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

Minutes of the meeting held on Tuesday, 5th July 2016 in Aviation House, London.

Present

Chairman:	Professor A Boobis		
Members:	Prof J Cade		
	Dr J Coulson		
	Dr R Crevel		
	Dr M Graham		
	Dr C Harris		
	Prof D Harrison		
	Prof R Harrison		
	Prof B Lake		
	Prof I Morris		
	Prof R Smith		
Food Standards Agency (FSA) Secretariat:	Ms C Mulholland	Scientific Secretary	
	Mr B Maycock		
	Ms H Gbormittah		
	Dr D Benford		
	Ms F Hill		
	Ms R Acheampong		
	Ms L Buckley		
	Dr D Hedley		
	Dr J Shavila		
	Mr A Sbaiti		
Public Health England (PHE) Secretariat:	Dr O Sepai	PHE Scientific Secretary	
Invited Experts and Contractors:	Prof P Aggett	SMCN	
	Mr P Thomas	Specialist Cheesemakers Association	Item 4
	Mr A Kuyk	Provision Trade Federation	Item 4

	Dr K Okona-Mensah	PHE-Supported Toxicology Unit. Imperial	Item 5
	Dr R Boyle (by phone)	Imperial College London	Item 6-7
	Dr P Turner	Imperial College London	Item 6-7
Officials:	Ms R Elsom	PHE	Items 6-7
	Dr V Swaine	HSE	
	Ms E Kendall	FSA Food Allergy Branch	Items 6-7
Assessors:	Prof T Gant	PHE	

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Announcements

1. The Chair welcomed Members and Assessors to the meeting.

2. The Chair reminded those attending the meeting to declare any commercial or other interests they might have in any of the agenda items.

Item 1: Apologies for absence

3. Apologies were received from Members Prof F Williams, Prof B Houston, Dr N Plant, Dr J Thompson, Mr D Bodey and Dr A Hansell.

Item 2: Draft minutes of the meeting held on 24h May 2016

4. The minutes were agreed without amendments.

Item 3: Matters arising

Item 3: Matters arising from previous meetings

5. Para 6: In Dr Hansell's absence it was not possible to provide an update on the COT-Committee on Carcinogenicity (COC) Synthesising Epidemiological Evidence Subgroup.

6. Para 7: The next meeting of the COT/SACN potassium working group was planned for 27th September.

7. Para 8: The FSA Board discussed the report of the FSA's Triennial Review of its Scientific Advisory Committees at its open meeting on 18 May 2016, in Belfast. The Chair of the General Advisory Committee on Science (GACS), Professor Sir Colin Blakemore, was present for the discussion to relay directly to the Board the concerns GACS had raised with regard to the review and its implementation. The Board endorsed the recommendations of the review and agreed that they should be implemented. It welcomed the input from GACS which had highlighted important features of the operation of the SACs which should be maintained. The Board reiterated its commitment to science and evidence-based decision making and that the SACs should continue to operate to high standards of openness, transparency and independence. It confirmed there would be no change to the principle of lay membership of Committees, including the new Science Council, and that FSA would maintain and develop effective co-ordination between SACs and their Chairs, including with wider groups of 'non-FSA' SACs (including SACN). The Board also agreed to take stock of the changes made in 12-18 months' time. The FSA was taking forward work to implement the recommendations and would continue to work closely with the SACs and their Secretariats in this work. The Board Paper and the related correspondence with GACS, along with video and audio recordings of the

discussion, were available on the Board web pages at the link below[1]. Minutes would be published there in due course.

8. Para 13: Statement on the potential risks from aluminium in the diet of infants and children. This had been finalised and cleared by the Chairman. It was with the SACN Subgroup on Maternal and Child Nutrition (SMCN) for comments. A lay summary was to be prepared and circulated to members for comment shortly.

9. Para 14: The COT part of the draft annual report had been finalised and the COM section had also been received. The report was to be compiled and published shortly.

Item 4: Third draft addendum to the 2013 COT statement on potential risks from lead in the infant diet- TOX/2016/18

10. Para 19: The addendum on lead had been revised and was with the Chairman to check before circulating to members to confirm they were content with the revised conclusions. It would then be shared with SMCN and a lay summary drafted and circulated to members for comment in the near future

Item 5: Review of risks arising from the infant diet and the development of atopic and autoimmune disease: Systematic review B – timing of introduction of allergenic foods to the infant diet

11. Para 27 and reserved minutes para 8: A second draft statement covering review B – the timing of introduction of allergenic foods – would be considered at this meeting under agenda Iitem 7. A first draft statement covering reviews A and C (on breastfeeding and dietary exposures) would be considered at this meeting as agenda item 6.

Item 7: First draft statement on the potential risks from arsenic in the diet of infants aged 0 to 12 months and young children aged 1 to 5 years

12. Para 30: The statement was being revised for clearance by Chairman's action. It would then be shared with SMCN and a lay summary drafted and circulated to members for comment in the near future.

Item 4: Histamine in food: additional information – TOX/2016/24

13. Paul Thomas (Specialist Cheesemakers Association Technical Committee) and Andrew Kuyk (Provision Trade Federation Director General) were in attendance.

14. No interests were declared.

[1] http://www.food.gov.uk/sites/default/files/meeting/minutes/board-final-minutes-18-may-2016_0.pdf

15. Histamine poisoning can occur as a result of the consumption of foods such as fish, sausage and cheese which contain high levels of histamine as a result of bacterial spoilage or due to fermentation. Incidents of histamine poisoning in cheese appeared to have increased in recent years. Although there was specific legislation covering histamine in fish, there was no legislation on histamine levels in other foods.

16. When potential histamine poisoning incidents occurred, the FSA have given advice taking into account data from case reports and volunteer studies in the literature as well as the European Commission's action level for histamine in fish (200 mg/kg) where the portion sizes for fish and cheese were comparable. More recently, the FSA have begun to take into account the acute reference dose (ARfD) for histamine that was established by the EFSA BIOHAZ panel. Typically, the FSA modelled various consumption scenarios and compared them to the ARfD to establish the level of risk to the consumer, taking into account the type of cheese involved, the likely consumers (particularly children) and the expected quantity consumed. However, since precautionary as well as incident advice was now being requested, the secretariat had asked the Committee to comment on the approach being taken; this was discussed in June 2015. Members had been broadly content but had requested additional information on some points. In response the Specialist Cheesemakers Association (SCA) and Provision Trade Federation (PTF) trade associations had surveyed their members on a number of issues the COT had raised. The results of these surveys were given in TOX/2016/24. It had been hoped to obtain additional background monitoring data to establish what routine histamine levels were, but this had not been possible.

17. The Chairman thanked the representatives of PTF and SCA for their assistance. Members agreed that the information they had provided was reassuring.

18. The ARfD set by the EFSA BIOHAZ panel was set on a per meal basis rather than a per kg bodyweight basis as would be more usual. This was due to histamine being an acute toxicant and because the dose response data used in the assessment were taken from controlled human volunteer studies where the results had been reported in that format. Exposure assessments had been calculated for some foods to compare against the ARfD; these were based on histamine occurrence in a range of foods and consumption data (cumulative exposure for a consuming day) from a number of EU member states; these were all lower than the ARfD.

19. The ARfD had not been scaled for children by the BIOHAZ panel but the FSA had done so in their advice; the COT considered that scaling the dose for children was appropriate. It was uncertain why there seemed to be more incidents occurring in children – whether this was due to increased sensitivity to histamine, the type of cheese being consumed or that clusters of cases were more noticeable in a nursery

or classroom setting. Mr Kuyk suggested that since the incidents often occurred in mass catering situations it might also be imperfect storage or handling that was leading to increased histamine levels.

20. The reaction of individuals to consumption of high levels of histamine in a food was sometimes wrongly described as allergic. This was due to confusion between the effects of consumption of high levels of histamine already present in a spoiled or fermented food and the effects of histamine being produced by the body during an allergic response to an antigen. Members wondered whether previous exposure to allergens and production of histamine might prime the system making an individual more sensitive. However the cases appeared to relate to consumption of excess histamine rather than mast cell effects.

21. It was noted that potential fatality due to biogenic amine toxicity was cited in the EFSA report but it was unclear whether this related to a specific case or was a potential effect based on the pharmacological properties of biogenic amines. The secretariat agreed to check the original reference.

22. It was agreed it would be helpful to clarify that histamine was not destroyed by cooking; this was noted in the literature and cases had also been reported to the FSA following consumption of meals such as lasagne or macaroni cheese supporting resistance to cooking.

23. In reply to a member's question, Mr Thomas explained that the smaller, artisan producers did not supply schools and nurseries due to the higher cost of their products. He added that European colleagues did not consider excess histamine to be a concern.

24. It was pointed out that one respondent to the PTF had stated that production of biogenic amines was linked to carbon dioxide formation which would lead to other deviations in the product such as cracking. This in turn would lead to the cheese being declassified and not sold as table cheese. It was unclear whether the cheese would be destroyed or reprocessed after this had occurred.

25. Members considered that the information provided by SCA and PTF did not alter their previous views that the approach taken by the FSA to histamine poisoning was sound and pragmatic and agreed it would be important to maintain a watching brief on this topic with the assistance of the trade associations.

Item 5: Scoping paper on the potential risks from electronic nicotine (or non-nicotine) delivery systems in users and non-users (bystanders): a focused review – TOX/2016/25.

26. No interests were declared.

27. At the February 2016 horizon-scanning exercise, Members considered that the possible human health effects of electronic nicotine (or non-nicotine) delivery systems (E(N)NDS) was a topic of concern and PHE agreed that this should be evaluated by the COT. It was considered that a more focussed rather that a full systematic review was most appropriate: this would consider additives, nitrosamines and other tobacco-related toxicants that might be produced by ENDS/ENNDS and secondary exposure to exhaled products as key areas.

28. Paper TOX/2016/25 was a scoping paper intended to summarise available information. Each key area was considered in a section which addressed evidence from: analytical studies that measured the levels of analytes in E(N)NDS liquids or aerosols; toxicity studies conducted in animals or *in vitro*; and evidence from studies evaluating health effects/exposure in humans (where possible). The final section highlighted relevant conclusions from reports produced by key national and international health organisations. It was noted that nicotine had not been included as the effects of this compound were well established.

29. Members discussed the different E(N)NDS products and the increasing use of "do it yourself" electronic cigarettes, whereby customers had the option to mix and create a product made from a range of over 7000 flavouring compounds. Members expressed concern that although many of these compounds were already present in foodstuffs, there was a lack of information on the effects of exposure to these flavours from inhalation as opposed to ingestion. It was noted that the recent report from the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) provided a potential significant resource for information on inhalation toxicity studies conducted on flavourings that were also used in E(N)NDS products.

30. It was also noted that whilst there had been studies outlining the number of particles inhaled; there was a lack of information on the composition and solubility of these particles.

31. Members expressed concerns over secondary exposures. Simulations were not typically representative of inhalation in use, and did not model well the passage of vapour into the lungs. Studies outlined that there were substantial PM2.5 concentrations indoors where there was heavy use of the product, but the nature of the particles was unclear. Members agreed that the literature was sufficient to indicate a possible concern, but not conclusive enough to allow full evaluation of the risk. Members questioned the quality of current data when considering bystander exposure, particularly with regards to children's exposure. It was agreed that there would need to be careful consideration of exposure to vulnerable populations.

32. The functions of e-cigarette devices were also discussed; some devices had controls that allowed users to change parameters such as the voltage and temperature, thus the composition of the vapour would vary. Therefore it would be difficult to establish a worst case scenario that was truly representative of human exposure. In many studies, the voltage and temperature of the devices were not recorded.

33. It was noted that under current UK legislation on tobacco products only devices that were smoked were banned from use indoors. As e-cigarettes were not smoked, they do not come into this category, although a number of organisations were banning use in their premises.

34. A number of follow up questions were agreed by the committee for further consideration. These included: the composition of particles, bystander exposure to key analytes, effects of long term inhalation of the main constituents and emissions, the situation regarding flavourings (exposure, thermal products, toxicity on inhalation), and the exposure to metals from the device components.

35. The committee agreed that further discussion papers should be prepared to address the above questions. These would be submitted to the committee for consideration at future meetings.

Item 6: First draft statement on evidence regarding maternal and infant dietary exposures and risk of atopic outcomes and autoimmune disease (reserved business) – TOX/2016/26

36. The Chair declared a non-personal, non-specific interest in this item as he is employed at the same institution as the contractors who had performed the review.

37. Dr Paul Turner (Imperial College London) was present and Dr Robert Boyle from the Contractor team was available via teleconference for some of the discussion, to offer advice to the Committee on this topic.

38. Members made a number of comments on the wording and structure of the draft statement; it was agreed that a revised draft would be considered at the next meeting.

39. The final statement and minutes of this item from previous meetings are currently reserved as they include pre-publication data. These would be published as soon as practicable.

Item 7: Second draft statement on the introduction of allergenic foods to the infant diet and influence on the risk of development of atopic outcomes and autoimmune disease (reserved business) – TOX/2016/27

40. The Chair declared a non-personal, non-specific interest in this item as he is employed at the same institution as the contractors who had performed the review.
41. Dr Paul Turner (Imperial College London) was present and Dr Robert Boyle from the Contractor team was available via teleconference for some of the discussion, to offer advice to the Committee on this topic.
42. Members made a number of comments on the wording and structure of the draft statement; it was agreed that a revised draft would be considered at the next meeting.
43. The complete minutes of this item are currently reserved as they include pre-publication data. These will be published as soon as practicable.

Item 8: Review of potential risks from hexabromocyclododecanes in the diet of children aged 1 to 5 years and updated exposures for infants aged 0 to 12 months – TOX/2016/28.

44. The Chair and Dr Benford declared a non-personal, non-specific interest in this item as they had been members of the CONTAM panel involved in the 2011 EFSA review on hexabromocyclododecanes (HBCDD).

45. This review of HBCDD was part of the series related to the risk from chemicals in the infant and young child diet, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. There was currently no Government dietary advice for infants and young children which related to HBCDDs.

46. This discussion paper provided estimated HBCDD exposures for children in the UK aged one to five years and also provided an update to exposures for infants aged 0-12 months as new data on exposure from dust had become available since the 2015 COT statement.

47. Since HBCDD in the diets of infants aged 0-1 had been initially discussed by COT, some new toxicological information had also become available. The study by Maurice *et al.* (2015)[2] was not available to EFSA and, if considered valid, would suggest that adverse effects might occur at lower levels of exposure than previously thought, with much lower MOEs being estimated.

[2] Maurice N, Olry JC, Cariou R, Dervilly-Pinel G, le Bizec B, Travel a, Jondreville C and Schroeder H. Short term effect of a perinatal exposure to the HBCDD a-isomer in rats: Assessment of early motor and sensory development, spontaneous locomotor activity and anxiety in pups. Neurotoxicol Teratol. 2015 Nov-Dec:52(Pt B): 170-80. doi: 10.1016/j.ntt.2015.08.005. Epub 2015 Sep 5.

48. Members considered the paper of Maurice *et al.* (2015), which reported a non-monotonic dose-response relationship for α-HBCDD in a developmental study in rats fed eggs from hens consuming α-HBCDD-contaminated feed. Estimated doses in the rats were 22 and 66 ng/kg/bw. Members expressed a number of reservations about this study. It was noted that the group sizes were relatively small with a large number of comparisons, possibly compromising the validity of the statistical analysis, some HBCDD-related effects were transient, there was no dose response relationship, yet the higher dose was still appreciably lower than the BMDL10 for the most sensitive effect previously reported, raising questions as to the biological credibility of a non-monotonic dose-response relationship at these exposure levels, and the chemical composition of the dosing material was not fully known because of the design of the study (feeding to hens and then using the eggs to administer HBCDD to the rats). It was also agreed that a positive control would have been useful. However, it was helpful that a defined isomer had been used, and that it had been presented to the animals in a matrix that approximated exposure in food and that the authors themselves recognised shortcomings in their findings, which required further study.

49. Although the data presented were regarded as insufficient to modify the current reference point for risk assessment, the Committee agreed that these data should be noted and further work related to that of Maurice *et al.* (2015) on the HBCDDs should be monitored since confirmation of their results would change the estimate of the potential for harm from these compounds.

50. Dietary HBCDD exposure levels in children from 0 to 5 years of age were not regarded by Members as being a cause for concern, given the high margins of exposure.

51. The methodology for assaying levels of HBCDDs in domestic dust in the paper by Kuang *et al.* (2016)[3] was considered by the Committee to be comparable to that in the paper of Abdallah and Harrad (2008)[4] and hence the results could be compared directly. Members suggested that the raw data in the Kuang *et* al (2016) paper could be requested from the authors to explore the possibility of meta-analysis. While Members felt that the lower levels seen in the more recent paper may reflect a reduction in levels following the 2014 ban on HBCDD use in domestic products, they recognised that many people would still be exposed to pre-ban levels and sporadic high levels of exposure could not be ruled out, such that there might be some concern. The Committee recommended that further monitoring be carried out to assess the effect of the ban.

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[3] Kuang J, Ma Y and Harrad S (2016). Concentrations of “legacy” and novel brominated flame retardants in matched samples of UK kitchen and living room/ bedroom dust. *Chemosphere* **.** 149: 224-230

[4] Abdallah MA, and Harrad S (2009). Personal exposure to HBCDDs and its degradation products via ingestion of indoor dust. *Environ Int.* 35(6): 870-6.

52. The Committee concluded that presenting aggregate data would be of little value since the dietary levels were minimal compared with the non-dietary exposures.

53. Members concluded that the new data were insufficient to warrant a new statement on the HBCDDs but an addendum should be written to be appended to the 2015 COT Statement and presented to the Committee at the September meeting.

Item 9: Discussion paper on the results of the 2014 survey of metals and other elements in infant foods – TOX2016/29

54. The Chair declared that he had been a Member of the European Food Safety Authority's (EFSA) Panel on Contaminants in the Food Chain (CONTAM) when the scientific opinions on arsenic, cadmium and lead in food had been adopted. He had also chaired the Working Group (WG) that had prepared the CONTAM Panel's scientific opinion on lead. The FSA Scientific Secretary, Dr Benford, declared that she had been a Member of the EFSA CONTAM Panel when the scientific opinions on arsenic, cadmium, chromium, lead, mercury, and nickel had been adopted. Dr Benford had also been a member of the Working Groups (WGs) that had prepared the CONTAM Panel's scientific opinions on arsenic and mercury, and the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives' (JECFA) addenda on aluminium and arsenic. Professor Aggett, a Member of the Scientific Committee on Nutrition (SACN) and their Subgroup on Maternal and Child Nutrition (SMCN), declared that he had been a Member of the EFSA's Panel on Dietetic Products, Nutrition and Allergies (NDA) when the scientific opinion on dietary reference values for iodine was adopted.

55. In 2014, the FSA completed a survey of 15 metals and other elements in infant formula, commercial infant foods, and other foods (i.e. those which were not specifically manufactured or intended for infants and young children but were known to be or could be consumed by them such as bread, fruit and vegetables). The results of the FSA's survey had provided information on the concentrations of aluminium, antimony, arsenic (including inorganic arsenic), cadmium, chromium, copper, iodine, iron, lead, manganese, mercury, nickel, selenium, tin and zinc in these foods. Based on these concentration data, and food consumption data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC), dietary exposures to these elements had been estimated for UK infants and young children aged 4 to 18 months.

56. Discussion paper TOX/2016/29 provided the aforementioned concentration data and exposure estimates, alongside brief summaries of the toxicology of each

element and comparisons of the exposure estimates with the relevant health-based guidance values. The Committee was invited to comment on the information provided, and to consider the draft conclusions that had been reached for each element. Members were informed that a Food Surveillance Information Sheet (FSIS) would be drafted by the FSA with a view to publishing later in the year; the FSIS would incorporate the COT's comments and conclusions.

57. The Committee questioned the approach taken in extrapolating the upper levels for some elements from adults to the age group being assessed, with respect to the assumptions about body weight scaling, and requested that these upper levels be recalculated. The subsequent conclusions should be redrafted where necessary. Members also requested the inclusion of information on other significant sources of exposure (e.g. water or environmental) for some of the contaminants, most notably cadmium and lead, and suggested the addition of information on sufficient intake levels in the text accompanying the conclusions for all essential elements.

58. Overall, the Committee agreed that, based on the results of the FSA's survey, the current estimated dietary exposures of UK infants aged 4 to 18 months to aluminium, antimony, chromium, copper, iodine, iron, mercury, selenium, tin, and zinc, were not of toxicological concern. Members requested a minor clarification to the explanatory text that accompanied the conclusion for chromium.

59. Members agreed with the conclusion that although the current average dietary exposures to inorganic arsenic would be considered of low concern, the high level exposures could present a small risk to consumers, and it should therefore be reiterated that efforts to reduce the levels of inorganic arsenic in food should continue. Members requested clarification in the accompanying text as to the reason that a conclusion had not been drafted for total or organic arsenic (i.e. the focus is on inorganic arsenic as this is the form that is carcinogenic).

60. The Committee requested that the conclusion for cadmium be reworded slightly, and the reason for using the EFSA's health-based guidance value rather than the JECFA's one be explained further.

61. Members agreed that the conclusion regarding exposures to lead should be redrafted and aligned with the conclusions set out in the recently drafted addendum to the 2013 COT statement on potential risks from lead in the infant diet. Members also requested that it be explained in the text that this age group are particularly vulnerable to the adverse effects of lead because they absorb a higher percentage of ingested lead, *and* because of their developing nervous system.

62. Members requested that the appropriateness of the health-based guidance values used to assess exposures to manganese be checked, and the conclusion be redrafted if necessary.

63. The Committee did not agree with the conclusion for nickel as the EFSA's current tolerable daily intake was based on an adverse reproductive effect which was not relevant for this age group. Members suggested that an alternative health-based guidance value should be sought, and the conclusion be redrafted.

64. Lastly, Members suggested that future surveys of this kind should include the same foods if at all possible, so that temporal changes in exposure can be tracked and trends can be assessed. Trend data such as this would make it simpler to prioritise work on these elements in the future.

65. A brief discussion paper would be circulated to the Committee containing the necessary redrafted text and conclusions for approval by Members

Item 10: Paper for information: FSA Scientific Advisory Committees (SACs) update

66. This paper was provided for information only.

Item 11: Any other business

Shisha smoking

67. A Member had raised the question of whether there were up-to-date risk assessments for shisha smoking, including for neighbours or bystanders who may be exposed to the smoke involuntarily. It was noted that there had been changes to the legislation on tobacco products with effect from May 2016 (the Tobacco and Related Products Regulations 2016). The Committee presumed that shisha smoking would not be permitted in indoor public areas, as this was a product that was smoked, but that there would be no specific control on the use of shisha outdoors, and asked to be provided with an overview at a future meeting on what was and was not legal. In addition, the Committee could be provided with a summary of the available information on exposures from shisha.

Cross committee working on epigenetics

68. The Committee was informed that the Committee on Mutagenicity (COM) had started to consider the topic of epigenetics and had identified this as an appropriate topic for cross-committee working between the COM, COT and the Committee on Carcinogenicity (COC). The suggestion had been made that a possible joint meeting of the three Committees be held next year. Members agreed this would be relevant and useful.

COT recruitment

69. The Chair noted that a recruitment exercise for nine new COT members would be launched soon. Members were encouraged to distribute the advertisement to anyone who may be interested.

Date of next meeting

70. The next meeting was to be held on Thursday 1st September 2016 in Conference Rooms 4&5, Aviation House, 125 Kingsway, London, WC2B 6NH.