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

Minutes of the meeting held on Tuesday 4th September 2007 in Aviation House, London

Present

Chairman	Professor I Hughes	
Members:	Dr D Bell	
	Dr A Boobis	
	Prof D Coggon	
	Dr J Hinson	
	Dr P Jackson	
	Dr G McNeill	
	Professor I Morris	
	Dr N Plant	
	Professor D Ray	
	Dr D Tuthill	
	Dr C de Vries	
	Ms A Williams	
	Ms A Ward	
FSA Secretariat:	Dr D Benford	(Scientific Secretary)
	Dr S Creton	
	Ms B Gadeberg	
	Dr D Gott	
	Ms R Harrison	
	Mrs F Hill	
	Dr D Mason	
	Mr B Maycock	
	Dr C Tahourdin	
HPA Secretariat	Mr J Battershill	Health Protection Agency (HPA)
Assessors:	Dr S Dyer	Department of Health (DH)
	Mr I McManus	Pesticides Safety Directorate (PSD)
	Mr P Ridgeway	Health & Safety Executive (HSE)
Other officials in attendance:	Dr N Renn	Veterinary Medicines Directorate (Item 4)
	Dr P Edwards	HPA
	Dr P Dicks	FSA Scotland
	Ms H Garavini	DH Toxicology Unit
External observers	Dr A Cook	NC3Rs (Item 6)

Contents

Announcements

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

Item 1: Apologies for absence

2. Apologies for absence were received from Dr R Dearman, Prof I Rowland, Prof D Harrison, Dr J Foster and Prof J Konje.

Item 2: Draft minutes of the meeting held on 3rd July 2007 – TOX/MIN/2007/04

3. The minutes of the 3rd July 2007 meeting were agreed subject to a number of minor editorial changes.

Item 3: Matters arising (reserved item)

4. Members were informed that the statement on 'food additives and children's behaviour' had been finalised by Chairman's action. The Committee were thanked for their email discussion and comments on drafts of the statement since the July meeting. The final version of the COT statement together with the FSA press release would be forwarded to Members immediately. On Thursday 6th September at 00:01 the COT statement, the Lancet publication and the FSA press release outlining revised advice to consumers would be published on-line. The study authors' technical report was expected to be available on-line within the next week. Members were advised that if they were approached for opinion/comment, it would be preferred for any enquiries to be referred to the FSA press office or the Secretariat in the first instance.

5. Members were also informed that the statement on cabin air environment had been finalised and would be published on the 20th September 2007. No other matters were raised.

Item 4: Organophosphates and human health research projects – TOX/2007/21

6. Professor Boobis declared a non-personal, specific interest with respect to funding for Research Project 10. Professor Ray declared non-personal, specific interests with respect to funding for Research Project 5i and Research Project 9.

7. In 1999 the COT published a report entitled "Organophosphates," which considered whether prolonged or repeated low level exposure to organophosphates, or acute exposures to organophosphates at levels insufficient to cause overt toxicity, can cause long-term adverse health effects (available online at http://www.food.gov.uk/science/ouradvisors/toxicity/cotreports/). The background to the COT consideration had been concern in relation to reports of possible long term neurological effects, primarily in farmers who had used organophosphate-containing sheep dip products. The Government had sought the advice of the COT, which had established a temporary working group to consider the issue in-depth. One current COT member (Professor Coggon) had been a member of the working group.

8. The COT report had drawn conclusions from the available data and made recommendations for further research to address outstanding issues. It recommended research in five different areas, expressed in the form of questions to be addressed. After consideration, Government was of the opinion that research projects to address two of the questions had already been commissioned prior to publication of the COT report. Subsequently, the remaining three research requirements were advertised in the Ministry of Agriculture, Fisheries and Food (MAFF) Research Requirements 2000-2001, entitled “The chronic effects of organophosphates on human health”. An additional requirement to investigate the effects of organophosphates on children and unborn children was also identified and advertised at the same time.

9. As a result, a total of six research projects were commissioned which addressed the COT recommendations, with a seventh on the effects on children and *in utero* exposure. The COT was asked to

- consider the research reports as they currently stood, and advise on the significance of the findings reported; and
- advise on the extent to which the COT research recommendations had been addressed.

10. In addition, ten other research projects had been commissioned by the Government with relevance to the effects of organophosphates. Reports on these projects were also provided, and the COT was asked to advise on how these projects contributed to understanding of possible effects of organophosphate exposure on health in humans. Results were not yet available for all projects and in these cases, the Committee was asked to advise on how the projects would be expected help to increase understanding of effects of organophosphates assuming that they achieved their objectives.

11. It was clarified that although a number of organophosphates had previously been used in sheep dips, diazinon was the only organophosphate still used, as the active ingredient in three products. Although products containing non-organophosphate active ingredients were used to treat certain ectoparasites, diazinon was the only currently authorised active able to treat all of the ectoparasites which affect sheep. Authorisations for cypermethrin-containing products had been suspended due to environmental concerns.

12. Members noted that there were uses of organophosphate insecticides other than in sheep dips, for example in agriculture and in the home. Members noted that other work had been published in the scientific literature and there would be a need to review all of the available research in order to advise on the current state of knowledge regarding organophosphates. However the Committee had been asked to review only the Government-funded projects at this time. The Committee considered each research project in turn. It was noted that several of the reports made comments about the relative contributions of different sources of exposure to organophosphates or pesticides, which did not seem to be substantiated.

<u>Research project 1</u>

13. This was a survey of symptoms and organophosphate exposure histories reported in farmers self-selected as suffering ill health which they attributed to organophosphate exposure. Members were informed that there was a further phase to the study, a clinical study of 70 individuals; however, publication of this phase of the study had been delayed.

14. It was noted that this study could not assess causality and was not designed to do so. Its purpose was to ensure that all possible relevant clinical effects would be identified so that they could be included in future epidemiological studies. In this respect it had served its purpose. A follow-up of respondents in the long term to gain information on the progression of symptoms would have been useful.

15. Previous work had shown that handling sheep dip concentrate was a major determinant of exposure. The difficulty of assessing exposure by recall was noted. For example, individuals could have exposures to sheep dip concentrate which they were not aware of. However, assessing exposure was not the main purpose of the study.

16. The level of long term exposure appeared to be as would be expected in farmers in general, although there was a very high number of reported acute exposure episodes. It would be useful to know if these incidents were associated with acute toxicity and, if so, how severe the toxicity was. It was observed that there had been little analysis of patterns of reported symptoms. It would also have been useful to compare the profile of reported symptoms in this cohort to those of individuals not exposed to organophosphates.

Research project 2

17. A limitation of this prospective cohort study of sheep dip exposure and "dipper's flu" was that it did not include ex-farmers, who might include a disproportionate number of susceptible individuals if there were variations in susceptibility from person to person. The recruitment rate was low; however, this was of less concern with respect to recruitment bias since this was a prospective study. It was noted that "dipper's flu" was not an established occupational hazard, but a phenomenon talked about by those involved in sheep-dipping. If a toxicologically mediated effect, it would be of interest since it could be an indicator of high exposure to organophosphates. However, the study did not provide evidence for a flu-like condition related to sheep-dipping or of acute organophosphate exposure being a cause of "dipper's flu". A Member advised that the results were consistent with other research which had not indicated any unusual clustering of flu-like symptoms following sheep dipping (Solomon *et al*. Occup. Med. 2007. doi:10.1093/occmed/kqm066).

18. An increase in endotoxin levels in sheep dip was observed after dipping, and it was noted that very high endotoxin exposures could cause respiratory effects. Organophosphate exposures in the sheep dippers appeared to be low; only three farmers showed a decrease in plasma cholinesterase activity following dipping, and this was unlikely to have been sufficient to result in ill health. This low exposure contrasted to the reports of high acute exposures in research project 1.

Research project 3

19. This was a cross-sectional survey of farmers identified from records of people who were farmers in the 1970s. The distribution of respondents was difficult to interpret. Response may have been driven by motivation, which could mean that individuals with depression were less likely to respond. Alternatively, Members heard that the communications to farmers explained the purposes of the study, and this could also have introduced a different response bias. In addition recall bias was possible in identifying previous symptoms and exposure. However, a lack of association between ill health and sheep farming in general was observed.

20. A member referred to research which had indicated that neurological symptoms were more common in people who had worked with sheep dips, but that the association was not specific for working with sheep dip or insecticides (Solomon *et al*. Occup. Environ. Med. 2007, **64**: 259-266).

21. The questionnaire to screen-identify ill health appeared to have been well validated. However, a limitation of screen-identified ill health was that people who somatise are more likely to report both current and previous ill health. This may be relevant to the association between reporting current ill health and having ever sought advice for pesticide poisoning.

22. It was noted that farming practices were likely to have changed significantly since the 1970s.

Research projects 4 and 10

23. Research Project 4 was a case-control study comparing the prevalence of PON1 polymorphisms and diazoxonase activities in dippers with self reported ill health to healthy dippers. A member discussed the history of the assay for metabolic activity of PON1 used in research project 4. The assay had been widely used to determine PON1 activities, although it had not been developed originally for this specific purpose but rather for phenotypic assignment. It had since been discovered (research project 10) that the non-physiological conditions of the assay gave misleading results for PON1activity with some substrates. Research project 10 had shown that the RR genotype actually conferred higher PON1 activity towards diazoxon, not lower. This had been confirmed independently in work by the researchers who had originally developed the assay. It had also been demonstrated *in vivo* in transgenic mice with human allelic variants of PON1.

24. The results of research project 4, taking into account the subsequent findings of research project 10, indicated that faster metabolisers of diazoxon were more likely to report chronic ill health. This was the reverse of the hypothesis being tested. A Member considered whether the multiple statistical testing could have given false associations by chance alone. However, as a prior hypothesis was being tested the concern was not as great as it would otherwise have been.

25. Members agreed that the results of research project 4 may have reflected genetic differences in susceptibility to ill health, but that if so, these were unlikely to be related to organophosphate toxicity.

Research project 5i

26. The antibody generation to two capture antigens shown in this study was interesting, although the health consequences of this were unknown. It was thought unlikely that there would be an immunological response which would have resulted in ill health, but this was a data gap. As the study had shown an association between the antibody responses and ill health it would be useful to consult an immunologist and possibly to research this further.

27. It was noted that the main protein in blood is albumen, and therefore the most likely antigen *in vivo* would be organophosphate-adducted plasma albumen. This had potential for development as a long-lasting biomarker for organophosphate exposure.

Research project 5ii

28. The objectives of this project had been to identify novel protein targets of organophosphates. Changes in concentrations of a number of proteins had been detected at exposure levels to oxons of organophosphates which produced less than 30% brain acetylcholinesterase inhibition. These proteins were expressed at extremely low levels compared to other proteins, which had caused difficulties in identifying them. A 30 kDa protein expressed in the brain and immune system remained unidentified, as did others. Members considered whether the latest tandem mass-spectrometry techniques would help in protein identification. This was possible; however, the main difficulty was in separating the target proteins, which are expressed at extremely low levels, from other proteins which are much more abundant.

Research project 6

29. This was a literature review of the effects of low level exposure to organophosphates on fetal and childhood health. Members discussed the authors' assumption that the diet was likely to be to be the greatest source of exposure to pesticides by young children, which contrasted to conclusions of evaluations by the US EPA that the main sources of exposure were non-dietary. It was noted that sources of exposure differed in the US from the UK because of differences in the use of pesticides in the home. It was also noted that regionalisation was important as studies in the US have shown differences in pesticide exposures in rural children compared to urban children. A member considered that it might be important to distinguish between the contributions from different exposure sources in children overall and in the subset of children with the highest exposure levels.

30. It was observed that published studies on developmental effects of pesticides had used dose levels much higher than would be expected from the diet.

Research project 7

31. This project investigated whether exposure of marmosets to diazinon caused electrophysiological changes. It was considered to be a valuable study, and the endpoints assessed were considered to be clinically relevant. Members agreed that medium to high acute exposures to diazinon had not produced long-term effects in marmosets in this study.

Research project 8

32. This was an analysis of reports of suspected adverse reactions to organophosphate sheep dips in the Veterinary Medicines Directorate's Suspected Adverse Reaction Surveillance Scheme (SARSS). It was not possible to assess causality from such data. All the data were on individuals reporting ill health, which was a necessary limitation of the database. The symptoms reported were observed to be common in the general population. It was considered that the results of this analysis should be considered in the context of research projects 1 and 3, and that the contractors should consider this further between themselves.

Research project 9

33. The relevance of the concentrations of diazinon used in this *in vitro* research investigating effects on differentiating neurones was questioned. The degree of acetylcholinesterase inhibition was modest despite the high concentration of diazinon used. Cytochromes P450, which would have been low in the cells tested, are required to metabolically activate diazinon to diazoxon, indicating possible non-specific effects of diazinon, unrelated to diazoxon. However, it would have been expected that some diazoxon would have been produced. Diazoxon, at concentrations which produced similar levels of acetylcholinesterase inhibition to diazinon, had a similar level of effect on neurite outgrowth. However, it was noted that commercial sources of diazoxon are unstable, so that the cells may have been exposed to compounds in addition to the oxon.

34. It was observed that when activated microsomes were added, the effect on neurite outgrowth was abolished, and the relevance of this was unclear. The combination of cypermethrin and diazinon had a lower than expected effect on neurite outgrowth, suggesting possible interference with cytochrome P450-mediated metabolism.

35. Cytoskeletal proteins are expressed at high levels. Therefore effects on these proteins are more likely to be seen than for other proteins. If neurite outgrowth is reduced, the levels of these proteins will be lower, but that did not necessarily indicate a causal relationship. It was considered that the effect should be investigated *in vivo*, though a Member recalled that diazinon had been studied *in vivo*, with no marked effects that would be consistent with the findings of this study.

36. It was unclear how the results of this study would extrapolate to the *in vivo* situation, where the developing neurite is better protected. Neurite outgrowth is important in the developing brain and might also be involved in learning and cognition. However, Members agreed that the health impact of any *in vivo* effect on neurite outgrowth was unknown. Members considered that any proposal for follow-on work needed a clear rationale to ensure the results could be interpreted in relation to possible health consequences.

Research projects 11 and 14

37. This pilot study and follow-on research to assess whether organophosphates are causing gastrointestinal effects in children were considered. It was pointed out

that urinary metabolites of organophosphates provided a measure of intake of both organophosphates and their metabolites, for example residues in treated sheep. Also, the levels of such metabolites would be affected both by the level of exposure and also how recently the exposure had occurred.

38. The purpose of the clinical study was to address concern that organophosphate toxicity might occasionally cause gastrointestinal symptoms in children which would not be recognised as they would be assumed to be due to infections. However, as planned this would be difficult to do, particularly taking into account that gastrointestinal symptoms presenting at clinics are more likely to be chronic effects than acute. Any exposure of children to organophosphates at levels sufficient to cause acute gastrointestinal symptoms was thought likely to be rare. Members advised that it was important that research project 14 involved relevant epidemiological and microbiological expertise. The study design and techniques should be considered very carefully and peer reviewed.

39. There is a very high prevalence of gastrointestinal symptoms in children, which are mostly caused by infections, with a wide range of causal organisms. It was pointed out that gastrointestinal symptoms could affect intake of foods and excretion, and that the potential diluting effect of increased faecal volume associated with diarrhoea needed to be considered. Urinary levels of metabolites can be normalised against urinary creatinine, but this is not possible for faeces. The measurement of acetylcholinesterase in faeces was interesting. However, acetylcholinesterase was very highly expressed in parasitic worms which might importantly confound results.

Research projects 12 and 15

40. The literature review of pesticide exposure and risk of Parkinson's disease had been commissioned at the recommendation of the Advisory Committee on Pesticides. There was a general consistency across studies associating past exposure to pesticides in general with Parkinson's disease, although these were mostly case-control studies. Few studies had investigated associations with individual pesticides or groups of pesticides, and these had produced inconsistent results. If the relationship were causal, studies of the specific pesticides or groups of pesticides that were responsible would be expected to show substantially higher odds ratios or relative risks than studies investigating exposure to pesticides in general. It was noted that further studies had been published since this literature review was completed.

41. It was not possible from the available epidemiological or mechanistic data to identify any specific pesticides that increase the risk of Parkinson's disease. Members discussed the plausibility of the bipyridyl herbicide paraquat being a risk factor. It was noted that paraquat was originally suspected due to its structural similarity to MPP+, a metabolite of the recreational drug contaminant MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine), which had been shown to cause acute Parkinsonism in experimental animals and humans. Paraquat had originally been thought to be unable to cross the blood-brain barrier, but there was now emerging evidence that active carrier mechanisms transport paraquat across the blood brain barrier and into cells.

42. Research project 15, on possible mechanisms of Parkinson's disease, involved combinations of the dithiocarbamate fungicide maneb and the bipyridyl herbicide paraquat. It did not involve any organophosphates. It was considered to have a good study design, which adequately addressed the toxicokinetics, toxicology and pathology, and should address the question on which it focused. A Member observed that there was evidence that brain exposure to paraquat following inhalation could be 2-3 times higher than would be predicted from levels in the systemic circulation, due to preferential access to the carotid blood flow to the brain. However, exposures would still be low.

Research project 13

43. This project investigated inter-individual differences in DNA damage produced by oxons of organophosphates and subsequent repair. The differences in DNA damage observed in lymphocytes from different individuals *in vitro* were considered marginal and very small compared to the inter-individual background variability. The level of DNA damage varied widely, which had been attributed to differences in DNA repair, but this was not convincing. It was inconclusive whether diazoxon had an effect on DNA repair. The data from the Spanish cohort occupationally exposed to organophosphates compared to a UK unexposed cohort showed a lower median level of DNA damage in the Spanish cohort, and a higher mean. Overall, it was not considered that this study provided evidence of genotoxicity of organophosphates. It was noted that this was a pilot study and the Committee questioned where it was intended that this research should lead. It was recommended that officials read the statement of the COM on biomonitoring studies of genotoxicity in pesticide applicators before considering funding any further research on this. It was not considered that there was a need to refer the project to the COM.

Research project 16

44. This project, collecting and analysing data from enquiries to the National Poisons and Information Service (NPIS), had been recommended by the Advisory Committee on Pesticides. It was noted to be one of a number of different sources of information through which information on acute poisoning incidents was gained. Taken together, the information from these sources was considered useful.

45. The Committee considered the research recommendations made by the COT in turn, and considered the extent to which they had been addressed:

What are the most common patterns of exposure, clinical presentation and subsequent clinical course among people in the United Kingdom with chronic illnesses that they attribute to organophosphates?

46. This had partially been addressed by research projects 1, 8 and 16. Information was still lacking on long-term outcomes in affected individuals.

How common is dipper's flu, and what causes it?

47. Some useful information had been provided by research project 2. Dipper's flu did not appear to be a specific syndrome. It was considered that this should not be a high priority for future work.

Does low-level exposure to organophosphates cause disabling neurological or psychiatric disease in a small subgroup of exposed persons?

48. There was evidence of long term neurological illness in persons who had used organophosphates. However, there were also associations with use of other pesticides. Whether these effects were due to toxicological mechanisms of pesticides or other mechanisms was uncertain. Other research which had been conducted in relation to this should also be considered, and research project 3 should be reconsidered when complete.

Do people with chronic disabling illness that is suspected of being related to organophosphates differ metabolically from the general population?

49. Research project 4 had addressed this recommendation. There was evidence of a metabolic difference but this did not correlate to enhanced toxicity of organophosphates. It was possible that this was a chance finding. It was noted that differences in susceptibility did not necessarily require a polymorphism in a metabolising enzyme; there could be a polymorphism in the biological target. Further research on the role of polymorphisms of organophosphate disposition was not considered a high priority.

Other than acetylcholinesterase inhibition, what mechanisms play an important role in the causation of adverse health effects by organophosphates?

50. Some interesting data had been generated - *in vitro* effects, detection of novel protein targets, developmental effects *in vivo* - but much more research would be required to fully address this question. It was considered important to better characterise exposure, since even if toxicological mechanisms other than acetylcholinesterase inhibition were identified, if these occurred at higher levels of exposure than people received, they would not be relevant to human health effects. It was noted that health beliefs and expectations and somatisation tended to predict the reporting of ill health attributed to organophosphate exposure, and the possibility that part of the illness may have a non-toxicological basis should not be ignored. It was disappointing that medically unexplained symptoms had not been investigated as part of the research.

51. The draft minutes would be circulated to members for urgent comment so that the COT advice could be reported to Ministers in October. When available, the results of ongoing research would be provided to COT for further comment.

Item 5: Updating the Code of Practice for Scientific Advisory Committees – TOX/2007/22

52. The Office of Science & Innovation (OSI) is in the process of updating the Code of Practice for Scientific Advisory Committees and is consulting on a draft proposal. The Committee was asked if it wished to respond to the consultation, and also to consider the implications of the changes for its working practices. Attention was drawn to the *universal ethical code for scientists* and minor changes to two of the *seven principles of public life*. The key proposed changes to the Code of Practice related to having access to a variety of experts; the balance between transparency

and the handling of sensitive information; and the need for regular “light touch” monitoring, evaluation and spread of good practice.

53. The Chair considered it opportune to review the adequacy of the informal induction available to new Committee members. Newer Members confirmed that the current ‘welcome pack’, together with the opportunity to learn from experienced Members was more appropriate than a formal induction process. One Member noted that improved guidance on definitions of types of interest would be helpful. The Secretariat had already noted this and would provide definitions of “specific” and “non-specific” in the near future.

54. Members questioned the proposed wording of paragraph 3, noting that whilst the advice from scientific advisory committees should be robust, the evidence basis is frequently not. It was suggested that the wording could be modified to reflect that the appropriate evidence had been identified and to require a rigorous process for assessing the robustness of evidence.

55. Members also questioned why some information might be withheld from a committee (paragraphs 45 and 71) and considered that examples of such situations might be helpful.

56. A question was raised with respect to whether attributing comments to individual Members would be more open. However it was generally agreed that COT opinions reflect consensus, rather than a collection of thoughts and opinions of individual members.

Item 6: Evident toxicity as an endpoint in acute toxicity testing – TOX/2007/23

57. The UK-led development of a fixed concentration procedure (FCP) guideline (TG 433) for testing chemicals for acute inhalation toxicity within the OECD Test Guideline programme had been severely hindered by reluctance of some OECD member states to accept evident toxicity as a reliable endpoint in acute inhalation toxicity studies. This difficulty was unexpected, given the acceptance of the principle of evident toxicity indicated by the adoption of an analogous guideline (TG 420) for testing acute oral toxicity.

58. A paper from the DH Toxicology Unit on regulatory requirements for acute toxicity data would be circulated for comment by correspondence and a further paper on the proposed definition of evident toxicity for acute inhalation studies on chemicals would be presented for discussion at the December meeting. Members were asked for their views and suggestions on the work planned to support the international acceptance of evident toxicity as an endpoint in acute inhalation studies.

59. Members supported the intention of the proposals to reduce and refine the use of animals in acute inhalation toxicity studies but requested further information on the international objections to the UK proposals as this would help inform the decision making process. Members were advised that a formal response to the UK position had not been received but it was understood that there was concern that “evident toxicity” was not defined. This was being addressed as part of the work plan.

60. Members considered that describing evident toxicity for inhalation exposure might be more complex than for oral exposure, for example if a substance caused local respiratory irritation. The endpoints incorporated in the TG420 would not provide an adequate basis for deriving an acute reference dose. Lethality, or a surrogate for lethality, might be more appropriate in certain circumstances, for instance when testing highly toxic gases for the purpose of emergency planning. However, this would not be appropriate for the vast majority of chemicals tested, for instance under REACH. Members were informed that the original acute inhalation toxicity Test Guideline, which allows estimation of an LC_{50}, was not expected to be deleted but rather to be extended to include examination of the effect of exposure time as well as concentration on toxicity.

61. It was considered that the refined methodology would not only help in the primary objective of refining and reducing animal use, but might also produce data of a more useful nature. As an example, more detailed information on acute effects of chemicals in animals could help clinicians dealing with acute toxicity in humans recognise symptoms and treat patients more effectively.

62. The HSE explained that a validation exercise for the refined acute inhalation toxicity test guideline was not proposed because a large number of animals would be required and the validation exercise carried out for the acute oral toxicity test guidelines was also considered relevant for the inhalation test guidelines. Members advised the need to confirm the transferability of endpoints from the oral to inhalation route, and suggested that some form of validation exercise, not requiring extensive additional animal testing, should be possible. For example, video could be used to check the consistency of interpretation by experts from different laboratories; concurrent use of traditional and refined methodology in the same animals would allow comparison of results.

63. Members were informed that a survey was being conducted to determine the industry perspective on selection of tests with lethality or evident toxicity as endpoints.

64. COT members were requested to send further suggestions and offers of support to the Secretariat.

Item 7: Any other business

65. Members were informed of next year's out of town meeting, which is to take place on the 6th February 2008. The topic of 'transgenerational effects of methylation' had been proposed, but it was agreed that the programme should be broadened to 'epigenetics and toxicology'. Members were invited to forward suggestions for specific lecture topics and speakers to the Secretariat.

Item 8: Date of next meeting

66. The next meeting of the Committee would take place on 23rd October 2007 in Aviation House, London.