

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

Minutes of the meeting held on Tuesday 17<sup>th</sup> October 2006 in Conference Rooms 4 and 5, 4<sup>th</sup> Floor, Aviation House, London

### Present

Chairman                      Professor I Hughes

Members:                      Dr D Bell  
                                         Professor A Boobis  
                                         Dr R Dearman  
                                         Dr Foster  
                                         Dr J Hinson  
                                         Dr P Jackson  
                                         Professor J Lunec  
                                         Professor D Ray  
                                         Professor I Rowland  
                                         Dr L Rushton  
                                         Dr L Stanley  
                                         Ms A Ward  
                                         Ms A Williams  
                                         Dr C de Vries

FSA Secretariat:              Dr D Benford                      (Scientific Secretary)  
                                         Mrs J Shroff                      (Administrative Secretary)

Dr D Gott  
 Ms C Mulholland  
 Dr C Tahourdin  
 Dr S Creton  
 Ms F Cleaver  
 Ms R Harrison  
 Dr D Mason  
 Dr N Rajapakse  
 Dr N Thatcher  
 Mr A Furmage  
 Ms B Gadeberg

HPA Secretariat              Mr Battershill                      Health Protection Agency (HPA)

Other officials  
 in attendance:              Dr Joelle Buck                      FSA Food Allergy Branch  
                                         Graham Smith                      Home Office (Item 5)  
                                         Sarah Croft                      Home Office (Item 5)  
                                         Insp. Rob Blackburn              Assn of Chief Police Officers (Item 5)  
                                         Dr K Hargin                      FSA Primary Production Division (Item 9)  
                                         Sekai Ngarize                      DEFRA (Item 8)

Invitees:

David Barney  
Prof. Clive Thompson  
Eran Bauer

Geest Ltd (Item 4)  
Alcontrol Laboratories (Item 4)  
Civil Defence Supply (Item 5)

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## **Announcements**

1. The Chairman, Professor Hughes, welcomed Members and other attendees to the meeting.

### **Item 1: Apologies for absence**

2. Apologies were received from Professor Strobel and Dr Carthew.

### **Item 2: Draft Minutes of the meeting held on 17<sup>th</sup> October 2006 – TOX/MIN/2006/05**

3. The minutes of the 5<sup>th</sup> September 2006 meeting were agreed subject to the following amendments (in italics):

- Para 16, lines 3-5: "*The current TEFs are based on administered dose and there is a need for development of TEF values based on body burden.*"
- Para 21, line 2: "do not *necessarily* have"
- Para 33, line 5: "met" to replace "meet"

### **Item 3: Matters arising**

4. No matters were raised.

### **Item 4: Discussion paper on the results from a commercial study investigating the occurrence of disinfectants and disinfection by-products in prepared salads (CLOSED SESSION) - TOX/2006/31**

5. Wash aids, such as those employed by salad manufacturers, were identified as a potential future topic in the horizon scanning paper of February 2005 (TOX/2005/02). Wash aids were included as a horizon scanning issue due to the concern about the potential generation of by-products on or in foods as a result of the use of chlorine-based disinfectants. The Food Standards Agency had recently received the results of a study conducted on behalf of the Fresh Prepared Salads Producer Group, investigating the occurrence of disinfectants and disinfection by-products in prepared salads. A discussion paper was presented providing information on the nature and levels of disinfection by-products analysed in a range of bagged salads. Representatives of the Producer Group and the testing laboratory were present to provide additional information to the Committee. The data were commercial in-confidence and therefore the item was discussed in closed session.

6. Members noted that there was no information on the disinfection process used for the bagged salads and whether the results represented a worst case scenario. Mr Barney informed Members that because a range of bagged salads from a variety of manufacturers and retail outlets were tested, these were expected to represent the range of practices used in the UK. Typical wash practices in the UK involve a 1-2 minute washing time with 15-20 ppm free chlorine, as measured at the end of the wash system.

7. In response to a question about the purpose of chlorine wash systems, Mr Barney stated that it keeps the wash water clean, allowing a larger amount of product to be washed, and also reduces the content of microorganisms responsible for spoilage. The method of analysis was clarified, it being a water extraction method, with various salad:water ratios tested to obtain maximal recovery.

8. In all samples, calculated ingestions for each compound, based on salad consumption data, were at least several orders of magnitude lower than tolerable daily intakes set by the World Health Organization (WHO). It was agreed that the results were reassuring and that even if the tested samples were not completely representative, a worst case disinfection scenario would be likely to also result in intakes below the tolerable daily intakes. Mr Barney informed Members that although chlorine washes of up to 200 mg/L were cited in the discussion paper, such wash practices are not employed in the UK and were reported for use on a range of vegetables and fresh-cut produce. He anticipated that all UK salad manufacturers will have moved away from chlorination wash processes to alternative wash options by early 2007. Additionally, in the UK greater emphasis is placed on agricultural practice control.

9. Members agreed that the results of this study did not indicate cause for concern with respect to the use of chlorine washes. Given the current trend away from chlorination wash processes, there was no need for the generation of additional data to confirm the results from the limited study presented. However, Members agreed that alternative wash options need to be kept under review in the future.

**Item 5: Reformulation of PAVA (Nonivamide) as an incapacitant spray (CLOSED SESSION) - TOX/2006/33**

10. Professor Boobis expressed a non-personal specific interest as some clinical trials on PAVA had been undertaken at Hammersmith hospital but he had not been involved. The Chairman considered he could take part in the discussion conclusions. Discussion of the paper was held in closed session at the request of the Home Office Science Development Branch (HOSDB), as there is a need to formulate policy in this area. The relevant section of the minutes, and a statement will be published after the COT has concluded its advice.

11. Inspector Rob Blackburn from the Association of Police Officers attended the discussion and Eran Bauer of the Civil Defence Supply was invited into part of the discussion to provide additional information to the Committee.

**Item 6: Developing an appraisal system for Committee members (CLOSED SESSION) - TOX/2006/35**

12. The purpose of proposing an appraisal system is to enable an objective and evidence based review of the performance of each Committee member. This is increasingly required to demonstrate that Committees are robust. It would also support recommendations for reappointment to the Committee and enable the Chair to provide

feedback, if necessary, to members on their performance. The Secretariat provided an example of an appraisal form currently used by the Scientific Advisory Committee on Nutrition (SACN) and invited members to comment on whether it would they would find it suitable for use by the COT.

13. The Committee agreed an appraisal system was likely to become a requirement and wished to comment on the format. The Chair would also need to be included in the appraisal system. Members wished to see clear objectives for appraisal, some benefit to themselves, and the opportunity to see what was written about them. It could not be comparable to employment appraisal systems, and the term “self-assessment” might be more appropriate. The Chair did not envisage holding meetings to discuss the forms, although some dialogue might be necessary to reach agreement.

14. One of the concerns of the Committee was that information on an individual’s contributions may be used in a judicial enquiry, which would be contrary to the principle that the committee reaches a collective decision. The Secretariat stressed that the performance reviews would be confidential but that the existence of a process for performance review could contribute to demonstrating that the Committee complies with best practice and guidance for scientific advisory committees.

15. The Committee agreed in principle to a self-assessment system subject to clarification of the objectives and assessment criteria. The Chair offered to discuss the potential benefits to Members with the SACN Chair.

**Item 7: Recruitment of new Committee members (CLOSED SESSION) - TOX/2006/36**

16. At the end of March 2007, four committee members would have served the maximum of three full terms. As a result the secretariat will seek to fill vacancies that will arise from 1 April 2007. Members were asked to comment on the balance of expertise required in the Committee and to make suggestions for suitable candidates.

17. The Committee agreed the list of essential expertise provided in the paper and suggested that cell biology, bioinformatics, probabilistic modelling and statistical aspects of experimental design should be added. It would not be necessary to have an individual member for each listed expertise as some people would have a combination of the required skills. It was noted that two opinions on toxicopathology would be helpful and respiratory toxicology could be important. The Committee agreed that additional key experts could also be invited to attend meetings for specific topics to supplement missing knowledge.

**Item 8: First draft COT working paper on the revision of WHO toxic equivalency factors for Dioxins and Dioxin-like compounds - TOX/2006/32**

18. Dr Bell declared an indirect non-personal interest, in that his employer had previously been paid for him to make a presentation to Dow Chemicals.

19. Members were presented with the first draft working paper based on the discussion paper (TOX/2006/27), which the Committee discussed at the September 2006 meeting. Attention was drawn to the sections which differed from the information provided in paper TOX/2006/27. As requested, these included: a Non Technical Summary; more background on why the WHO/IPCS re-evaluation was performed; details of the Relative Effect Potency (REP) database used in the re-evaluation; the context of toddlers' exceedance of the TDI; and the Committee discussion and conclusions.

20. Members were satisfied with the overall structure and content of the draft. They found the Non Technical Summary and more detailed explanations in the introduction useful. Several specific points were highlighted which need clarification in the final statement, including helping to put the toddlers' intake data into context.

21. It was agreed that the final statement could be approved by Chairman's action.

**Item 9: Risk assessment of marine biotoxins of the okadaic acid, azaspiracid, pectenotoxin and yessotoxin groups in support of public health – TOX/2006/34 & TOX/2005/35 Annex 2**

22. In December 2005, the Committee considered paper TOX/2005/35 on the risk assessment and monitoring of marine biotoxins in support of public health. Members were presented with information relating to several classes of biotoxins, but discussion at that meeting and at subsequent meetings focussed on the toxins responsible for paralytic shellfish poisoning (PSP). A COT statement on PSP was published in September 2006.

23. At the present meeting Members considered biotoxins of the okadaic acid (OA), azaspiracid (AZA), pectenotoxin (PTX) and yessotoxin (YTX) groups, with a view to advising on appropriate acute reference doses (ARfD), i.e. the amount that can be ingested in a period of 24 hours or less without appreciable health risk.

24. The OA group of toxins are known to cause diarrhetic shellfish poisoning (DSP). On the basis of available epidemiology data relating to DSP outbreaks, three recent risk assessments of marine biotoxins performed by international bodies had identified a lowest observed adverse effect level (LOAEL) for OA group toxins of 0.8-1 µg OA equivalents (eq)/kg bodyweight (bw). In each case, a safety factor of 3 was applied to derive an ARfD of 0.27-0.33 µg/kg bw.

25. These risk assessments had been conducted by a European Commission (EC) working group in 2001, a Joint FAO/IOC/WHO ad hoc Expert Consultation in 2004 and a working group of the Community Reference Laboratory on Marine Biotoxins (CRLMB) in 2005. Since these risk assessments had taken place, data had become available from a DSP outbreak that occurred in the UK in June 2006.

26. Members considered that the totality of epidemiology data for OA toxins that was available prior to the recent UK outbreak indicated a LOAEL of around 1 µg/kg bw. It was noted that the limited information from the UK incident may suggest a lower LOAEL of 0.6 µg/kg bw, based on a 70 kg bw. However, the data from this incident

were difficult to interpret as the shellfish associated with the outbreak also contained biotoxins of the PTX group. It is uncertain whether the presence of the PTX toxins may have contributed to illness. In addition, two shellfish portion sizes had been sold at the restaurants involved in the incident, and it was not known which had been eaten by individuals who became ill. Had all individuals eaten the larger portion size, a LOAEL of 1.1 µg/kg bw would be indicated, in line with the earlier epidemiology data.

27. Overall, the Committee considered that 1 µg/kg bw should be viewed as the most appropriate LOAEL for deriving an ARfD for OA toxins. However, the 2006 DSP outbreak indicated a reported response rate of up to 10%, suggesting that more than the most susceptible minority were affected at this dose, and therefore that a safety factor of 3 would not be sufficient for extrapolation from a LOAEL to a NOAEL. It was agreed that a safety factor of 10 should be applied resulting in an ARfD of 0.1 µg OA eq/kg bw.

28. For AZAs, limited epidemiological information is available from an incident that occurred in Arranmore Island, Ireland in 1997. The most recent risk assessment of AZAs was published by the Food Safety Authority of Ireland (FSAI) in August 2006. FSAI had reassessed the information arising from the Arranmore incident in the light of recently published information relating to the tissue distribution of AZAs in mussels, ratios of different AZA analogues, and the influence of cooking on AZA levels in shellfish. On the basis of these new data an ARfD of 0.63 µg/kg bw had been proposed, a value higher than those suggested in previous risk assessments.

29. As the AZA content of mussels eaten by individuals who became ill was unknown, a probabilistic exposure assessment had been conducted by FSAI. This exposure assessment was based on measurements of AZAs present in mussels collected from the Arranmore area in the months following the incident.

30. Members were concerned that the absence of information on levels of AZAs in mussels associated with illness represented a significant source of uncertainty in the risk assessment. In addition, there were concerns over the appropriateness of the safety factor of 3 applied in the FSAI assessment. This was based on toxicodynamic variability with an assumption of no toxicokinetic variation due to a lack of clear evidence for metabolism of AZA resulting in a more toxic compound. The potential for variation in renal elimination of AZAs did not appear to have been considered.

31. However, the absence of reported AZA poisonings since the introduction of the regulatory limit in 2001, despite evidence of two major incidents of AZA contamination of shellfish between 2001 and 2005, provided some reassurance that the proposed ARfD was sufficiently protective. The proposed ARfD of 0.63 µg/kg bw is comparable to the maximum intake of 0.67 µg/kg bw for a 60 kg individual consuming 250 g of shellfish containing AZAs at the current regulatory limit (16 µg/100 g shellfish flesh). Before the adoption of the regulatory limit, there were five recorded incidents of AZA poisoning involving between 58-88 individuals following the identification of AZAs in 1995.

32. There is no evidence directly linking PTXs to adverse effects in humans. However, these toxins are known to co-occur with toxins of the OA group, leading to uncertainty as to whether the presence of PTXs may have contributed to effects seen in human cases of DSP.

33. The potential for PTXs to induce diarrhoea in experimental animals is also a matter of some debate. A study published in 1988 reported induction of diarrhoea in mice following oral administration, with a LOAEL of 250 µg/kg bw, while no diarrhetic effects were reported in later studies with PTX-2, PTX-2 seco acid and PTX-1. Most recently, data presented at a conference in September 2006 indicated that oral administration of PTX-2 induces intestinal fluid accumulation in mice and rats, with a NOAEL of 300 µg/kg bw in mice and a LOAEL of 300-400 µg/kg bw in rats.

34. The 2001 EC working group had applied a safety factor of 1000 to the LOAEL from the 1988 study to derive an ARfD of 0.25 µg/kg bw for PTXs. A safety factor of 1000 has been chosen to account for the use of a LOAEL as well as inter- and intra-species extrapolation. FAO/IOC/WHO had considered that the database was insufficient to establish an ARfD. The most recent information relating to induction of intestinal fluid accumulation in mice had been available to the CRLMB working group, which had applied a safety factor of 3 to the NOAEL of 300 µg/kg bw to derive an ARfD of 3 µg/kg bw.

35. The Committee considered that it was appropriate to take the lowest identified LOAEL of 250 µg/kg bw, and apply a safety factor of 1000 to derive an ARfD of 0.25 µg/kg bw. This followed the precautionary approach adopted in the EC risk assessment. Noting the incomplete nature of the database for PTXs, Members recommended that this ARfD should be reviewed when further data become available.

36. The only adverse effects reported in experimental animals following oral administration of YTXs are ultrastructural alterations in cardiac myocytes, detected by electron microscopy. A recent unpublished report involving oral administration of YTX seven times in 21 days indicates that these alterations are not observed 3 days following treatment with doses up to 5000 µg/kg bw.

37. Members questioned the relevance of the observed alterations in cardiac myocytes, and of the apparent recovery from injury following treatment. Cardiac tissue does not readily regenerate following injury, and alterations were not observed by light microscopy at doses up to 5000 µg/kg bw. It was considered possible that the electron microscopy findings may have been artefactual, but the available evidence was insufficient to draw firm conclusions.

38. Despite the uncertainty over the significance of the reported alterations in cardiac muscle cells, it was considered that it would be conservative to use these data to establish an ARfD for YTXs. A safety factor of 100 was applied to the NOAEL of 5000 µg/kg bw identified in the 21 day repeat-dose study, resulting in an ARfD of 50 µg/kg bw. FAO/IOC/WHO and the CRLMB working group had also taken this approach.

39. A working paper, describing the rationale for the proposed ARfDs, would be drafted for discussion at a future meeting.

**Item 10: Second draft working paper on the meeting report on the development and function in adulthood of the male reproductive system – potential chemical induced effects - TOX/2006/37**

40. Dr Dearman declared a personal non-specific interest, in that she has conducted research on the allergenicity of phthalates.

41. The Committee had discussed the first draft working paper (TOX/2006/29) at the September 2006 meeting and requested a small number of changes be made to the document before circulating to the speakers at the meeting for comment. Comments received from the speakers were generally positive. The second draft working paper (TOX/2006/37) attempted to reflect the speakers' comments, and highlighted that although data from some animal studies support the hypothesis proposing anti-androgens, such as phthalates, are implicated in testicular dysgenesis disorders in humans, this may be only one of several potential causes.

42. Members were satisfied with the changes made to the working paper and agreed that following minor editorial corrections the working paper could be finalised by Chairman's action prior to publication.

**Item 11: Any other business**

**11.1: Third draft working paper on cyanogenic glycosides in bitter apricot kernels - TOX/2006/38 (Tabled)**

43. The draft working paper on cyanogenic glycosides in apricot kernels had been circulated twice for comment by e-mail. Comments from individual members had developed the conclusions originally reached at the May 2006 COT meeting, notably introducing the concept of a nominal acute reference dose. The Secretariat therefore wished to ensure that the full Committee was content with the final draft discussion and conclusion section which had been tabled to ensure this properly reflected their views.

44. Several changes were suggested to emphasise the limitations of the available database, and the potentially lethal implications of consuming bitter apricot kernels. It was agreed that the working paper could be finalised by Chairman's action.

**Item 12: Date of next meeting**

45. Members were reminded that the next meeting of the Committee would take place on Tuesday, 5<sup>th</sup> December 2006 in Aviation House.