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

Meeting of the Committee at 10:00 on 4th May 2021 on Microsoft Teams

Present		
Chair:	Prof Alan Boobis	
COT Members:	Dr Phil Botham Ms Jane Case Dr Stella Cochrane Dr James Coulson Dr Rene Crevel Dr Caroline Harris Professor Gary Hutchison Dr Sarah Judge Dr Gunter Kuhnle Dr David Lovell Dr Mac Provan Ms Juliet Rix Dr Michael Routledge Dr Cheryl Scudamore Dr Natalie Thatcher Professor Mireille Toledano Professor Philippe Wilson Prof Paul Haggarty Prof John O'Brien	 SACN Liaison Science Council Liaison
Food Standards Agency (FSA) Secretariat:	Ms Cath Mulholland Dr David Gott Mr Barry Maycock Ms Claire Potter Dr Barbara Doerr Dr Douglas Hedley Dr Olivia Osborne Chloe Thomas Ms Sabrina Thomas Ms Chara Tsoulli Ms Frederique Uy Ms Cleanncy Hoppie Ms Jocelyn Frimpong-Manso	FSA Scientific Secretary
Public Health England (PHE) Secretariat:	Ms Britta Gadeberg	PHE Scientific Secretary

Invited Experts and Contractors:	Dr Sarah Bull Dr Ruth Bevan Dr Kate Vassaux	IEH IEH IEH
Assessors	Prof Tim Gant Ms Frances Hill Dr Mindy Dulai Ms Susannah Brown	PHE BEIS BEIS PHE
Observers	Dr Simon Wilkinson Prof Thorhallur Ingi Halldórsson Prof Shirley Price Dr Stephen Ruckman	 TSG consulting
FSA and other Officials:	Ms Sophy Wells Ms Aisling Jao Dr Ovnair Sepai Ms Kerry Gribben Mr Will Munro Ms Krystle Boss Ms Marianne James Dr Ovnair Sepai Mr Daragh Doyle	FSA FSA PHE FSA NI FSS FSS FSS PHE DHSC (item 9)

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Announcements

1. The Chair welcomed Members and other attendees.

2. Members were informed that Professor Shirley Price, Professor Thorhallur Ingi Halldórsson and Dr Simon Wilkinson have been appointed to serve on the Committee. They attended the meeting as observers and introduced themselves briefly.

3. Dr Stephen Ruckman from TSG consulting and Professor Erik Millstone, Professor of Science Policy at the University of Sussex were present as external observers. The observers were reminded that they would have to adhere to the Observers' code of conduct.

4. Members were informed of a number of staff changes in the COT secretariat. Ms Frances Hill has left the FSA to join BEIS as Head of Toxicology at OPSS, she will be responsible for consumer products and will still be working with the Committee in her new role. Ms Chloe Thomas has left the exposure assessment team on promotion. Dr Olivia Osborne and Dr Barbara Doerr have both been promoted within the chemicals team. The Chair congratulated them and wished them the best in their new roles. Mr Michael Dickinson has joined the chemical team but was unable to attend the meeting.

5. Members were informed that a finance drop-in session would be available at lunchtime.

Interests

6. 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

7. Apologies were received from COT Members Professors Matthew Wright and Maged Younes. Apologies were also received from Dr Alex Cooper of the Secretariat.

Item 2: Draft Minutes from the meeting held on 2nd of February 2021 (TOX/MIN/2021/01)

8. There were no comments and the minutes were accepted as an accurate record.

Item 3: Matters arising from the meeting held on 1st of December 2020

Matters arising from previous meetings

JEGS update

9. The Secretariat provided an update with regards to the activities of the Joint Expert Groups (JEGs). Members were informed that the majority of the regulatory product applications received to date were novel food authorisations for CBD.

10. The Food Contact Materials JEG was scheduled to review their first regulatory product dossier at their May meeting.

11. Members were also told that regulated product applications and requests had been received by the FSA for animal feed, supplement products and food additives and enzymes. The applications were undergoing validation checks and had not yet been allocated to the JEGs for review.

12. Discussion of Regulated products by COT members was not anticipated until September/October 2021.

Item 4: The potential effects that excess vitamin D intake may have during preconception, pregnancy and lactation - First draft statement (TOX/2021/20)

13. Personal, non-specific interests were declared by Drs Natalie Thatcher and Stella Cochrane as their employers produced products containing vitamin D. It was agreed they could participate in the discussion.

14. The COT had been asked to consider whether exposure to excess vitamin D would pose a risk to maternal health in a discussion paper (TOX/2021/05) in February 2021 as part of the COT contribution to the Scientific Advisory Committee on Nutrition (SACN) review of the maternal diet.

15. A number of comments were provided on the content of the draft statement.

16. The Committee commented that in paragraph 2, the current definition of a hormone would need to be revised; it was suggested that vitamin D should be described as a hormone due to its mode of action involving interaction with receptors and not only because it is synthesized internally.

17. The Committee noted that paragraph 29 reported that vitamin D formed in response to UV exposure contributed to total vitamin D levels, but it was unclear how much sunlight could contribute. It was further noted that vitamin D formation as a result of UV exposure may be self-regulating. The Secretariat was asked to contact SACN for confirmation of this and to provide some suggested wording.

18. It was also noted that the conversion factor for ng/L to nmol/L should be stated in paragraph 29.

19. The Committee highlighted that supplement studies using high oral doses tended to be conducted in elderly people and it was suggested that data should be

extracted from younger populations such as the Stafford (2018)[1] report of vitamin D poisoning cases in infants in Denmark.

20. In reference to paragraph 15, the Committee indicated that the threshold for toxic symptoms of serum 25(OH)D levels of 750 nmol/L should be put into context with the levels that can be achieved by exposure to sunlight. Additionally, the relationship between oral intake of vitamin D in µg to serum levels in nmol/L should be included.

21. The Committee compared the following quotes "doses of 7500 µg at intervals of 3 months or longer would not be expected to cause adverse effects in adults" in paragraph 67 to "the duration of consumption in these toxication cases ranged from 4 days - 10 years" in paragraph 15. The former referred to high single doses of vitamin D used therapeutically rather than the case reports of intoxication in the latter and this would be clarified.

22. Members were uncertain of consumer habits regarding vitamin D intake and how much intake levels might have increased during the COVID-19 pandemic. It was stated that the National Institute for Health and Care Excellence (NICE) had published guidance on vitamin D usage in the context of COVID-19 in December 2020, which could be included.

23. The Committee recognized that the exposure assessment for total intake was conservative and that exposure from sunlight might need to be included with exposure from supplements.

24. It was suggested that reference be made to the 2016 EFSA paper[2] that discusses a threshold of vitamin D toxicity of 250 µg/day, in the conclusion.

25. Members suggested the possibility be noted in paragraph 57 that women who were unaware of their pregnancy could be consuming high dose supplements not intended for pregnant women.

26. It was agreed that the functional consequences of polymorphisms in the vitamin D receptor (VDR) were more associated with effects of vitamin D deficiency than with effects related to excess vitamin D intake. Hence, they did not need to be addressed in detail in the statement.

27. The Committee advised that the circulating levels of vitamin D, which were potentially of concern, should be provided in addition to the sources of vitamin D.

28. Finally, the Committee concluded that contribution of vitamin D from the diet is reasonably lower than from supplements, and the major risk is in relation to consumption of supplements rather than foods. Additionally, the consumption of supplements reported is likely to be an underestimate as it based on a limited

[1] Stafford, N. (2016). Vitamin D supplements poison dozens of Danish children. https://www.bmj.com/content/354/bmj.i4534

[2] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). (2016). Dietary reference values for vitamin D. EFSA Journal, 14(10), p.e04547. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2016.4547

number of supplements available in the UK, and a significant portion of the population may be consuming high vitamin D doses from more than one supplement.

29. It was agreed that a revised version of the statement would be presented at a future COT meeting.

Item 5: Addendum to the statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes): presence and pharmacokinetics of nicotine salts.

30. Apart from those already noted in December 2018 and January 2020, no new interests were declared.

31. This paper followed the discussion in December 2020 and presented the information on nicotine flux requested at the meeting. Annex A contained a draft addendum to the current statement on the potential toxicological risks from E(N)NDS (COT Statement Number 2020/04)[3].

32. Members agreed that it should be clear in the draft addendum that there were two factors affecting systemic exposure of nicotine salts compared to free-base nicotine in ENDS vapour. Firstly, there were differences in physicochemical properties that affect the diffusibility of the nicotine across membranes, and this was less for nicotine salts than free-base nicotine. Secondly, the tolerability to the user of nicotine in salt form compared to free-base form would affect depth of inhalation, and as salts were better tolerated by users this led to greater exposure in the respirable region of the lungs and thus greater systemic exposure.

33. Regarding nicotine flux as reported by Shihadeh & Eissenberg (2015)[4], Members were of the opinion that this could be useful to compare technologies where puff topography as well as nicotine concentration in the ENDS vapour affected exposure. It was noted however, that there was not sufficient pharmacokinetic data to quantify the difference between free-base nicotine and nicotine salts, and without this information a nicotine flux model would not be helpful. Members further discussed an optimum nicotine flux scenario, and presented thoughts on how it may affect exposure to other ingredients/excipients within the product and so a holistic exposure of the nicotine salt product would be needed.

34. Due to the limitations of pharmacokinetic data on nicotine salts, it was unclear as to how at this stage the nicotine flux model could be used to aid evaluation of these products.

35. Members agreed that the addendum could be cleared via Chair's action.

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[3] COT Statement Number 2020/04 is available on the COT website.
[4] Shihadeh, A. and Eissenberg, T. (2015) Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine & Tobacco Research, 17, pp. 158-162.

ITEM 6: A summary of data on the bioavailability of nicotine and other ingredients from the use of oral nicotine pouches and assessment of risk to users. (TOX/2021/22)

36. Professor Alan Boobis declared that he chaired ISO TC126 WG10 on the intense testing regime for CC and is a member of the WHO Study Group on Tobacco Product Regulation. No other interests were declared.

37. The Committee was asked to consider the toxicological risks from tobacco-free oral nicotine pouches by the Department for Health and Social Care (DHSC) and the Public Health England (PHE) Tobacco teams.

38. PHE informed the Committee that these products were being considered as part of the harm reduction approach as an alternative to use of tobacco products.

39. The paper provided the publicly available information for the ingredients present in these products and focussed on the oral bioavailability of nicotine to support assessment of any potential risks associated with their use.

40. The Committee raised concerns that the possible risks to children and adults through non-intended use, e.g. accidental consumption, should be noted. In addition, dual use of these products alongside tobacco products or other nicotine containing products, would be of potential concern due to the increased nicotine exposure compared to a single source.

41. Members noted the toxicological risk profile would be different between oral and inhalation exposure. Risk comparison also changed as the formulation of the different nicotine containing products changed as well as how the consumer was exposed to them e.g. chewed vs inhaled. It was suggested that pharmacokinetic data be presented in tabular form for a future meeting, to enable some comparison across products. The possibility of there being an impact of changing formulation of these tobacco-free oral nicotine pouch products leading to different systemic exposure was also noted.

42. Members considered that within the tobacco-free oral nicotine pouch class of products, there would be different risks according to the different batches of tobacco used to derive the nicotine, and the extraction process used, as well as due to differences in the other ingredients used, and the pouch material itself. With respect to extraction of nicotine from tobacco, the possibility of contaminants such as heavy metals, pesticides and nitrosamines should be considered, and where possible avoided.

43. It was recognised that IARC had made a number of conclusions on oral tobacco products that it would be helpful for the Committee to review. Another aspect that could influence risk was food or beverage consumption as these could influence temperature and/or pH in the mouth which in turn could affect nicotine absorption from the pouches. Potential irritancy or other local effects at the site of use was also raised as a potential issue.

44. The Committee raised concerns over the current regulatory framework for these products as they did fall into any specific category; and recommended this be given consideration in the future. It was noted that the different regulatory frameworks for different potential harm reduction products also made it difficult to compare such products as the data requirements varied.

45. The Committee concluded that there was limited information available to be able to draw any conclusions regarding the risk of nicotine pouch use. It was agreed that a future paper would be provided with a summary table on the pharmacokinetics of nicotine in different product types which would allow comparison of exposure and risk in so far as the data were available. Such a paper would also provide the IARC opinions on oral tobacco products.

Item 7: Second draft Statement on COT principles for assessing risks from less than lifetime exposure or variable exposure over a lifetime (TOX/2021/23)

46. At the March 2020 meeting the COT considered a set of principles produced by the COC on considering less than lifetime exposure to genotoxic and non-genotoxic carcinogens. Subsequently, at the October 2020 meeting, the COT considered a paper which included two test cases from the COT's work on chemicals in the diets of infants and young children, cadmium and fumonisins. The COT agreed that COT-specific principles should be produced based on the COC principles. The title was expanded to reflect that the COT does not often consider exposure that is shorter than a lifetime and then ceases, but rather exposure that is over a lifetime but varies over that lifetime, being higher for a specific portion of that lifetime.

47. The first draft COT Statement was discussed at the February 2021 meeting. Members requested additional wording to be added to the text at step 2 to include consideration of whether there is progression of the toxicity and a decrease in the NOAEL with increasing duration of exposure, and what the sensitivity is of the chronic endpoint compared to specific life stages. The Committee also discussed bioaccumulative chemicals further, including the need for the kinetics to be studied carefully, expert judgement being required on a case-by-case basis, and the cases in which a Haber's rule-based approach may be an acceptable approximation.

48. The draft Statement had been revised in line with these comments. Members were invited to consider and comment on the revised draft Statement.

49. Members requested editorial changes, primarily to step 1B, "Define the exposure scenario", and step 2, "What are the hazards being assessed?" Members also requested the addition of bullet points to explain Haber's rule and Risk21.

50. Members agreed that, where possible, toxicokinetic or toxicodynamic modelling would be helpful in assessing risks from less than lifetime or variable exposure. Information on mode of action would also be useful.

51. Members agreed that following the requested revisions the Statement could be cleared by Chair's action.

Item 8: Discussion paper for the prioritisation of dietary components and xenobiotics for future papers on their effects on maternal health – Part 2 (TOX/2021/24)

52. No interests were declared.

53. 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; this would include the effects of chemical contaminants and excess nutrients in the diet.

54. SACN agreed that, where appropriate, other expert Committees would be consulted and asked to complete relevant risk assessments e.g. in the area of food safety advice. This subject was initially discussed during the horizon scanning item at the January 2020 meeting with a scoping paper being presented to the Committee in July 2020. This included background information on a provisional list of chemicals proposed by SACN. It was noted that the provisional list of chemicals was subject to change following discussion by COT who would be guiding the toxicological risk assessment process: candidate chemicals or chemical classes can be added or removed as the COT considered appropriate.

55. A paper submitted to the Committee in February covered chemical entities of biological origin. The list of remaining chemical and food entities for consideration was: **heavy metals (including arsenic), selenium, heterocyclic amines, acrylamide, dioxins and dioxin-like PCBs, non-dioxin-like PCBs, bisphenol A, legacy pesticides and components of oily fish**.

56. From the data provided in the paper, the Committee decided that the heavy metals should be prioritised and addressed in separate papers.

57. The effects of lead on infant neurodevelopment should have been taken into account in the previous work on the infant diet but fetal health would need to be considered if pre-natal exposure had not been addressed.

58. Members considered that a MOE should have been used to assess risk for cadmium.

59. For arsenic, it was noted that the PTWI values derived by EFSA and JECFA were deemed inappropriate because of the carcinogenicity of arsenic and BMDL values were now used. Members felt that the paper[5] referred to in paragraph 22 where a history of depression was correlated with arsenic exposure seemed to have cause and effect reversed.

60. It was noted that there were 4 types of heterocyclic amines but not all types had been listed and carbolines, which were known to have the highest exposure

[5] Valdés M, Hanchey A, Muñoz MP, Baumert B, Iglesias V. Low-level arsenic exposure during pregnancy and its association with postpartum depression: A cohort study of women from Arica, Chile Revue d'Epidémiologie et de Santé Publique 2017 65(6):427-435.

values, were absent. The Committee were confused about the MOEs given in the summary table since they could not find them in the cited papers. Some compounds, for example MeIQx, were known to have exposures in the ng range so a MOE of <10,000 was unexpected. Further studies would be needed to look at the impact of cooking on exposure but Members did not consider this a priority and thus the heterocyclic amines could be put into an overarching statement.

61. Members agreed that any assessment of bisphenol A should await the outcome of the forthcoming EFSA paper.

62. For acrylamide, Members suggested that the EFSA colloquium on acrylamide should be considered for data on endocrine involvement in tumorigenesis, rather than just considering genotoxicity.

63. It was agreed that any assessment of dioxin and dioxin like PCBs should await the outcome of the COT working group consultation on the new EFSA opinion on dioxins.

64. The Committee decided that there was too little data on non-dioxin-like PCBs for a meaningful assessment to be made of this group of compounds .

65. It was agreed that the levels of legacy pesticides in the environment and in breast milk were declining, so these compounds were of low priority for review.

66. It was pointed out that both the paper and other documentation on the subject on the risks arising from oily fish consumption had become confused. The risk from mercury comes from consumption of jarge predator fish like swordfish, whereas the risk from dioxins comes from consumption of oily fish. Large predatory oily fish, such as tuna, pose a risk from both mercury and dioxins, whereas small oily fish, such as anchovy, pose a risk only from dioxins.

67. The Committee decided that selenium should be considered as a priority and would be reviewed in an individual paper.

68. Overall, the Committee recommended prioritising heavy metals, selenium and the non-genotoxic effects of acrylamide. Separate papers should be prepared for each metal but there was no need for these to be extensive, because the metals had been assessed relatively recently in the context of the infant diet. Recent reviews could be summarised with a change in focus on exposure in target groups.

69. The Committee were asked about any other compounds they might consider being added to the list and PFAS and possibly phthalates were mentioned. The notes of a DEFRA meeting on PFAS were recommended to the Secretariat as a source of data. The Secretariat should also consult the EU biomonitoring project HBM4EU, and NHANES.

70. A summary table covering the outcome of the triage process should be compiled and circulated to Members.

Item 9: Alcohol and the maternal diet: The 2016 Chief Medical Officers report (TOX/2021/25)

71. No interests were declared.

72. As part of the work on the maternal diet, a discussion paper proposing chemicals for review was considered at the February COT meeting. As part of the discussion, it was asked whether alcohol should be considered. Alcohol *per se* was not within the SACN remit but could be considered as a wider health issue.

73. As the database for the potential effects of alcohol in pregnancy was extensive, the Secretariat agreed to identify the most recent recommendations and the data on which they had been based in order to establish whether further work in this area would be of value.

74. The UK Government suggests that women who are pregnant or trying to become pregnant should avoid alcohol altogether. The advice, which is given on, for example, the NHS website, is based on recommendations from the Low Risk Drinking Guidelines produced by the UK Chief Medical Officers (CMO) in 2016, which were based on the findings of a number of systematic reviews and meta-analyses. The results of these studies were largely inconclusive regarding the effects of low levels of alcohol exposure and methodological flaws in the studies have generally been noted. Since 2011, a number of additional systematic reviews and meta-analyses have been published covering the same end points considered in the CMO report, but as previously, the results for low levels of exposure were inconclusive and methodological failings were noted.

75. Sunderman et al[6]. quantified the risk of alcohol consumption. However, Members noted that the statistical power of those findings was weaker than initially thought and that there were recall biases, given that the outcome of the pregnancy was already known when the women were recruited. Furthermore, the incidences of miscarriage in the 1st trimester and 2nd/3rd trimester individually were not statistically significant and the non-survival data was not entirely in keeping with the survival data. In addition, the dose-response data was difficult to interpret and Members would require further information on this dose-response effect to comment/conclude on the effect.

76. The COM reviewed alcohol in 2005 and their discussion surrounding the data on alcohol was similar to today's discussion by the Committee. Members of the COM concluded that there was no clear evidence for a risk from (low) alcohol consumption during pregnancy but equally were not able to fully exclude a risk either. The COM further concluded that alcohol itself is probably not genotoxic, however acetaldehyde most likely is. Overall, the COM was unclear what other chemicals may be present in alcoholic beverages that might cause an effect.

[6] Sundermann, A., Zhao, S., Young, C., Lam, L., Jones, S., Velez Edwards, D., Hartmann, K. (2019). Alcohol Use in Pregnancy and Miscarriage: A Systematic Review and Meta-Analysis. Alcohol Clin Exp Res, 43(8):1606-1616.

77. Members noted that alcohol was produced endogenously and metabolic enzymes have been proven to be extremely effective at preventing cellular damage in the body and aiding the elimination of alcohol. Hence, the biology would need to be taken into account when considering the epidemiology and it was possible there was a threshold for the effects of alcohol.

78. Members considered the CMO report thorough and agreed the approach and conclusions on alcohol in pregnancy were reasonable, given the data considered in the report. The evidence was not strong enough to completely rule out some risk from low levels of alcohol exposure in pregnancy.

79. The Committee agreed that data published since 2011 did not greatly add to the CMO report on the clarity of the issue. Given the work and resources involved, a further review would be unlikely to change the current advice to women. Members therefore agreed not to take this review further.

80. Members asked for feedback from SACN as there was concern whether all aspects of interest had been addressed.

Item 10: The potential effects of ginger and ginger supplements during pregnancy and lactation (TOX/2021/26)

81. Dr Stella Cochrane declared that Unilever manufactures teas containing ginger. No other interests were declared.

82. As part of the work on the maternal diet, the Committee considered the use of dietary supplements during pregnancy. A discussion paper (TOX/2020/51) was presented reviewing the commonly used dietary supplements used during pregnancy. These were supplements that were not officially recommended by the relevant authorities, but which were promoted by anecdotal evidence and unofficial sources as having various purported benefits.

83. The review was confined to herbal dietary supplements which would be regulated under food law and which would not be considered to be traditional herbal medicines which are the responsibility of the Medicines and Healthcare Products Regulatory Agency (MHRA). Following this review, the COT agreed ginger required further investigation, noting that human, animal and *in vitro* data were available.

84. Paper TOX/2021/26 reviewed the available data on toxicity to the mother, effects on the development of the fetus or embryo, and possible interactions with drugs as well as data on potential exposure.

85. Regarding the *in vitro* data, it was noted that the Inhibitory Concentration $(IC)_{50}$ values collated were based on a small amount of data, from only 5 different cell lines.

86. The animal studies reported nothing conclusive in either males or females. It was noted that a study by Hosseini et al (2015)[7] reported an increase in testosterone in F1 generation males, leading to a decrease in FSH + LH, which would be expected with an increase in testosterone.

87. Members noted that associations with haemorrhagic effects were reported following exposure to ginger, though these were not conclusive. A study by ElMazoudy and Attia (2018)[8] linked follicular failure to haemorrhagic effects. It was noted that this might be worth further investigating. However, it was also noted that other factors could be contributing to the results observed.

88. The results of studies in pregnant women were also varied and the overall findings inconclusive. There were reports of an increase in spontaneous abortion, but also some contradictory studies. There were no reported effects of defects post-partum.

89. Members questioned what the mode of action for the purported beneficial effects of ginger on nausea might be. It was suggested that ginger might decrease prostaglandin levels, which were linked to nausea. Further studies would be needed to determine if this effect was linked to early termination of pregnancy.

90. The variability of composition for the supplements and extracts compared to food was noted. It was difficult to compare exposure from supplements with that from diet. It would be better to separate diet from concentrates and extracts to clarify this.

91. It was also noted that it was difficult to compare studies, due to the variability of substrates used and the possible presence of environmental contaminants where the natural root had been used.

92. It was noted that contrary to the stated findings, the paper by Willets *et al.* (2003)[9] did not show strong evidence of an effect on spontaneous abortion. The Committee considered that this needed more detailed consideration.

93. The exposure levels from food were very low compared to those used experimentally, but when supplementation was taken into account, exposure levels were closer to those used in the reported studies. Background levels of ginger in the diet were expected to be much less than those in supplements or highly

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[7] Hosseini, E; Jahandidea, A; Mehrabani, D. (2015). Effect of alcoholic extract of Ginger during fetal life and breastfeeding on serum level of testosterone, LH, FSH and spermatogenic cells line in male mature offspring rats. *Journal of Gorgan University of Medical Sciences*. 17. 29-34.

[8] ElMazoudy, Reda & Attia, Azza. (2018). Ginger causes subfertility and abortifacient in mice by targeting both estrous cycle and blastocyst implantation without teratogenesis. *Phytomedicine*. 50. 2018, 300-308.

[9] Willetts KE, Ekangaki A, Eden JA. (2003). Effect of a ginger extract on pregnancy-induced nausea: a randomised controlled trial. *Aust N Z J Obstet Gynaecol*. 2003 Apr;43(2):139-44.

concentrated drinks. Assumptions would have to be to made on how many of products such as ginger shots were consumed per day. The Committee noted that, as it is commonly understood that ginger suppresses morning sickness, it could not be ruled out that pregnant women would be using the supplements in this way. In terms of exposure, diet plus supplements would need to be considered as well as diet plus shots depending on the exposure period of concern.

94. It was noted that the general public would assume that ginger supplements and shots would be safe. Members agreed that it should be clarified that, whilst ginger consumption in the diet was not considered to be of concern since there was a history of safe use, problems could arise from consumption of products such as the various forms of supplements and that should be the focus of the risk assessment.

95. The amount of human evidence is limited, so this would need to be reflected in any risk communication.

96. Ginger was reported to have antiplatelet activity, with some studies reporting effects in animals at doses of 500 mg/kg bw. This further highlighted the need to differentiate exposure from the normal diet to that from supplements.

97. Human data showed possible interactions with medicines. A point of departure for this effect was difficult to determine, however, an estimated level of 100 mg/kg was suggested from animal studies.

98. It was noted that some of the toxicity observed varied according to the nature of extraction solvent - organic solvent extracts exhibited more toxicity than aqueous extracts, which presumably indicates extraction of differentially toxic compounds. Hence, studies of individual extracts might not give the whole picture of the uncertainties involved.

99. The best estimate of a point of departure from available animal studies was around 50-100 mg/kg based on the reproductive studies. The Committee suggested looking at the animal data in closer detail to determine the point of departure (NOAEL), followed by calculating the potential exposure to supplements to determine whether there was cause for concern.

100. It was also noted that any characterisation data of the material used in supplements would be important information, since the products were very variable.

101. Overall, it was concluded that there was limited data. The human data presented were not strongly indicative of any toxicological concern but there were some indications of possible effects and a lot of uncertainties. Ginger did not appear to be systemically toxic but did appear to have reprotoxic effects at high supplemental doses.

Item 11: Paper for information: Update on the work of other scientific advisory committees (TOX/2021/27)

102. This paper was circulated for information.

Item 12: Any other business

103. The Chair updated COT Members on discussions at the recent SAC Chairs meeting.

104. No other business was raised by Members or the Secretariat.

Date of next meeting

105. The next meeting of the Committee Meeting will be at 10:00 on the 6th of July 2021 via Skype and Teams.