CC/MIN/2020/02

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

Minutes of the meeting held at 10.30am on Thursday 16th July 2020 by Teams.

Present

Chair:	Professor D Harrison	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr M Cush	
	Dr R Dempsey	
	Dr J Doe	
	Dr R Haworth	
	Dr R Kemp	
	Dr D Lovell	
	Professor N Pearce	
	Dr L Rushton	
	Dr L Stanley	
	Professor H Wallace	
Secretariat:	Miss B Gadeberg	PHE Scientific Secretary
	Ms C Mulholland	FSA
Assessors:	Dr H McGarry	HSE by teleconference
	Mr N O'Brien	VMD
	Dr O Sepai	PHE
	Dr H Stemplewski	MHRA
Officials:	Professor J O'Brien	FSA Science Council
Invited Experts and Contractors:	Dr R Bevan	IEH Consulting
	Dr P Rumsby	IEH Consulting
Observers:	Professor L Levy	IEH Consulting
	Ms A van der Zalm	PETA International Science Consortium

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ITEM 1: Announcements and apologies for absence

1. The Chair welcomed Members, and other attendees to the meeting. Apologies were received from Assessors and Officials: Dr J McElhiney (FSS), Dr W Munro (FSS) and Dr T Netherwood (DHSC).

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

ITEM 2: Minutes of meeting held on 12th March 2020 (CC/MIN/2020/01)

3. Amendments were suggested for the draft minutes, with clarification to follow by correspondence.

Minutes of the meeting of 16th July 2019

4. The minutes of Item 4 of these minutes had been circulated by correspondence and no comments received, so these were agreed for publication.

ITEM 3: Matters arising

Item 3 Matters Arising – Scoping paper on the synthesis and integration of epidemiological and toxicological evidence in risk assessments

5. The subgroup on synthesis and integration of epidemiological and toxicological evidence in risk assessments had met by teleconference on 17th April and 22nd June 2020.

Item 3 Matters Arising – Guidance statement G01 – A strategy for risk assessment of carcinogenicity

6. The document had been circulated for COC comments by correspondence and would be finalised by Chairs action.

Item 3 Matters Arising – Guidance statement G08 – Risk assessment of the effect of combined exposures to multiple chemicals on carcinogenicity

7. The document had been circulated for COC comments by correspondence and would be finalised by Chairs action.

ITEM 4: Draft position paper: The Tumour Microenvironment (CC/2020/05)

8. Dr Cush declared that she worked with a cosmetics manufacturer on assessment of products intended to work in conjunction with the skin microbiome. The was not deemed to be a conflict, and Dr Cush was able to participate fully in the discussion. [BG1]

9. Following discussion of a short overview of the immunological and stromal cell modulations relevant to cancer in November 2019 (CC/2019/13) and the scoping paper on the tumour microenvironment at the March 2020 meeting (CC/2020/01), the Committee agreed to published a COC position paper on the topic.

10. A draft position paper was presented ~~in this paper~~[RD2]. It outlined the roles of the different cell types and events in the microenvironment in terms of the carcinogenic process and examples of how chemicals might interact~~intact~~ with these.

11. During discussion, the importance of publishing a document to indicate awareness of this ~~important~~ topic[RD3] by COC was agreed. It was considered that the paper would not take the form of guidance nor a comprehensive review ~~with~~ as the evidence is not at a point where the Committee would provide a formal position. As such a 'Watching Brief' was agreed as an appropriate description for this document.

12. The paper was seen as an important part of the transition of the Committee towards consideration of the entire carcinogenic process in the risk assessment of chemicals.

13. A number of amendments to the draft position paper were suggested and it was agreed that a second draft would be prepared and circulated to the Committee for agreement by correspondence before finalising by Chair's Action.

ITEM 5: Guidance Statements - Overview (CC/2020/11)

14. No interests were declared for this item.

15. The COC carries out a rolling review of its guidance statements to ensure that the content of these is current and applicable, with documents typically being reviewed every 2-3 years, to consider whether any minor update or full revision is required. During this process it has become apparent that two guidance statements in particular, G03 (Hazard Identification and Characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies) and G07 (Alternatives to the 2-year bioassay) require comprehensive revision, in light of current Committee discussions concerning a contemporaneous approach to the risk assessment process for carcinogenicity. Although the current framework recommended by COC is still applicable, it is most easily used for data-rich chemicals with long-term exposure scenarios. However, Government Departments and Agencies are often asked to provide opinions for chemicals for which data are limited.

16. As part of the ongoing discussions by the Committee, a potential overview framework was presented to the COC for the risk assessment of carcinogenicity, based on a dynamic cancer risk model, that captured current understanding of the carcinogenic process, including new sources of evidence. An assessment approach considering how a chemical modified underlying cancer risk was suggested. Such an approach would continue to start with a review of the evidence of carcinogenicity, mutagenicity and relevant toxicity, however~~,~~ this would be done in a different way. The proposed framework assumes that carcinogenicity occurs continuously at a low level, meaning there is a background risk, in a dynamic process where the cell is repaired or dies. Chemicals can interfere with this process at several risk modification points, for example by altering the cell microenvironment. It is also possible to consider the impact of additional risk factors such as obesity on the framework. Sources of evidence include ~~non-carcinogenic and~~ short-term studies which may show pre-cancerous effects, mode of action studies (*in vivo* and *in vitro*)

and *in silico* knowledge. The importance of being able to quantitate risk and communicate that risk effectively was also highlighted, which could be based on current guidance.

17. In general, the COC was supportive of the proposed framework. During discussions two examples, heated tobacco products and dioxins, were considered where current epidemiological and mechanistic evidence could be extrapolated/interpolated for use in a 'modification of cancer' risk approach. Recognition of the successes of the current approach recommended by COC was seen to be important as this could be built on and as some studies may still be required to be carried out from a regulatory aspect. It was agreed that updating the guidance statement series documents should be undertaken and progressed incrementally, integrating this new approach as appropriate. ~~where possible to encompass this new approach should be progressed~~[BG4], The requirement to ~~whilst~~ maintain~~ing~~ consistency ~~therebywhile also ensuring thaint~~ the guidance statements to ensure that there is sufficient clarity and continuity for them to remain useful to end users, ~~and~~ in particular Government Departments and Agencies, was noted.[RD5][BG6]

ITEM 6: Guidance Statement G03: Hazard identification and characterisation: Conduct and interpretation of animal carcinogenicity studies - First draft update (CC/2020/06)

18. No interests were declared for this item.

19. The COC has periodically published guidelines for the evaluation of chemicals for carcinogenicity, including the separation of the overall guidance into individual documents during 2012 – 2014, to allow faster revision. This included a separate document addressing Hazard Identification and Characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies (G03).

20. Guidance statement G03 was last updated in 2018. The paper presented (CC/2020/06) proposed some additional amendments for consideration. The COC was also asked to consider whether a full revision of G03 was required to incorporate recent Committee discussions around whether the carcinogenicity bioassay remains an appropriate tool for human health risk assessment.

21. Following discussion, it was proposed that G03 should be revised and combined with G07 (Alternatives to 2-year Bioassay). Further discussion of this and Committee decisions regarding this are given later in these minutes under Item 8: Guidance Statement G07: Alternatives to the 2-year bioassay - First draft update (CC/2020/08).

ITEM 7: Cancer Risk Characterisation Methods G06 Update (CC/2020/07)

22. No interests were declared for this item.

23. As part of the COC published guideline series on the evaluation of chemicals for carcinogenicity, a separate document addressing “Cancer risk characterisation methods” (G06) was published. This was last updated in 2018.

24. This paper presented some proposed updates to the document. The Committee considered the document in the context of the earlier overarching discussions concerning modified approaches to the risk assessment of potential carcinogens. Statements were also made to COC from representatives of PHE and HSE, on the usefulness of G06 in supporting their approaches to risk assessment. It was felt that this would be particularly needed following EU exit where an increase in enquiries about the carcinogenic potential of chemicals, in addition to current requirements, was foreseen. In light of these, it was agreed at this time the current version G06 would be updated rather than undertaking a full revision.

25. A number of comments and suggestions for improvement to the first draft update were made and it was agreed that a second draft would be prepared and circulated to the Committee for comment and agreement before finalising by Chair’s Action.

ITEM 8: Alternatives to 2-year Bioassay G07 Update (CC/2020/08)

26. No interests were declared for this item.

27. As part of the COC published guidance series on the evaluation of chemicals for carcinogenicity, a separate guidance statement addressing “Alternatives to the 2-year bioassay” (G07) was published. G07 comprised four parts as an overview of approaches developed as potential replacements to the 2-year bioassay, with the final update added in 2018. It was developed due to the increasing recognition at the time that the 2-year bioassay may not be relevant to human exposure or modes of carcinogenic action. In addition, there was also a growing concern that COC should recognise the need to refine testing strategies to be in line with the principles of Replacement, Refinement and Reduction (3Rs). This paper proposed updates to the current version of G07 for Members to consider.

28. The Committee picked up from the discussion under Item 5 and considered development of a weight-of-evidence approach to carcinogenic risk assessment which would take into account all of the available information on the effects of a chemical on stages of cancer development. Alternative strategies such as that of OECD Integrated Approach to Testing and Assessment (IATA), the use of in vitro, in vivo and in silico evidence on mechanisms of action, as well as structure activity relationships, and the need for robust exposure and epidemiological data were important to include.

29. It was agreed that G03 and G07 should be combined with a wider scope to outline new strategies for a weight-of-evidence approach to the risk assessment of the carcinogenic potential of chemicals. It was noted that substantial parts of both documents were still relevant, with some updates required to aspects from G03 and moving emphasis in the topics in G07 away from primarily alternatives to the two-year bioassay, towards being relevant tools in their own right. Inclusion of the two-

year bioassay, accepting its limitations, as one source of evidence would continue to be important, while ~~was~~ giving appropriate recognition to other sources of evidence and highlighting the total weight of evidence was key. It was also noted that the required degree of confidence in the evidence available would depend on knowledge of levels of potential exposure.

30. The Committee agreed that an outline should be drafted based on the framework discussed in Item 5. This would be circulated to the COC prior to the next meeting in November 2020. It was also noted that there may be a need to consider updating the contents of other guidance statements in the series, in light of any new approach adopted for G03 and G07, which would be undertaken as part of the rolling review.

ITEM 9: Guidance Statement G05: Carcinogenic dose response: defining points of departure and potency estimates - Third draft revision (CC/2020/09)

31. No interests were declared for this item.

32. This document had previously been discussed at the March 2020 meeting when further modifications were requested to remove historical information and make the opinion of COC clearer throughout. This paper presented the third draft update with the structural changes as well as additional input provided by a Member on the benchmark dose section in particular.

33. The Committee agreed some further minor additions to aid clarity for the reader. Once completed, it was agreed that the document could be finalised by Chair's action.

ITEM 10: Follow up to Horizon Scanning (CC/2020/10)

34. No interests were declared for this item.

35. This paper presented the update to Horizon scanning outlining the activities of IARC and EU Scientific Committees, including those of EFSA, and providing the COM and COT horizon scanning activities.

36. The update was noted and it was agreed that the full horizon scanning discussion would take place as usual at the November 2020 meeting.

ITEM 11: Any other business

37. No other business was raised.

ITEM 12: Date of next meeting

38. The next meeting would be held on 24th November 2020 with format to be confirmed nearer the time.