CC/MIN/2018/01

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

Minutes of the meeting held at 10.30am on Thursday 12th July 2018 at Public Health England, CRCE, Chilton, Didcot, Oxon, OX11 0RQ.

Present

Chair:	Professor D Harrison	
Members:	Mr D Bodey	
	Dr J Doe	
	Dr G Clare	
	Professor R Kemp	
	Dr D Lovell	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	
	Dr R Waring	
	Professor S Warnakulasuriya	
Secretariat:	Miss B Gadeberg	PHE Scientific Secretary
	Dr B Dörr	FSA
Assessors:	Mr A Axon	HSE (by teleconference)
	Dr O Sepai	PHE
Other invited Experts and Contractors:	Dr S Bull	WRc NCET (Items 1-4)
	Dr K Burnett	for WRc NCET
	Professor L Levy	IEH Consulting
	Miss S Lloyd	WRc NCET
Observers:	Dr Michael Wilde	University of Kent
	Professor Jon Williamson	University of Kent

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ITEM 1: Announcements and apologies for absence

1. The Chair welcomed Members, and other attendees to the meeting, including two observers from the University of Kent who were interested in medical methodology.

2. Apologies were received from Professor N Pearce, Dr D Gott (FSA Secretariat) who was represented by Dr B Dörr and Dr R Bevan (IEH Consulting) who was represented by Professor L Levy. Apologies were also received from assessors Dr H McGarry (HSE) who was represented by Mr A Axon by teleconference, Ms L Lawton and C Green (Defra), Mr I Martin (EA) and Mr N O'Brien (VMD).

3. Dr Peter Greaves had finished his term of office as a COC Member on 31st March 2018, and the Chair expressed his thanks for all his contributions over the last 9 years.

4. The Committee was informed that no appointments had been made to the vacancies for a pathologist and an epidemiologist advertised in the spring.

5. There were a few Members' appraisals left to complete, which would be undertaken in the margins of the meeting.

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

ITEM 2: Minutes of meeting held on 16th November 2017 (CC/MIN/2017/03)

7. One amendment was made to the November 2017 minutes.

ITEM 3: Matters arising

Item 3: Matters arising

Synthesising Epidemiological Evidence subgroup

8. The revised SEES report had been circulated for Members comments in March 2018, and the comments passed back to the SEES Secretariat. The final amendments to the report were in progress and it was expected that the report would be published in the coming months.

9. COC Members of SEES requested sight of the amendments made to the report prior to publication, which would be passed on to the SEES Secretariat.

Draft statement on possible carcinogenic hazard to consumers from Insulin-like growth factor 1 (IGF-I) in the diet

10. The revised statement and lay summary had been circulated to Members for comment, and subsequently approved by Chair's action. Publication was expected soon.

Guidance statements

11. Guidance Statement G03 on Hazard identification and characterisation: conduct and interpretation of animal carcinogenicity studies had been revised, approved by Chair's action and published on the COC website.

12. The update to G07 Alternatives to the two-year bioassay Part C: Omics, high-throughput screening, and bioinformatics had been delayed, but was expected to be progressed for the November meeting.

Heat-not-burn tobacco products

13. The COT statement on heat-not-burn tobacco products, now known as heated tobacco products, had been published in December 2017.

14. Written evidence from the COT, supported by the COC and COM, had been submitted to the House of Commons Science and Technology Committee inquiry on e-cigarettes. The submission described the planned work on e-cigarettes by the COT and outlined the conclusions on heated tobacco products from the 2017 statement, as these were also being considered by the inquiry. The COC Chair, who is also a former COT member, had been a witness to an oral evidence session focussing on the toxicology of these products. The inquiry report would be published in due course.

Item 7: Draft statement from a joint committee workshop on the use of epigenetics in chemical risk assessment

15. The joint statement had been presented to COT and COM at their February 2018 meetings, and comments addressed in the second draft statement that had been circulated for comment by correspondence in May 2018. These comments were in the process of being addressed before approval by the Chairs of the three Committees.

Item 10: Horizon scanning – including topics from July 2017 and joint COC, COM and COT meeting

16. The expected COT-IGHRC meeting on the microbiome had been deferred and the Secretariat would keep the Committee informed when more information was available.

17. It had been hoped that a presentation on immunological and stromal cell modulations could be arranged for the present meeting. The Chair was following up with a few names who would consider the approach in the context of the carcinogenic process, so a presentation might be arranged for November.

Item 12: Any other business

EU Exit

18. It was noted that the new EFSA Panels and Committees had approximately 50 % fewer UK experts than previously.

ITEM 4: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes) – overview of available data on carcinogenicity (CC/2018/01)

19. No interests were declared for this item.

20. The COT was considering the potential toxicological risks of electronic nicotine (or non-nicotine) delivery systems (E(N)NDS). A paper (TOX/2018/16) had been presented at the COT, in which a literature search for evidence on genotoxicity and carcinogenicity had been undertaken and full lists of publication titles retrieved were presented. After follow-up analysis of the abstracts, it was agreed that the COM and the COC should consider the available papers on genotoxicity and carcinogenicity, respectively. The aim was for the COC (and COM) to assess absolute and relative risks from E(N)NDS compared to conventional cigarettes, and if feasible, to heated tobacco products.

21. Members raised concern around the use of flavourings in E(N)NDS products and queried whether there was an 'approved' list for use in such products, as there was for addition to conventional cigarettes and food flavourings. The extent of carcinogenicity testing of the flavourings via the inhalation route was considered to be a potential issue, with most testing presumed to be by the oral route. Diacetyl butter flavour was highlighted as an example that should be flagged up to COT as of concern for potential carcinogenicity.

22. Thermal decomposition of flavourings and other materials within E(N)NDS products was considered to be of potential concern. Members commented that where thermal decomposition within E(N)NDS products had been compared to conventional cigarettes, it was unclear how the values had been derived. It was difficult to reach a conclusion on the relative risks from thermal decomposition in E(N)NDS compared to conventional cigarettes.

23. The Committee was informed that there was guidance available from WHO regarding use parameters for E(N)NDS to minimise the risks to the user. Although it was acknowledged that this was aimed at regulators and industry, Members suggested consideration be made of whether this could be modified for dissemination for customers and users of the devices.

24. It was noted that the risk to new users taking up the use of E(N)NDS products had not been considered in the papers. One of the papers had carried out a comparison of the risk associated with using conventional cigarettes, heat-not-burn products and E(N)NDS products. The members considered that the risk for tobacco-containing products was implicit to the user as tobacco doesn't need to be heated to be carcinogenic. For E(N)NDS products, the available evidence suggested that nicotine itself was not a carcinogen.

25. There was some discussion on the potential risks to bystanders from exhaled aerosols and whether there was a difference between second hand smoke from conventional cigarettes when compared to E(N)NDS products. It was noted that only limited data were available on this topic.

26. One member noted that the COM had also reviewed mutagenicity studies as part of the COT review. They considered that although there was a breadth of

evidence reported, those studies conducted to OECD Test Guidelines showed negative results and these had been sponsored by industry. The non-test guideline studies generally reported positive results, but they did not show consistency and had not been repeated by other investigators. COM members had also expressed concern that some studies reported genotoxicity only when wider toxic effects were observed. The COM concluded that the limited evidence base did not indicate any specific mutagenic risks from E(N)NDS that were not observed with conventional cigarette products. However, COM members considered that greater consistency and demonstrable reproducibility in both product, exposure and methodologies were needed before any view could be taken on absolute risks of E(N)NDS products.

27. The COC concluded that relative risk of E(N)NDS compared to conventional cigarettes appeared to be lower, but there was still some risk associated with the chemicals and particles in the emissions from E(N)NDS. This risk should be emphasised to new users. In addition. Members concluded that the possibility of bystander effects should also be considered.

28. A brief discussion on the possible value of co-ordinating animal studies on E(N)NDS products in the UK in the future led to the conclusion that these would not be very useful for carcinogenicity assessment, as animal models had not been good proxies for the human health effects of cigarettes.

ITEM 5: Development of a framework (algorithm) for consideration of risk due to less than lifetime exposure (CC/2018/02)

29. No interests were declared for this item.

30. COC members have previously considered the provision of guidance on how to estimate the risk to humans from acute, short-term or less than lifetime (LTL) exposures to genotoxic and non-genotoxic carcinogens. Following an update on approaches used by various authoritative bodies given to COC in November 2017, it was agreed that a general set of principles, that could be considered when assessing LTL exposures, would form a key part of any future COC guidance. This paper provided a draft set of principles aimed at guiding the risk assessment process for a specific LTL scenario.

31. Members considered that a flowchart based on the steps of the draft ‘set of principles’ presented in the paper would assist the reader. A worked example would be a useful addition to the document.

32. In addition, some areas that were already included in the draft ‘set of principles’ were thought to need greater emphasis. These were: identifying existing information about the chemical concerned; the evaluation of dose-response relationships; description of uncertainty factors and an assessment of uncertainty (COT and EFSA have guidance on this); toxicokinetic properties and the identification of susceptible groups. Members also considered that the document should include directions for refining the assessment (e.g. with more accurate exposure estimates) in cases where the LTL exposure exceeds the long-term HBGV.

33. Members considered that the RISK21 software and TTC would be appropriate tools to include for use in the draft ‘set of principles’. Discussion of any differences

between use of the ‘set of principles’ for prospective and retrospective risk assessment was also highlighted as a necessary inclusion.

ITEM 6: Risk assessment of the effects of combined exposures to chemical carcinogens – an update (CC/2018/03)

34. No interests were declared for this item.

35. The COC previously considered risk assessment of combined exposures to carcinogens in a statement published in 2010. Since the COC website had been migrated to www.gov.uk this statement has served as the COC guidance statement G08 on risk assessment of mixtures of chemical carcinogens. This paper described the developments in risk assessment approaches for mixtures since the 2010 statement and included two EFSA consultation documents for consideration.

36. It was agreed that it would be important for the Committee to submit comments on the two EFSA consultation documents. Comments should be provided to the Secretariat by mid-August and the consolidated response would be circulated to Members for their approval before submission.

37. For the frameworks and approaches described, the Committee noted that little consideration was given for carcinogenicity. They were useful as generic tools to for assessing how to handle mixtures of chemicals to which people might be exposed. However, carcinogenicity was considered to be a multi-stage process, resulting from failures at points of control, and combination effects could arise between substances to which exposure may occur at different points over time and affecting different parts of the process.

38. Members agreed that a broader approach should be explored for the carcinogenic process considering the potential for chemicals with different modes of action to act together to induce carcinogenesis. The complexity of the multi-stage process of carcinogenicity was recognised, but often this was distilled even for single chemicals to determining whether a substance was genotoxic or not to progress to risk assessment. The COC considered that classification of substances as initiators or promoters as has been used previously did not show where the potential for interactions between chemicals might occur in the carcinogenic process.

39. It was noted that the ‘hallmarks of cancer’ hypothesis attempted to provide a more extensive classification, and in theory, a more realistic approach to the consideration of multiple exposures to potential carcinogens. The potential for chemically-induced immunosuppression was discussed and it was considered to be particularly relevant to human exposures. It was believed that individual susceptibility to immunosuppression would also need to be taken into consideration.

40. The Committee was of the opinion that an approach as wide-ranging as that described in the ‘hallmarks of cancer’ hypothesis could risk classifying chemicals as carcinogens when they only impact on one, isolated aspect of tumour development. Members also highlighted the fact that the hypothesis was a literature-based evaluation that had not as yet generated any experimental results to support the hypothesis.

41. With respect to development of the guidance statement, the Committee agreed that, following a general introduction, the potential usefulness of the different frameworks with specific regard to carcinogenesis should be addressed. However, overall it was suggested that G08 should cross-refer to the EFSA Harmonised Guidance on risk assessment of combined exposures to multiple chemicals, once it was published, as this captured the most widely accepted approaches. A section on the characteristics of cancer and how individual chemicals, including pharmaceuticals, had the potential to act together by affecting different pathways and processes was suggested.

42. The Committee agreed that the current statement (2010) being presented as G08 was still valid and reflected the approaches that were recommended at the time of publication. Therefore, it was considered appropriate to remain on the COC website until it had been revised.

ITEM 7: Guidance Statements

43. No interests were declared for this item.

Item 7a) The use of biomarkers in carcinogenic risk assessment (G04) – second draft version 1.1 (CC/2018/04)

44. This second draft updated statement incorporated changes requested when it was discussed by the COC in July 2017, including contributions from specific members.

45. One minor further amendment was suggested and it was agreed that the statement could be approved by Chair's action.

Item 7b) Cancer risk characterisation methods (G06) – second draft version 1.1 (CC/2018/05)

46. This second draft updated statement incorporated changes requested when it was discussed by the COC in November 2017, including contributions from specific members.

47. A few minor amendments were suggested and it was agreed that the statement could be approved by Chair's action.

Item 7c) Defining a point of departure and potency estimates in carcinogenic dose response (G05) – third draft version 1.1 (CC/2018/06)

48. This third draft updated statement incorporated changes requested when it was discussed by the COC in November 2017.

49. It was noted that the EFSA work on TTC was progressing well, and a new reference on benchmark dose modelling was highlighted. It was agreed that a full revision would be required soon, and would be considered for the 2019 work programme.

50. Minor amendments were suggested, as well as restructuring one of the sections. It was agreed that the updated statement could be approved by Chair's action.

Item 7d) Introduction to the COC guidance statement series – third draft (CC/2018/07)

51. This third draft introduction to the guidance statement series had been updated as agreed at the July 2017 COC meeting.

52. It was suggested that the risk assessment diagram be included in the document. It was agreed that this document could be approved by Chair's action. This document would be frequently updated to reflect the publication of updated or revised statements in the series.

ITEM 8: Any other business

OECD Integrated Approach to Testing and Assessment for non-genotoxic carcinogens

53. Members had been contacted in May 2018 for a request from the OECD for submission of assays to support the development of an integrated approach to testing and assessment for non-genotoxic carcinogens.

54. While the deadline for the request had passed, the Secretariat had been informed that assays were still being accepted and Members were encouraged to submit relevant assays to the OECD.

Committee Expertise

55. The expertise required on the Committee in the future was raised as there was likely to be a turnover in membership of the Committee in the coming years. The difficulty in recruiting to the recent vacancies was noted, and Members were encouraged to identify any new areas of expertise that might be required in the future as well as existing areas that would need to be maintained. Where Members knew of people who would be suitable to apply to vacancies, they were asked to recommend the Committee to them, and as appropriate the Chair and Secretariat would be willing to also discuss the roles with the individual concerned.

Committee meeting venue

56. It was noted that at times the Secretariat had difficulty in securing rooms for the COC to meet within London, so a few meetings had been held in PHE Chilton in recent years. Members were invited to comment on any preferences in geographical location of the Committee meeting venue by email to the Chair.

57. Members agreed that it would be preferable to consistently use the same venue rather than having to arrange travel to different places each time.

ITEM 9: Date of next meeting

58. The date of the next meeting was 8th November 2018, and the venue would be confirmed in due course.