors exist, primarily *in utero*. They considered the extent to which standard toxicology tests were sufficient to cover these windows of susceptibility. There are suitable

studies, for example, the extended one generation reproductive toxicity study. However, they have not been used for many chemicals assessed by the COT.

77. Most Members did not consider that a COT subgroup at this stage would be able to progress the topic beyond this scoping paper and the recent discussions in the scientific community. The Committee was asked if it would be able to conduct risk assessments for endocrine disruptors if requested. Members considered that they would be able to conduct risk assessments for endocrine disruptors if sufficient data were available.

78. The Committee briefly considered, if a subgroup were to be established, what it would consider. Suggestions were how a low dose effect could be demonstrated robustly, and generating a check-list of data requirements against which existing data for endocrine disruptors being considered by the Committee could be compared.

Item 8: Review of hepatotoxicity of dietary turmeric supplements- TOX/2019/52

79. Turmeric is the common name for the rhizome (underground stem) of *Curcuma longa L.,* a herb cultivated in tropical and subtropical regions of the world. For centuries, turmeric has been widely used for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases. However, contamination of turmeric may occur either during its cultivation (if grown in lead-rich soil) or downstream processing where xenobiotics or powders of other *Curcuma* species may be introduced.

80. Over the last few years, a number of hepatitis outbreaks related to the consumption of dietary turmeric supplements have been reported. The paper reviewed some of the human case reports, in addition to studies of hepatotoxicity in animals.

81. One member noted that in the subacute study, the dietary turmeric powder the mice were administered may have been contaminated since in the published paper it was stated that these turmeric rhizomes were “purchased locally”.

82. It was noted that the human case studies showed a link to turmeric because the effects occurred upon challenge and were reversed after withdrawal. The symptoms were considered to be an idiosyncratic drug reaction due to underlying susceptibilities in the affected individuals. However, a role for a possible contaminant was not ruled out. It was concluded the animal data were consistent with the human data.

83. The Committee concluded that there was no need to review the current ADI for curcumin that was currently based on reproductive toxicity.

84. The Committee agreed substantial exceedances of the ADI represented a potential health risk to humans, especially if other medicines were being taken concomitantly.

85. Given past reported contamination issues with turmeric supplements, the Committee agreed there would be value in commissioning a chemical analysis of turmeric supplements available on the UK market.

Item 9: Review of potential risks from contamination in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. Mycotoxins – additional information (TOX/2019/54)

86. As part of the ongoing work by the COT on contamination of infants and young children aged 0 to 5 years of age, additional information on aflatoxin and citrinin were provided to the Committee. The additional information included cancer studies in neonatal/prenatal rats exposed to aflatoxins and additional information on IARCs classification of citrinin and further details on the reproductive/maternal toxicity studies.

87. The Committee noted that only one of the papers provided for aflatoxin allowed for a direct comparison of young rats and adult rats. However, the study duration was not appropriate to look at sensitivity differences between infants and adults. Members agreed that to enable a conclusion, information on cancer potency in newborns and adults by the same route of AFB1 administration would be required as well as quantitative data on the activation of AFB1 by liver fractions from newborns and adults (rat and human), if available.

88. Based on the additional information provided, the Members agreed with IARCs classification of citrinin and concluded that it was currently not possible to confirm the carcinogenicity of citrinin. The members also noted that based on the *in vitro* and *in vivo* data provided, the reproductive toxicity might be secondary to maternal toxicity.

89. The Committee agreed for both, aflatoxins and citrinin, to be part of the Addendum of the Overarching Statement, however, the Members asked for additional information on aflatoxins to be provided, as discussed above, to conclude on the sensitivity differences between infants and adults.

Item 10: Update paper for information: FSA Scientific Advisory Committees (SACs) – TOX/2019/55

90. This paper was tabled for information.

Item 11: Any other Business

91. No other business was discussed.

Date of Next Meeting:

92. Tuesday 22nd October 2019 at Broadway House Conference Centre, Tothill St, London, SW1H 9NQ