TOX/MIN/2015/03

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

Minutes of the meeting held on Tuesday, 30th June 2015 in Aviation House, London.

Present

Chairman:	Professor A Boobis		
Members:	Mr D Bodey Dr R Brimblecombe Prof J Cade Dr J Coulson Dr M Graham Dr A Hansell Prof D Harrison Prof R Smith Dr J Thompson Prof F Williams		
Food Standards Agency (FSA) Secretariat:	Dr D Benford Ms R Acheampong Ms L Buckley Ms H Gbormittah Dr D Hedley Ms F Hill Dr L Kent Mr B Maycock Ms C Mulholland Ms C Potter Dr J Shavila	Scientific Secretary	
Public Health England (PHE) Secretariat:	Ms F Pollitt	Scientific Secretary	
Invited Experts and Contractors:	Professor Peter Aggett	Sub-group on Maternal and Child Nutrition (SMCN) of the Scientific Advisory Committee on Nutrition (SACN)	Items 6 & 9
	Dr Robert J Boyle	Imperial College, London	Item 6
	Prof Ian Kimber	University of Manchester	Item 6
	Dr Paul Turner	Imperial College, London	Item 6
Officials:	Ms Elaine Boylan	PHE	Items 6 & 9
	Ms Rachel Elsom	PHE	Items 6 & 9

	Ms Elizabeth Kendall	FSA, Food Allergy Branch	Items 6 & 9
	Mr Graham Smith	Home Office Centre for Applied Science and Technology (CAST)	Items 4 & 5
	Inspector Nick Sutcliffe	Police Advisor for CAST	Items 4 & 5
	Dr Manisha Upadhyay	FSA, Microbiology Risk Assessment Team	Item 7
Assessors:	Ms Michaela Benton	Health & Safety Executive (HSE)	
	Prof Tim Gant	PHE	
Observers:	Mr Terry Jones	Specialist Cheesemakers Association	Item 7

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Announcements

1. The Chairman, Professor Boobis, welcomed Members and assessors to the meeting, which was his first as Chair.

2. The Chairman particularly welcomed Dr James Coulson, who was attending his first meeting as a new Member of the Committee. The Chairman also welcomed Professor Aggett who was in attendance for Items 6 and 9 in particular, as he had resumed his role as liaison with the Scientific Advisory Committee on Nutrition's (SACN) Sub-group on Maternal and Child Nutrition (SMCN). For the benefit of the new Chairman and Member, Members of the Committee and the Secretariat briefly introduced themselves.

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

Item 1: Apologies for absence

4. Apologies were received from members Professors Roy Harrison, Ian Morris, Brian Houston and Brian Lake, and Drs Rene Crevel, Nick Plant and Caroline Harris. Written comments had been submitted by one Member. Apologies were also received from assessor Sam Fletcher (Veterinary Medicines Directorate).

Item 2: Draft minutes of the meeting held on 17th March 2015 – TOX/MIN/2015/02

5. The minutes were agreed subject to minor editorial amendments.

6. The PHE Scientific Secretary would check with the Home Office whether the reserved minutes for Item 4 (submissions for the reformulation of nonivamide (PAVA) and 2-chlorobenzylidene malononitrile (CS) as incapacitant sprays) would be published at some stage.

Item 3: Matters arising

Item 3: Matters arising from previous meetings

7. Paras 5-7: The former Chair, Professor Coggon, had written to the Parliamentary Under-Secretary at the Department for Transport (DfT) to again raise the problem of inaccurate representation of the Committee's conclusions in official replies. A reply had been received by Professor Boobis, copied to Professor Coggon, from Kate Jennings, Head of Aviation Policy Division, on 20th May. This stated that "Given the current understanding of the level of risk (*from fume events)*, DfT does not

plan to undertake any additional research on this issue.". It did not address the fact that COT advice to Government had been repeatedly misrepresented in ministerial communications, including answers to Parliamentary questions, or the Committee's view that there is a continuing imperative to minimise the risk of fume events that give rise to symptoms. Professor Boobis would consider further how to convey COT concerns the DfT Minister.

8. Para 10: The membership of the proposed COT/Committee on Carcinogenicity (COC) subgroup to document how epidemiological evidence was assessed would be holding its first meeting on 3rd July.

9. Para 12: The COT statement on polybrominated diphenyl ethers (PBDEs) in the infant diet had been published on 27th March.

10. Para 20: The COT statement on hexabromocyclododecanes (HBCDDs) in the infant diet had been published on 7th April.

Item 4: Submissions for the reformulation of nonivamide (PAVA) and 2-Chlorobenzylidene Malononitrile (CS) as irritant sprays (TOX/2015/15)

11. No interests were declared.

12. Mr Graham Smith from the Centre for Applied Science and Technology (CAST) at the Home Office, and Inspector Nick Sutcliffe, police advisor to CAST, were in attendance to advise the Committee.

13. This item was reserved business as it contained commercially-sensitive information.

Item 5: Second draft statement on potassium-based replacements for sodium chloride and sodium-based additives

17. The draft statement had been revised and cleared by Chair's action. Since the statement was to support work on salt replacers by the SACN, the statement had been shared with the SACN prior to publication. The SACN had raised some questions with the statement and its implications. As these would need to be resolved prior to publication, the Secretariat would discuss the way forward, and inform the Committee of their decision at the next meeting.

Item 6: Third draft statement on the effects of soya consumption on thyroid status

18. The draft statement had been revised and cleared by Chair's action, and would be published after clarifying the status of the unpublished data.

19. No other matters were raised.

Item 4: Further submission for the reformulation of 2-chlorobenzylidene malononitrile (CS) as an irritant spray – TOX/2015/16 – RESERVED BUSINESS

20. No conflicts of interest were declared.

21. Mr Graham Smith (CAST) and Inspector Nick Sutcliffe (police advisor for CAST) were in attendance for this item.

22. This item was reserved business as it contained commercially-sensitive information.

Item 5: Assessment of the safety of the propellant HFC-134a – TOX/2015/17 – RESERVED BUSINESS

28. No interests were declared.

29. Mr Graham Smith (CAST) and Inspector Nick Sutcliffe (police advisor for CAST) were in attendance for this item.

30. This item was reserved business as it contained commercially-sensitive information.

Item 6: Review of risks arising from the infant diet and the development of atopic and autoimmune disease: Systematic review A – exclusive/predominant breastfeeding, solid food introduction and risk of developing atopic and autoimmune disease – TOX/2015/18 – RESERVED BUSINESS

38. The Chair declared a non-personal, non-specific interest in this item as he was employed at the same institution as the contractors who had performed the review. This was not considered a conflict and Members were content for him to chair this item.

39. Professor Ian Kimber and Dr Paul Turner were present to provide the Committee with additional expertise on allergic and atopic disease. The contractor who prepared the review, Dr Robert Boyle from Imperial Consultants, was also present. Prior to the meeting, Dr Turner had provided details of his potential conflicts of interest; he gave a brief outline of these interests at the meeting.

40. Dr Turner's declarations of interest included that he worked within the same group as the contractors at Imperial, but had had no involvement in the work on the review, and that he had an academic "sponsor" who had conducted work that had been funded by infant formula manufacturers, but had made no contributions to this work. In addition to this, Dr Turner had academic links with researchers at the University of Utrecht who were part-funded by Nutricia Research, but had not received any funding, gifts or products as a result of this collaboration, and he had declared that Nutricia Research were the industry partner for the fellowship held by a post-doctorate student that he supervised, but that he had had no contact with Nutricia through this work.

41. Finally, Dr Turner had declared that he was a co-investigator on a possible National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) submission on formula in cow's milk allergy. The study would be a multi-centre study and the researchers would possibly accept a supply of formula from milk companies. Dr Turner would not be the co-investigator on the study, which would be conducted as per NIHR guidelines (i.e. the milk companies would have no influence on the study), and would be overseen by an Independent Data/Monitoring Committee to ensure its independence. The Committee considered that Dr Turner's interests should not exclude him from advising them on clinical aspects of allergic and atopic disease.

42. This item was reserved business pending publication of the research.

Item 7: Histamine in cheese – TOX/2015/19

54. No interests were declared.

55. The Chairman welcomed Mr Terry Jones, the Chair of the Specialist Cheesemakers' Association's (SCA) technical committee, who was in attendance to observe the item and to answer any questions that Members had on a joint submission that had been tabled by the SCA and Provision Trade Federation (PTF).

56. Members had been introduced to the topic of histamine in cheese during the horizon scanning paper (TOX/2015/01) at the meeting in February. At this meeting, Members had been informed that histamine poisoning was a well-established phenomenon that often arose from the consumption of spoiled fish, but that it could also result from the consumption of foods such as cheese where histamine was present as a consequence of fermentation. Members had also been informed that, in the absence of specific legislation, the FSA took a pragmatic approach when responding to incidents involving histamine in cheese. This approach took into account the current regulatory limits for histamine in other foods (e.g. fish), an acute reference dose (ARfD) for histamine taken from the European Food Safety Authority

(EFSA) scientific opinion on biogenic amines in fermented foods, which include histamine, tyramine, cadeverine and putrescine (EFSA (2011) *EFSA Journal* 9(10) pp.2393), the results of the available volunteer studies, and multiple exposure scenarios that considered the variability in the consumption of different types of cheese.

57. Following their brief discussion on histamine in cheese at the February meeting, Members had agreed to comment on the approach taken by the FSA to incidents involving histamine in cheese, and on the EFSA scientific opinion on biogenic amines in fermented foods. In order to be able to do so, Members had requested that data on the occurrence of histamine poisoning, information about potentially sensitive individuals, and information on the relationship between histamine concentration and salt content, be provided in a discussion paper. Paper TOX/2015/19 included this information along with information on the metabolism and toxicology of histamine, the key points from the EFSA scientific opinion, and a more detailed description of the current FSA approach.

58. In addition to TOX/2015/19, a brief joint submission was tabled by the SCA and PTF following a meeting held with members of the FSA secretariat on 24th June. COT Members were given a verbal update on this meeting by the secretariat. Overall, the FSA had found the meeting useful as it had provided an opportunity to outline TOX/2015/19, to explain the FSA's approach to incidents involving histamine, and to clarify that the FSA had raised the issue of histamine in cheese with the COT in order to seek guidance about their approach to incidents, not with a view to establishing regulatory limits.

59. The submission from the SCA/PTF outlined their histamine Working Group's (WG) technical comments on TOX/2015/19, provided a basic description of the results of a questionnaire about histamine testing that had been put to their members following an initial meeting with the FSA in September 2014, and highlighted some of their main concerns as trade associations. An important point that was detailed in the submission, and that had also been discussed at the meeting with the FSA in June, was the WG's concern about the EFSA recommendation to ensure that starter cultures should be encouraged to "*outgrow autochthonous microbiota under conditions of production and storage*". The WG felt that it would not be possible to follow this recommendation as the autochthonous microbiota is largely responsible for the organoleptic characteristics of matured cheeses. The WG also explained that during the maturation of hard cheese, the population of starter lactic acid bacteria (SLAB) declined while the population of non-starter lactic acid bacteria (NSLAB) developed (i.e. the autochthonous microbiota outgrow the starter culture); this appeared to be true of cheeses made from pasteurised milk as well as those made from raw milk.

60. In their submission, the SCA/PTF WG had also explained that the reduction of salt levels in cheese can have a positive or negative effect on the formation of biogenic amines, depending on whether the histidine decarboxylase activity (which converts histidine to histamine) is associated with SLAB, NSLAB, or an unrelated species (whether adventitious or added as part of a ripening culture).

61. Overall, the WG had concluded that the SCA and PTF were keen to protect their customers as well as their members, and would be happy to work with the COT and the FSA to better understand the overall issue, but that, as trade associations, they would have difficulty accepting a criterion (such as a maximum level) for histamine in cheese as the available information was currently limited. The WG also noted that it would be important that attempts to reduce the levels of histamine in cheese did not compromise the microbiological safety of the cheese.

62. During their discussion of TOX/2015/19, COT Members noted that, while histamine does not appear to interact with tyramine, there is a need to recognise the role of putrescine and cadaverine as potentiators of histamine toxicity, although there was currently insufficient information to determine the concentrations at which this potentiation could occur.

63. Members acknowledged that the effects of histamine poisoning can be quite severe and unpleasant but are short-lived. Members considered it notable that the data presented in Annex B, from incidents dealt with by the FSA involving histamine in cheese, showed that most of the individuals in whom symptoms of poisoning were reported were toddlers and young children. Members questioned whether this observation was evidence that young children are more sensitive to the effects of exogenous histamine, or whether the data had been subject to reporting bias (i.e. as multiple children were affected simultaneously, the likelihood of a diagnosis of histamine poisoning was increased). Members also questioned whether the incidents were related to the type of manufacturer involved (i.e. had the cheese been produced by a large or small manufacturer).

64. Based on the incident data provided in Annex B, Members queried whether risk management actions, such as labelling or the provision of catering guidance, might be appropriate to advise against the exposure of young children to mature cheeses where higher histamine levels were more likely, especially in a catering establishment such as a school canteen.

65. In response to the questions on which the views of the Committee were sought, Members commented that the ARfD (50 mg of histamine per meal per healthy adult) that had been established by the EFSA Panel, was sensible and conservative (i.e. adequately protective as it had been based on the responses of healthy and sensitive individuals). Members noted that, although the ARfD did not take into account the possible modulation of histamine sensitivity by other factors

such as medication, management of such risks may be better achieved through education of consumers or patients, as is done in the case of tyramine.

66. Members commented that the FSA's approach to assessing the risk from histamine in cheese was sensible and well-founded as it took into account the appropriate measures of exposure, including data from the National Diet and Nutrition Survey (NDNS), and adjusted the EFSA ARfD for toddlers and children by scaling for bodyweight. Members also considered that it was appropriate to build on the risk assessment already established for biogenic amines in fish, but concluded that it was still prudent for the FSA to adopt a case-by-case approach when considering histamine in cheese. Members noted that there was currently too much heterogeneity in the levels of histamine in cheese to establish an 'action' or guidance level that could inform the FSA's approach to risk assessments.

67. Following the Members' discussion, Mr Jones was invited to comment on behalf of the SCA/PTF. Mr Jones commented that the SCA and PTF were committed to working with the FSA and COT on the issue of histamine in cheese. He confirmed that, as with fish, the level of histamine in cheese is variable, and may differ within and between batches.

68. Mr Jones explained that following the questionnaire that the SCA and PTF had put to their members, it had become apparent that larger cheesemakers perform regular, widespread testing for histamine and might work to rejection limits set by retailers, while smaller cheesemakers test less often, if at all, due to the expense involved. He also explained that larger cheesemakers saw consistency in process control and other aspects of the make as one of the main ways in which they could substantially reduce the chances of histamine formation. In smaller scale cheesemaking, for a number of reasons, that degree of consistency might not be possible for all cheesemakers to achieve. Mr Jones informed the Committee that some larger cheesemakers were currently researching the conditions that favour histamine formation, and that the results of this research could perhaps be shared with the Committee once it had been received by the SCA/PTF and anonymised.

69. COT Members would be interested to see the results of any such research performed by the larger cheesemakers, as well as further information from the questionnaire put to SCA/PTF members and on the practices of the SCA/PTF's members, if it became available. If necessary, the Secretariat would write to the SCA/PTF to request further information, explaining that details of the rejection limits being used by manufacturers or retailers, the fate of cheese with histamine levels above the rejection limits, and the range of results from histamine testing including any outliers, would be of particular interest to them. Once this information was received, it would be reported to the Committee for further consideration.

Item 8: Follow up on the toxicokinetics (TK) workshop – TOX/2015/20

70. No conflicts of interest were declared.

71. In October 2014 the COT had agreed that a symposium would be held on the 18th March 2015 to discuss the effects of obesity on toxicokinetics. The aim had been to provide a basis for interpreting FSA-funded research on biomonitoring of persistent organic pollutants (POPs) in obese subjects, and to consider more generic implications for the risk assessment process. Members had been provided with a list of possible topics for presentations and speakers, and had been asked for their opinions on the proposals. They had agreed that such a symposium was timely. Paper TOX/2015/20 contained information on the symposium programme and summaries of the discussions.

72. Members noted that the issue of mobilisation of POPs during lactation and the potential impact of obesity on the amounts of these chemicals in breastmilk had not specifically been discussed.

73. It was decided that, at the current time, there were not sufficient data for a COT statement and that paragraph 8 from paper TOX/2015/20 provided a sufficient summary:

"The aim of the first discussion was to consider the tissue distribution data of persistent organic pollutants (POPs) measured in obese and non-obese patients in a FSA research project. The FSA was seeking discussion on available options and determine the optimum modelling solution for analysis of this data set. Some of the key points from these discussions were:

- *Different modelling options, such as PBPK [physiologically based pharmacokinetics] or simpler models, available for data analyses. Discussion was also had around the modelling that may be used for the analysis of the different subsets of data in this study.*
- *There are currently follow-up data from five individuals which have shown substantial heterogeneity in the results and there was discussion around how representative these results would be. Samples from four additional individuals were awaiting analysis.*
- *The need to consider other POPs/chemicals because dioxins are a historical problem whereas levels of other POPs, for example, BFRs [brominated flame retardants] have increased in recent years.*
- *Added value of comparing data in this study to other data concerning POPs, obese individuals and POP levels in tissues. There are also reviews on the influence of bariatric surgery on certain pharmaceuticals which may provide useful information for POPs.*

- *Discussion around whether anything could have been done differently and whether further studies should be considered.*
- *Current models do not predict the initial results. Possible factors that could explain this were discussed including CYP1A2 binding. There are a number of physiologic changes that take place subsequent to bariatric surgery and/or weight loss which could impact the kinetics of dioxins/POPs. Certain medications (lipid lowering drugs and statins) could play a role in disturbing the kinetics of these chemicals. It was highlighted that the data was likely to be congener specific."*

74. The Committee would reconsider the need for a statement once the data analysis from the project had been completed. They were informed that the project team would be presenting the data at the meeting in October.

75. Insufficient data had been presented at the symposium to consider building toxicokinetic (TK) models. It was considered that compared to pharmaceutical drugs, for environmental chemicals there was usually a lack of good TK data which can be used in modelling. The US had made a heavy investment into the replacement, reduction and refinement of animals in research (the 3Rs) and had started to take a bottom-up *in vitro* and *in silico* approach, in which toxicokinetic extrapolation plays a key role. It was noted that the COT should keep a watching brief on this topic.

Item 9: Paper for information: Update on hypoallergenic formula WG – TOX/2015/21

76. This paper was provided for information only.

Item 10: Paper for information: Aggregate and cumulative risk of pesticides: an on-line integrated strategy (Acropolis) – TOX/2015/22

77. This paper was provided for information only.

Item 11: Paper for information: FSA Scientific Advisory Committees (SACs) update – TOX/2015/23

78. This paper was provided for information only.

Item 12: Any other business

79. The EFSA Scientific Committee had published draft guidance on how to characterise, document and explain all types of uncertainty arising in its scientific

assessments (‘Draft Guidance document on Uncertainty in Scientific Assessment’). The document provided a framework and principles for uncertainty analysis, with the flexibility for assessors to select different methods to suit the needs of each assessment. This document had been launched for public consultation on 18th June 2015 with a deadline for comments of 10th September 2015. The Secretariat would forward the document to Members for comment before the next COT meeting, inviting comments on the draft guidance and for Members to consider possible implications for the work of the Committee. The Secretariat would then compile the responses for discussion and final agreement at the 8th September meeting before submitting a COT response to EFSA. It was noted that Members also had the option to respond to the EFSA directly.

80. The issue of a secure web-based area for Members to access documents electronically was discussed. Members asked for three options to be available: receiving all documents electronically, receiving hard copies of cover papers by post, with annexes available electronically or receiving hard copies of all papers by post.

81. No other business was raised.

Item 13: Date of next meeting

82. Date of next meeting – Tuesday 8th September 2015, Conference Rooms 4&5, Aviation House, 125 Kingsway, London, WC2B 6NH