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

Minutes of the meeting held on Tuesday, 13th September 2011 in Aviation House, London.

Present

Chairman:	Professor D Coggon		
Members:	Mr D Bodey Professor A Boobis Dr R Brimblecombe Professor J Cade Dr R Dearman Dr M Graham Professor J Konje Professor B Lake Professor I Morris Dr N Plant Dr J Thompson		
Food Standards Agency (FSA) Secretariat:	Dr D Benford Ms T Gray Miss R Acheampong Dr C Baskaran Mr T Chandler Mr J Elliot Dr D Gott Ms F Hill Mr B Maycock Ms C Mulholland Dr D Parker Dr J Shavila	Scientific Secretary Administrative Secretary	
Health Protection Agency (HPA) Secretariat:	Mr J Battershill	Scientific Secretary	
Assessor:	Dr C Pease	Environment Agency	Item 7
External Observers:	None		

Contents

Item		Paragraph
1.	Apologies for absence	5
2.	Draft minutes of the meeting held on Tuesday, 28th June 2011 – TOX/MIN/2011/03	6
3.	Matters arising	7
4.	Use of toxicogenomics data in risk assessment – TOX/2011/22	12
5.	Draft statement on a systematic review of the epidemiological literature on para-occupational exposure to pesticides and health outcomes other than cancer – TOX/2011/23	24
6.	Draft statement on the FSA-funded T05 research programme on phytoestrogens – TOX/2011/24	27
7.	WRAP risk assessment on anaerobic digestates – TOX/2011/25	30
8.	FSA Scientific Advisory Committees (SACs) Update – TOX/2011/26	44
9.	Update on regulatory and biomonitoring activities with regard to phthalate esters - TOX/2011/27	45
10.	Any other business	46
11.	Date of next meeting – 1st November 2011, Conference Rooms 4 & 5, Aviation House, 125 Kingsway, London WC2 6NH	47

Announcements

1. The Chairman, Professor Coggon, welcomed Members to the meeting.

2. The Chairman informed the Committee of plans for recruiting new members. Due to current Government restrictions on advertising, the aim would be to advertise the posts on learned society websites, the COT website and via contacts. Expertise would be sought particularly in:

- environmental exposure assessment
- chemical risk assessment
- statistics, particularly related to experimental design
- mathematical modelling and/or probabilistic modelling

The Chairman requested Members' help in this process, including suggestions about websites for advertising and names of possible candidates who might be notified about the call for applications.

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.

4. The Chairman welcomed Dr Pease of the Environment Agency who was present as an Assessor and also for Item 7. He also welcomed Ms Frances Hill (FSA Secretariat) who was back from maternity leave.

Item 1: Apologies for absence

5. Apologies for absence were received from Professors Houston, Harrison and Smith, and Drs Foster and Hansell. Written comments had been received from two members.

Item 2: Draft minutes of the meeting held on Tuesday, 28th June 2011 – TOX/MIN/2011/03

6. The minutes of the 28th June 2011 meeting were agreed subject to the following amendments (in italics):

- Members Present (page 1) ~~*Professor*~~ *Dr J* Thompson
- Para 41, last line: "conclusions *that* could be drawn"

Item 3: Matters arising

7. Item 4: Report of the 2011 Quinquennial Review of the COT

- The Committee's response to the quinquennial review had been agreed by chairman's action and would be published on the COT website.

- Para 16: Members agreed a format for a table listing ongoing and future topics to be published on the COT website. The EFSA approaches to horizon scanning would be considered as part of the COT horizon scanning discussion in February 2012.

- Para 25: Regarding the need for additional expertise in epidemiology, the HPA Secretariat clarified that when the need arose, they would seek advice from independent experts external to the HPA.

8. Item 5: The Chair thanked the members who had provided comments on the conclusions drawn from the FSA-funded research on mixtures of pesticides and similar substances – TOX/2011/17. These would be incorporated into a draft COT statement to be considered at a future meeting.

9. Item 7: Para 57: The COT work on vitamin D would be delayed until after the SACN work had commenced.

10. Item 8: Para 66: The peer-review comments on the report on 'Assessment of the COT uncertainty framework from a social science perspective' were yet to be forwarded to Members.

11. Item 10: Para 70
It had not yet been possible to provide the proposed secure website for COT papers, but it was hoped that this would be in place for the 1st November meeting.

Item 4: Use of toxicogenomics data in risk assessment – TOX/2011/22

12. Paper TOX/2011/22 contained a document published in 2009 by the United States Environmental Protection Agency (EPA) entitled "An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study"[1]. This was intended as a case study to initiate the Committee's consideration of the use of toxicogenomic (TGX) data in human health risk assessment.

[1] http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=213405

13. The EPA report was viewed as a useful reference document. Members observed that dibutyl phthalate (DBP) possessed an exceptionally large number of TGX datasets in comparison with most substances that might be evaluated. Even so, it was difficult to draw conclusions of relevance to risk assessment. Members commented that there were limitations to what could be derived from historical TGX studies that had been designed for purposes other than risk assessment. Ideally, experiments would be designed to address specific questions in risk assessment, using a range of doses to support dose-response modelling. It was noted that the report's authors had been appropriately cautious in their conclusions.

14. The EPA document had largely been based on a literature review conducted up until 2007, which meant it did not take into account more recent developments. The Committee noted that lately, there had been moves away from 'omics to pathway and whole cell/organism assessments, and a realisation that using single tools such as transcriptomics in isolation was not sufficient. It was notable that if conclusions for risk assessment could not be drawn from a TGX evidence base the size of that for DBP, it would be even more difficult to make use of historical studies for substances which had been less investigated. Special care would be needed in reaching conclusions on modes of action (MOA) from TGX results. In particular, where TGX changes matched an established MOA, it would be important not to ignore other changes that did not relate to what was already known, and which might point to other modes of action.

15. The EPA had set out ways in which TGX might be useful in risk assessment (informing on toxicodynamics, dose-response relationships, inter-species extrapolations, intra-species variability and low dose modelling where changes unrelated to the critical effect might be less pronounced).

16. Where a MOA was not known, TGX might be able to generate hypotheses about which pathways were relevant and should be a focus for follow-up testing. However, because chemicals frequently induce multiple toxicological and adaptive responses, it would not always be straightforward to distinguish which TGX changes indicated MoAs for critical effects. In particular, changes seen at high doses could be secondary effects.

17. Several practical challenges in the conduct of TGX studies (design, analysis and statistical approaches) were noted. Many different statistical approaches had been applied to address problems associated with multiple testing, and there was no consensus on the best method. In some studies, Bonferroni correction was applied, but this was simplistic since prior expectations were likely to differ from one finding to another. It was observed that some of the most striking TGX changes could stem from the way in which data were analysed, and that better standardisation of statistical methods was desirable.

18. When considering inter-species extrapolation, it was noted that apparent homology between species could be misleading because even minor differences in a single gene might alter function substantially. Pathway analysis could be helpful in 'averaging out' variation between different methodologies in a way analogous to a weight-of-evidence approach. Unless a single gene was known to be critical, the Committee considered that investigations should look at clusters of genes for

pathways. Members felt that in MOA analysis, TGX was most likely to be useful in qualitative assessment of whether a particular MOA could or could not occur in different species. In principle, TGX might be used to generate a hypothesis for a MOA, which could then be tested in functional systems. However, most currently available cell systems were of human or mouse origin, rather than from rats.

19. Given the problems in using published reports from TGX studies in risk assessment, the Committee suggested that it might be more informative to reanalyse the original data from such studies where they were available. Proposals could also be made for rules on data-generation to make datasets more useful when addressing future questions. It was noted that although DBP is an endocrine agonist, it also causes other gene changes in rodents. Knowledge of the internal dose at the target site was important, but not necessarily straightforward to generate. The internal dose could then be extrapolated to an external dose for use in risk assessment, for example using physiologically-based pharmacokinetic modelling. The Committee commented that the EPA report would have benefitted from a greater consideration of exposure assessment.

20. The Committee considered that the EPA's proposed framework for using TGX in risk assessment, was useful, but emphasised that it would best be applied to studies designed to answer specific questions. Projects such as ToxCast[2] were using functional assays with human cell lines to probe specific pathways, which could presage a move away from TGX. However parallel assessment of pathways with both functional assays and TGX would be desirable since TGX has the potential to integrate pathways. NexGen aims to integrate the outputs of projects such as Toxcast and Tox21 into risk assessment[3].

21. Within the EPA assessment of the TGX studies of DBP, reference was made to alterations in the expression of the hydroxysteriod hydrogenase (3β-HSD) gene at a lowest dose of 0.1 mg/kg b.w. per day,. The Committee had previously[4] noted that the Tolerable Daily Intake (TDI) for DBP established by the European Food Safety Authority (EFSA) was based on a Lowest Observed Adverse Effect Level (LOAEL) of 1.5 mg/kg bw per day. For risk assessment to be based on transcriptional changes the Committee considered that there should be clear understanding that the specific gene was critical to the MOA. In the case of DBP, a dose-response was not shown for 3β-HSD, and therefore this change should not be used as the basis for a TDI.

22. Members re-emphasised their view that the observation of a TGX effect (e.g. a gene expression change) did not necessarily imply that an adverse effect was occurring or would follow. A parallel was drawn with mild inhibition of acetyl cholinesterase, which did not indicate neurotoxicity.

23. The EPA document discussed training needs for risk assessors. Members felt that at this stage, the Committee's Secretariat did not need to undertake additional training specifically on TGX as the Committee was available to provide expertise when necessary. The view was expressed that TGX was still in evolution, and was far from providing a refined tool that could easily be interpreted. In future

[2] http://www.epa.gov/ncct/toxcast/
[3] http://www.epa.gov/risk/nexgen/docs/NexGen-Public-Conf-Summary.pdf
[4] http://cot.food.gov.uk/pdfs/tox201036.pdf

considerations of new approaches, the Committee would need to be aware of projects such as ToxCast and NexGen, but TGX should also remain a focus because of its rapid development. An outline of a future COT discussion paper on uses for TGX in risk assessment was presented orally and suggestions were made on its structure and regarding chemicals that might be used as examples. A Member agreed to advise the Secretariat on development of the paper.

Item 5: Draft statement on a systematic review of the epidemiological literature on para-occupational exposure to pesticides and health outcomes other than cancer – TOX/2011/23

24. The Committee had previously considered a background paper on this topic and subsequently a draft joint Statement with the Committee on Carcinogenicity (COC), both of which had covered cancer as well as non-cancer endpoints. The COC had subsequently decided to take a broad approach in their evaluation of evidence, covering studies of cancer in adults and children exposed to pesticides through application by professional operators in their homes, or schools, as well as in people with para-occupational exposures. Using this approach, they had published a COC Statement. A new draft COT Statement had now been prepared, which focused on non-cancer endpoints, and only on para-occupational exposures. It had been produced with input from a Member and the Chair. The Committee was asked to consider this new draft COT Statement.

25. The overall structure was considered first, and was agreed subject to some reordering of the text in a section entitled “Approach to review”.

26. The wording of the draft Statement was then considered in detail, and a number of changes agreed. In some cases the original papers from studies would be checked to clarify the way in which they were described. The wording of the conclusions was agreed subject to revision of the final conclusion. The agreed changes would be made, including the altered wording of the final conclusion, and a revised draft then circulated to Members by email for final agreement.

Item 6: Draft statement on the FSA-funded T05 research programme on phytoestrogens – TOX/2011/24

27. The T05 research programme had been commissioned in 1997, to improve understanding of phytoestrogens and their potential effects on human health. Over the years, a number of reviews of this programme had been carried out, including previous COT assessments. The current statement included an evaluation of the final tranche of projects, which had not been completed at the time of the most recent assessment by COT.

28. Members considered that the draft statement needed significant restructuring. This should include a more detailed introduction, a brief history of the T05 programme (including timings), a table summarising all of the projects included in the programme, details of the main findings, a summary of the previous COT reviews,

and an overview of the programme with an assessment of how well its objectives had been met. The statement should also explain why the programme was now being terminated.

29. A restructured draft statement would be considered by the Chair and then presented to the Committee at a future meeting.

Item 7: WRAP risk assessment on anaerobic digestates – TOX/2011/25

30. No interests were declared. As they were part of an unpublished draft report, Chapters 4 and 7 in Annex 1 were discussed as reserved business.

31. In December 2009 and February 2010 Members had discussed two risk assessments carried out under the Waste and Resources Action Programme (WRAP) initiative on "Confidence in Compost". Comments from the COT and also the Advisory Committee on the Microbiological Safety of Food (ACMSF) had been forwarded to WRAP in Autumn 2010, informing revision of these reports. The revised versions were expected to be available later this year.

32. WRAP had also undertaken work on anaerobic digestion, an alternative method of processing waste. The draft WRAP report on the use of anaerobic digestates in agriculture was out for consultation and the FSA had again agreed to consult ACMSF and COT on relevant sections of the report to provide the independent scrutiny that a number of stakeholders had requested. Relevant sections of the WRAP report had been provided to the Committee in TOX/2011/25 along with a copy of PAS 110; the equivalent of the PAS 100 specification used for composts. The risk assessments assumed that PAS 110-compliant feedstock was being used and were intended to reflect normal conditions of use. Members were invited to comment on the risks associated with application of PAS 110-compliant composts to land used for food production.

33. It was noted that the legislative position regarding the use of waste digestates on land was complex as the specific regulatory status of waste depended on various factors and, for example, could be changed by waste treatment processing. The feedstock was from commercial sources and would not contain silage. The digestate that had been used for analysis of chemical contaminants as part of the risk assessment was not yet PAS 110-compliant, as control of feedstocks had not been demonstrated, but work was being carried out towards compliance.

34. Chemical contaminants had been measured in composite samples so that they were representative. The chemicals analysed included polychlorinated biphenyls (PCBs), dioxins, perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA). Very few were found above the limits of detection, and thus no further risk assessment had been included in the report. The Committee considered that the sampling had been reasonably representative in that it covered 30% of the plants in England and used triplicate samples taken on two separate occasions, with only one unusual finding. Furthermore, the analyses appeared to have been well conducted. It was agreed that analysis of further samples would be useful once the digestate

was PAS 110-compliant. The rationale for the choice of chemicals to be analysed was uncertain but it was possible that they were the ones considered to be of most concern by stakeholders. It seemed unlikely that some of the chemicals selected for for study would be present in food at significant levels.

35. The digestate output was likely to show some variability because of variation in the feedstock. Members agreed it would aid risk assessment to know more about what was being digested, and whether certain types of feedstock were associated with high levels of particular chemicals. It was noted that the input was food-based but also included livestock manure, and that the food component should already be compliant with regulatory limits for contaminants.

36. Members agreed that it would have been helpful to assess a greater range of pesticides and herbicides, particularly if garden waste was being included in the feedstock. It was noted that contaminating herbicides had been considered only in the context of possible damage to crops. Similarly plant alkaloids were assessed only in the context of possible harm to livestock. It would be important to know whether chemicals could be concentrated in the course of the digestion process.

37. The calculations in the report were not always clearly set out – for example the conversion of kg/hectare to concentration in dry matter. The use of toxic equivalency factors (TEFs) in the report was also questioned. These had been used for dioxin-like PCBs, but did not appear to have been used for the dioxins themselves.

38. It was unclear whether the digestate would be used on ready-to-eat crops. Consumers were advised to wash and peel vegetables but this was to address microbiological rather than chemical risks.

39. Exposure to allergens from the digestate was likely to be extremely low. The allergens present were expected to be high molecular weight proteins. Very little evidence was available on whether proteins could be taken up by plants, but based on their physic-chemical properties, it was unlikely that proteins would be taken up by passive processes. Exposure of operators to allergens through direct contact was more likely to pose a risk. It was noted that COMEAP (Committee on the Medical Effects of Air Pollutants) were planning to assess bio-aerosols formed from compost.

40. Members agreed that the approaches employed were appropriate and sufficiently rigorous to assess fully the chemical risks associated with application of PAS 110-compliant anaerobic digestates to food-producing land. However, the basis of the draft EU limits for chemicals used in the risk assessment from the draft Sewage Sludge working document (2000) and draft Biowaste Directive (EU 2001) should be checked.

41. Members agreed with the conclusion of the report that risks from allergens in the food chain would be negligible, and also with its conclusions on chemical risks, although only for the range of chemicals considered in the report.

42. Members noted that possible risks to the food chain considered in this programme of work focussed on environmental contaminants and should take greater account of pesticides and natural toxins.

43. Members agreed with the overall conclusion that any risks associated with the use of PAS 110-compliant anaerobic digestates in agriculture would be similar to those from other materials used for these purposes.

Item 8: FSA Scientific Advisory Committees (SACs) Update – TOX/2011/26

44. Members were provided with a paper outlining the headline topics that other Committees were discussing, and were advised that it would be possible to obtain details on any of the topics if required.

Item 9: Update on regulatory and biomonitoring activities with regard to phthalate esters - TOX/2011/27

45. This paper was largely for information. Further information would be circulated to the COT shortly.

Item 10: Any other business

46. The Secretariat and Members did not have any other business to raise.

Item 11: Date of next meeting

47. The next meeting would take place on Tuesday 1st November 2011 in Conference Rooms 4 & 5, Aviation House, 125 Kingsway, London WC2B 6NH.