CC/MIN/2017/01

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Minutes of the meeting held at 10.30am on Thursday 23rd March 2017 at Department of Health, Skipton House, 80 London Road, Elephant and Castle, London, SE1 6LH.

Present

Chair:	Professor D Harrison	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr J Doe	
	Dr P Greaves	
	Professor R Kemp	
	Dr D Lovell	
	Professor N Pearce	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	(Items 1-7, 10-11)
	Dr R Waring	
Secretariat:	Miss B Gadeberg	PHE Scientific Secretary
	Dr D Gott	FSA
	Ms C Mulholland	FSA (Items 1-5)
	Ms C Potter	FSA (Items 1-5)
	Dr K Vassaux	Imperial College London
Assessors:	Dr P Carmichael	Defra
	Dr O Sepai	PHE
Invited Experts:	Dr A Hansell	Chair of Joint COT-COC Synthesising epidemiological evidence subgroup (Item 5)

ITEM 1: Apologies for absence and announcements

1. Apologies were received from Professor Warnakulasuriya, Dr Benford (FSA Scientific Secretary) who was represented by Dr Gott, Dr Karin Burnett and Mr Ken Okona-Mensah from the Toxicology Unit at Imperial College. Assessors Dr Henry Stemplewski (MHRA), Dr Helen McGarry (HSE), Mr Ian Martin (EA) and Mr Niall O'Brien (VMD) also sent apologies. Dr Steve Morris (Defra) sent apologies and was represented by Dr Penny Carmichael.

2. The lead contact at the DH for the COC had changed to Dr Trudy Netherwood. In addition the assessors for Defra and VMD were now Dr Steve Morris and Mr Niall O'Brien respectively.

3. Members had previously been informed that Dr Diane Benford (FSA) had been involved in an accident while on holiday. The Committee was updated on her progress and wished her continuing improvement.

4. Members would soon be requested to complete their appraisals, and were also reminded to send back their annual declarations of interest for the Joint COT, COM and COC 2016 Annual Report, if they had not already done so.

5. Members were reminded to declare any interests they may have in an item before its discussion.

ITEM 2: Minutes of meeting held on 17th November 2016 (CC/MIN/2016/03)

6. No amendments were made to the minutes of the meeting in November.

ITEM 3: Matters arising

Item 5: Horizon Scanning (CC/2016/02)

7. A draft programme for the joint COT, COM and COC meeting on 9th October 2017 was tabled. This would include a discussion of the use of epigenetics in risk assessment and be followed by a joint horizon scanning session.

Item 6b: First draft statement of COC/G07: Alternatives to the 2-year Bioassay, Part D: Alternative testing strategies for carcinogens incorporating results from short-term tests (CC/2016/15)

8. Members were thanked for their written comments on the revised draft circulated following the discussion at the last meeting. These changes were being finalised and would be cleared by Chair's action.

Item 7: Reserved business minutes

9. The Committee discussed the timing of the release of the reserved business minutes from the November meeting. It was noted that the item related to unpublished research and it would normally be under embargo until publication of the research. It was agreed that the Committee's considerations should not be reserved in perpetuity, instead the timing would be revisited in autumn 2017.

ITEM 4: First draft statement on possible carcinogenic hazard to consumers from Insulin-like Growth Factor-I (IGF-I) in the diet (CC/2017/01)

10. No interests were declared for this item.

11. This paper presented a first draft statement on the cancer hazard of IGF-I, bringing together the Committees discussions of the topic over the last few years.

12. The Committee discussed the document and it was agreed that a lay summary and short technical preface should be prepared to provide the key messages, alongside the more detailed draft statement presented.

13. The key messages would focus on the small contribution of dietary IGF-I to circulating levels, the majority of the epidemiological studies using circulating IGF-I rather than dietary IGF-I, and that overall the COC does not consider there is a concern from IGF-I levels in the diet.

14. A revised draft would be brought back to the Committee for discussion at a future meeting.

ITEM 5: Synthesising Epidemiological Evidence subgroup – draft report (CC/2017/02)

15. No interests were declared for this item.

16. This paper presented the two draft reports of the COT-COC Synthesising Epidemiological Evidence subgroup (SEES). One document was intended to form the basis of a guidance document, while the other provides recommendations and methods of working.

17. Dr Anna Hansell, Chair of SEES, thanked the subgroup Members and the Secretariat for their work on the report. The reports had been deliberately kept to a readable length, and the main guidance from the subgroup was provided in section 6 of the report. Dr Hansell noted that there was a lot of work ongoing internationally on combining evidence from epidemiological and toxicological studies so the subgroup had agreed that it was not necessary to propose a UK approach at this time.

18. The COC gave very positive feedback on the structure, contents and readability of the document, and noted that the guidance and recommendations were clear and helpful. It was suggested that the document would be helpful to provide as part of an induction pack for new Members, along with a similar document on toxicology.

19. Suggestions were made for additions to the document on uncertainty, in particular with reference to the European Food Safety Authority (EFSA) PROMETHEUS (PROmoting METHods for Evidence Use in Scientific assessements) project. It was noted that COT had undertaken work on evaluating uncertainty which was being trialled but adding a lot of work to the evaluations using it. Reference was also made to a Special Section of the International Journal of Epidemiology on Causality in Epidemiology (Vol 45, Issue 6), which discusses identification of a single study compared to integration of all evidence. The subgroup

members highlighted that there was ongoing work on this topic area across the world, and it had been difficult to determine the level of detail to provide on each section. Overall the Committee agreed there was not a single gold standard approach and that the balance of the weight of evidence needs to be considered in each case. It would also be important to keep a watching brief on the area.

20. Members suggested the addition of a glossary, and a short discussion on the current position on integrating toxicological and epidemiological evidence, for example, with reference to the trihalomethanes study funded by DH. The possibility of providing a flowchart format for section 6 of the guidance report was also suggested.

21. The audience of the documents was discussed, and it was agreed that there was a role for the Secretariat to trial the approach suggested and to ensure that others presenting evidence to the Committee were aware of this guidance. The COC agreed that the documents were sufficient to form its guidance statement G02: "Interpretation of Evidence of Carcinogenicity in Humans: Epidemiology and Case reports", but also that wider publication should be attempted.

22. With respect to the working methods and recommendations report, the need for training was noted including of new members as well as Secretariat staff. This might be possible to address through the Interdepartmental Group on Health Risks from Chemicals (IGHRC) Understanding Epidemiology for Chemical Risk Assessment course, or the EFSA workshop on systematic review.

23. The Chair thanked Dr Anna Hansell and the SEES subgroup members for their hard work on the reports.

ITEM 6: Guidance statements

Item 6a) Draft lay introduction to COC guidance statement series (CC/2017/03)

24. This paper presented a first draft of an introduction to the guidance statement series following the Committee's previous suggestion that a plain English introduction be provided.

25. Members agreed that rather than using the term 'lay' in the title, the introduction should either be called a 'general' or 'non-technical' introduction, and that as for IGF-I the Committee would move towards including non-technical summaries in its statements.

26. A number of wording changes were suggested for the next draft both overall and for the section on alternatives to the 2-year bioassay in particular. In addition it was felt that the document should enthuse the reader to continue reading and also outline the anticipated audience, beyond COC members and Government Departments and Agencies.

27. A revised draft would be brought back for discussion at the July meeting.

Item 6b) Draft updated General Introduction to G07 Alternatives to the 2-year Bioassay (CC/2017/04)

28. This paper presented an updated Introduction section to the guidance statement G07: Alternatives to the 2-year bioassay to reflect the drafts of parts c) and d) which were being prepared.

29. It was agreed that there should be an additional paragraph at the start of the document explaining the need for relevant alternatives to support the 3Rs (reduction, replacement and refinement of the use of animals for scientific purposes) in carcinogenicity testing, which are also cost-effective. In addition the document should refer to how animal carcinogenicity studies reflect human carcinogenicity, and the need to get more information from the studies undertaken.

30. Any further comments on the draft would be sent to the Secretariat, and the draft would be cleared by Chair's action.

Item 6c) First draft statement on COC/G07: Part c) Emerging technologies: omics and high-throughput screening (CC/2017/05)

31. This paper presented a first draft of part c of the COC guidance statement on alternatives to the 2-year bioassay which focuses on omics technologies and high-throughput screening.

32. Overall the draft received positive feedback. It was agreed that some discussion should be included on what to do with the data, especially from omics approaches and the need for big data methods. It was also suggested that the title should reflect that these technologies are established rather than emerging.

33. It was agreed that the points would be addressed and sent out to Members for comment by correspondence initially.

ITEM 7: OECD guidelines: Standard Project Submission Form for the ToxTracker assay (CC/2017/06)

34. This paper presented a submission made to the OECD Test Guidelines programme for a stem cell-based reporter assay for mechanistic genotoxicity and carcinogenicity hazard assessment, called the ToxTracker assay. The COC were asked to comment on the assay in general and in particular on the use of the assay for detection of non-genotoxic carcinogenicity.

35. The COC was informed that the COM had previously considered the assay and concluded that it could be used as an early screen before *in vivo* testing, or where this is not permitted, and that the assay could aid interpretation of weak positive results, and possibly identify non-genotoxic carcinogens, through exploring mechanisms.

36. The COC queried the reasoning for using mouse cells rather than human, organ specific, or induced pluripotent stem cells, and likewise the reasoning for using rat liver S9 extract rather than a metabolic system based on human metabolism.

37. With respect to non-genotoxic activity, there was little mention of this within the provided documentation, and no evidence provided to support the unfolded

protein response. Overall the Committee noted that non-genotoxic activity covers multiple mechanisms, and given the assay is based on a single cell line system, this would not be expected to cover all possible mechanisms. In particular the assay would be expected to have poor performance in detecting mechanisms such as immune suppression or hormone related effects.

38. In terms of performance, it was noted that toxicity varied between the labs. Additionally the statistics were based on positive prediction, and the COC acknowledged that it would not be possible for the assay to determine that a substance is not a carcinogen.

39. The Committee commented that the OECD has previously had reservations about proprietary studies especially with only one source of the cells.

40. Overall the COC concluded that based on the information provided in the submission, the ToxTracker was assay not ideally placed as screening assay to detect a non-genotoxic carcinogenicity effects.

ITEM 8: Scoping paper for evaluation of heat-not-burn tobacco products (Reserved business) (CC/2017/07)

41. No interests were declared.

42. This item was discussed in reserved session as it pertains to commercial data.

ITEM 9: Follow up discussion of horizon scanning topics (CC/2017/08)

48. This paper presented the list of topics discussed by the Committee at the November 2016 horizon scanning session, along with the topics currently under consideration by IARC and the EU Scientific Committees.

49. It was noted that epigenetics, novel tobacco products and e-cigarettes were already on the work programme to be covered in the coming year. Nanomaterials was considered a high priority with EFSA guidance on nanomaterials expected later in the year and a lot of work ongoing at the MRC on long-thin nanofibers and potential for mesothelioma. Effect of immunosuppression both by therapy and environmental chemicals would follow nanomaterials in priority.

50. Three recent papers were suggested as short agenda items for upcoming meetings for the Committee to have some discussion of the paper.

51. With the presentation of the current and upcoming work of IARC and the EU Scientific Committees it was queried how it would be determined what should be considered by the COC, or COT or COM, and how the Committee would take forward topics that have been addressed but in a different context. It was noted that the COC could investigate areas considered to be important in its own right and also to be proactive in longer term issues.

52. It was queried how new statements from e.g. EU Scientific Committees would be picked up and considered by the Secretariat, and the role of the Assessors from other Government Departments and Agencies was highlighted for whom these might

be more relevant. Likewise if a topic or statement was of concern to other Departments and Agencies, they were asked for input at horizon scanning, as well as having the option to put forward suggestions to the Secretariat at any time.

53. It was agreed that a scoping document on nanomaterials would be prepared for the July meeting, and the COT and COM informed of the COC's intention to look at this again.

ITEM 10: Draft 2016 COC Annual Report contribution (CC/2017/09)

54. This paper presented the COC contribution to the COT, COM and COC joint 2016 Annual Report.

55. It was suggested that more discussion was included on the COC alcohol work, which while completed in 2015, was published in parallel with the CMOs report on new alcohol guidelines in January 2016. This should emphasise the role and effort of the COC in the work, which had not been clear in the media at the time. Related to this the Committee discussed the role of the COC and its independence from Government, including the Secretariat, and it was agreed that this would be raised at the meetings of Chairs of scientific advisory committees.

56. The Committee requested feedback on how many people view the annual report, and also the website, as well as feedback on what happens with the advice provided by the Committee. The request for feedback and the Committee's approach to including non-technical summaries of statements, would be incorporated into the Chair's preface.

ITEM 11: Any other business

Glyphosate

57. The Committee had previously been kept updated on the evaluation of glyphosate, and were informed that the European Chemicals Agency (ECHA) Risk Assessment Committee had agreed not to classify glyphosate for carcinogenicity. This was reported in the press release: https://www.echa.europa.eu/-/glyphosate-not-classified-as-a-carcinogen-by-echa.

Chairs and Secretariats of DH Chemical and Radiation Committees meeting and meeting of Chairs of FSA Committees

58. The Chair had attended meetings with other Chairs of both DH and FSA Committees in January and February respectively. Aspects such as independence discussed under the Annual Report would be raised at these meetings to ensure appropriate communication of the Committees work.

PHE Secretariat support from Imperial College London

59. It was noted that the PHE contract for secretariat support currently with Imperial College London would expire at the end of June 2017, and that an open tendering process was underway to identify a provider for this service after that time. The Imperial College London Toxicology Unit and staff were thanked for their vital input to the work of the Committee.

Dr Diane Benford

60. Dr Diane Benford had decided, prior to her accident in January, to retire from the FSA at the end of May 2017. She was formally thanked in her absence for her substantial contribution to the COC's work since she had become the FSA Scientific Secretary in 2000.

ITEM 12: Date of next meeting

61. The date of the next meeting will be 20th July 2017.