Committee on CARCINOGENICITY

CC/MIN/2019/01

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

Minutes of the meeting held at 10.30am on Thursday 28th March 2019 at Public Health England, Centre for Radiation, Chemical and Environmental Hazards, Harwell Campus, Didcot, Oxon, OX11 0RQ.

Present

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

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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 Professor S Warnakulasuriya, and assessors: Dr W Munro (FSS), Dr C Ramsay (Health Protection Scotland), Dr J McElhiney (FSS), Dr H Stemplewski (MHRA), Mr I Martin (EA) and Ms S Geerts (DHSC).

2. This was the last meeting for Dr C Powell and Professor S Warnakulasuriya and they were thanked for their contributions to the work of the Committee during their terms of office.

3. The Secretariat were in discussions with DHSC about reappointments and recruiting to existing and expected vacancies as some Members were coming to the end of their current terms at the end of March 2019.

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

ITEM 2: Minutes of meeting held on 8th November 2018 (CC/MIN/2018/02)

5. No amendments were required to the draft November 2018 minutes.

ITEM 3: Matters arising

Item 3: Matters arising

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

6. Some issues had been experienced in getting publications onto the Committee website but the IGF-I statement was expected to be available on the COC website soon.

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

7. This statement had been approved by the COC, COM and COT Chairs and was being finalised for publication.

Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes) – overview of available data on carcinogenicity

8. The COC findings were presented at the December 2018 COT meeting. The outcome of the evaluation was noted and would be fed into the COT statement on these products when it was prepared

Guidance Statements

9. Some issues had been experienced in getting publications onto the Committee website but the guidance statements were expected to be available on the COC website soon.

Item 4: Immunological and stromal cell modulations relevant to cancer risk

10. Following the presentation in November, it was hoped that further speakers and discussion on this topic would be held at a future meeting. Speakers focussing on contribution of modulations of these systems to the carcinogenic process was the key aspect for COC.

Item 8: Guidance Statement G07c

11. This guidance statement had been approved and was expected to be available on the COC website soon.

Item 9: Any other business

Update on FSA Scientific Advisory Committees

12. The FSA advert for Members to join the COT, ACMSF and ACNFP and the joint expert groups, which would assess regulated products, had been published and a number of potential new Members interviewed. Submissions to the FSA Chair and CMOs to confirm appointments would be made shortly with the aim of Members being in place by May.

ITEM 4: Chemical carcinogenicity revisited – series of papers of interest (CC/2019/01)

13. No interests were declared for this item.

14. At a previous meeting, Dr John Doe had highlighted a series of papers, of which he was a co-author, that challenged the current chemical carcinogenicity assessment paradigm. These papers had been published and were provided in the discussion paper. Dr Doe had also agreed to give a short presentation on the key aspects from the three papers, which is attached at the end of these minutes.

15. In the presentation, members were reminded that the current paradigm was set up over 40 years ago and that new scientific approaches and understanding of the carcinogenic process may provide a new paradigm. The usefulness of identifying carcinogens per se using a long-term rodent bioassay was now being questioned for assessing carcinogenic risk in humans. The stochastic nature of the cancer process was outlined in which the probability of a cancer outcome being influenced by the number of replications of cells, hereditary related errors and environmental stressors (directly acting on the genome and/or increasing cell replication) was assumed.

16. Cancer aetiology was also described, and it was emphasised that a proliferative environment needed to be maintained to allow for the progression of tumourigenic development. The “current gold standard” for carcinogenicity testing, the 2-year rodent bioassay, was considered biased towards providing a sustained proliferative environment due to use of the maximum tolerated dose, which may therefore give a greater likelihood of tumour findings compared to controls.

17. Moving away from identifying carcinogens as a classification process, to assessing carcinogenic potential as part of risk characterisation was proposed. As cancer occurs as a downstream consequence of genotoxicity and/or toxicity, prevention of these through setting of guidance values would also prevent cancer. In

conclusion, Dr Doe outlined a suggested risk assessment approach using structure-activity relationship, toxicity testing, or mutagenicity testing as the starting point for cancer evaluation. It was also considered that the approach could be used to evaluate combined and less than lifetime exposures.

18. It was suggested that over the last 40 years most chemical and/or occupational carcinogens had been discovered through epidemiology studies. Although it was considered that the proposed outline model was a good and new way of thinking, it was anticipated that new carcinogens would be discovered that didn't fit the model and that the model's findings would be secondary to epidemiology findings. However, the Committee was reminded that epidemiology studies were not available for all chemicals, particularly newly introduced ones, and the animal data should not be dismissed for deriving protective health-based guidance values (HBGVs). The use of animal studies to provide information on mechanisms for both existing and new chemicals was also highlighted.

19. It was suggested that the model had some pragmatic issues, for example, in picking up immunosuppression and epigenetic or phototoxic carcinogens. Members recognised that IARC, which has traditionally used a hazard-based approach for classifying carcinogens, was increasingly considering dose-response data in their evaluations. Consideration of the importance of scale within the cancer process was discussed. At the largest scale of epidemiology, a person either has or has not got cancer. This new model informed on the cellular microenvironment that is crucial to cancer development. In addition, it was considered that animal models could be used more usefully to assess the influence of combined exposures, including presence of cancer risk factors such as obesity, as well as deriving HBGVs.

20. The logistics of how to begin replacing the existing paradigm were also explored. Industrial chemicals were considered a potentially useful starting point to test the model as they did not require a full toxicity testing package; if successful, the model could be applied to agrochemicals and pharmaceuticals etc. The Committee also considered that it was important to clarify the reasons for proposing any such change and to consider how this may eventually feed into the COC risk assessment process and its overarching purpose of giving advice on how to reduce the risk of an individual getting cancer. This discussion would therefore also be useful to feed into subsequent agenda items.

21. The Chair thanked Dr Doe for the presentation.

ITEM 5: First draft updated Guidance Statement (G01): A Strategy for Risk Assessment of Chemical Carcinogens (CC/2019/02)

22. No interests were declared for this item.

23. The COC has since 1982 periodically published guidelines for the evaluation of chemicals for carcinogenicity. A substantial revision, during the period 2010 to 2014, separated key topics into individual guidance statements, with an overarching summary statement (G01) reflecting the Committees overall strategy. This allowed for updates to the individual guidance statements to be made as frequently as needed, as driven by advances in the science. This paper incorporated the changes

in the individual documents since 2014 into G01 to provide an updated overarching summary statement.

24. The Committee considered that as a document, G01 reflected the philosophy of COC. As such G01 should incorporate a short introductory statement, describing the most current ways of thinking about carcinogenicity that had been discussed in the previous item. However, as there was still a current need to carry out risk assessment of chemicals, the testing strategy currently described was anticipated to continue in place until such time as a new approach/paradigm was in place.

25. Additional areas for clarification and re-structuring of the document were also discussed. It was agreed that due to the substantial number of changes this would be taken forward as a full revision of the document rather than a short update and a new draft would be presented to the Committee at the next meeting.

ITEM 6: First draft "Challenges for risk assessment of the effects of combined exposures to chemical on carcinogenicity" (CC/2019/03)

26. No interests were declared for this item.

27. At the November 2018 meeting the Committee discussed the potential for a novel carcinogen-specific risk assessment paradigm for combined exposures to possible carcinogenic chemicals. It was agreed that a draft manuscript should be prepared for submission to a peer-reviewed journal reflecting the COC's thinking on new approaches to the risk assessment of the effects of combined exposures on carcinogenicity. This paper presented a first draft of such a manuscript.

28. It was considered appropriate by the Committee for COC to state its opinion on the approaches and paradigms currently being developed to assess the risks of combined exposures to multiple chemicals over varying time intervals, as this issue was frequently being raised by risk assessors. However, the view was expressed that the document, while stating future aspirations for carcinogen risk assessment, did not sufficiently convey core issues of methodology such as additivity and synergy and the impact of uncertainty.

29. The Committee suggested the document, with some amendments, was more suited as a COC Statement. A structure for the statement was suggested to include an introduction discussing why mixtures are important in assessing the risks of potential carcinogens, stressing that one-third of IARC Group 1 chemicals are mixtures; current difficulties in assessing the risks of combined exposure to multiple chemicals including temporal and spatial considerations; assumptions currently made in the risk assessment of combined exposures such as synergy, additivity and interactions; human evidence requirements for risk assessment; examples of combined exposure to multiple chemicals; individual susceptibility and variability; and the place of specific Adverse Outcome Pathways/Mode of Action including the possible use of Hallmarks of Cancer in the development of chemically-induced cancer

30. It was agreed that a new draft statement would be brought to the next meeting for consideration.

ITEM 7: Revised draft "Framework for consideration of risk due to less than lifetime exposure" (CC/2019/04)

31. No interests were declared for this item.

32. The COC has previously considered the issue of less than lifetime (LTL) exposure to carcinogens and agreed to produce a "set of principles" to support assessment of such exposures. This paper presented the amendments requested at the November 2018 meeting.

33. One member suggested an alternative flow chart outlining a 2-tiered approach to provide more guidance to undertake assessments of less than lifetime exposure. Each of the steps in this flowchart were discussed and a number of amendments agreed so it could be added to the current set of principles. The Committee was reminded that at the current time it is only possible to offer pragmatic actions for LTL exposure as definitive answers and guidance could not be proposed with reasonable confidence.

34. A number of further amendments to the paper were suggested, including discussion of the use of Haber's rule for non-genotoxic carcinogens, and also the TTC approach.

35. Members agreed that the amended document should be circulated for comment and, subject to the comments received, could then if appropriate be approved by Chair's action.

ITEM 8: Recent paper: Experimental and pan-cancer genome analyses reveal widespread contribution of acrylamide exposure to carcinogenesis in humans (CC/2019/07)

36. No interests were declared for this item.

37. This paper presented a recent publication considering a mutational signature of glycidamide, which is the postulated reactive metabolite of acrylamide, identified from cell cultures. Human tumour genomes were then assessed to determine if this signature was present. The signature was found in one-third of the tumour genomes, and observed in over 50% of cancers of the lung, liver, kidney, bile duct and cervix, as well as being present to a lesser extent in other cancer types.

38. The Committee queried whether any information was available to determine the specificity of the mutational signature as a marker of glycidamide. Evidence for this was not provided in the published paper, though it was clear that the signature was different to those from acrylamide.

39. It appeared that controls had been part of the study but it was not clear what information had been obtained from these controls, how they were used or what was found. For the findings in the lung it was queried whether the signature might be a marker of historical tobacco smoke, rather than specifically acrylamide in the mixture. The Committee were informed that the COM will have a presentation on mutational signatures and this would be a useful paper to discuss alongside.

40. Overall the Committee considered that the paper provided only weak evidence of a widespread contribution of acrylamide in all human cancers. More work would be required to provide sufficient evidence of any such effect. Members requested to be kept updated both of any commentary paper on the publication as well as any follow up papers, and the COC would keep a watching brief on the topic area more generally.

ITEM 9: Follow up to horizon scanning topics (CC/2019/05)

41. Following the horizon scanning discussion in November 2018, this paper outlined the topics highlighted for consideration and provided the standing update on activities at IARC and the EU Scientific Committees.

42. The Committee was informed that the COT had also proposed that a joint COT-COC subgroup should be formed to investigate integration of toxicological and epidemiological evidence. A scoping paper would be prepared for discussion at COT and COC meetings before any subgroup was set up.

43. A further potential joint topic was assessment of risks from endocrine active substances in food. It was agreed that a scoping paper should be prepared and this could then be considered by COT and COC to determine how to progress this further.

ITEM 10: Draft COC Annual Report 2018 (CC/2019/06)

44. This paper presented the draft COC section for the joint 2018 COT, COM and COC Annual Report. No comments were raised at the meeting, but Members were invited to send in any amendments to the Secretariat.

ITEM 11: Any other business

45. No other business was raised.

ITEM 12: Date of next meeting

46. Several Members had indicated they were unable to attend the July 2019 meeting date, so this would a more suitable date would be identified and confirmed in due course.