CC/MIN/2018/02

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

Minutes of the meeting held at 10.30am on Thursday 8th November 2018 at Public Health England, 5 St Philips Place, Birmingham, B3 2PW.

Present

Chair:	Professor D Harrison	
Members:	Dr G Clare	
	Dr J Doe	
	Dr R Haworth	
	Professor R Kemp	
	Dr D Lovell	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	
	Dr R Waring	
Secretariat:	Miss B Gadeberg	PHE Scientific Secretary
	Mr B Maycock	FSA
Assessors:	Dr O Sepai	PHE
Other invited Experts and Contractors:	Dr R Bevan	IEH Consulting
	Dr S Bull	WRc NCET
	Professor N Gooderham	Imperial College London
	Dr P Rumsby	IEH Consulting
Observers:	Professor L Levy	IEH Consulting

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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 Mr D Bodey, Professor N Pearce, and Professor S Warnakulasuriya, and Dr D Gott (FSA Secretariat) who was represented by Mr B Maycock. Apologies were also received from assessors Dr H McGarry (HSE), Dr H Stemplewski (MHRA), Dr W Munro (FSS), Ms L Lawton and Dr C Green (Defra), Mr I Martin (EA) and Mr N O'Brien (VMD).

2. Dr Richard Haworth was welcomed to the Committee as a co-opted Member for the next two meetings to fill the vacancy for a Member with pathology expertise until the next round of recruitment.

3. The Secretariat were in discussions with DHSC about recruiting to existing vacancies and planning the actions required as some Members were coming to the end of their current terms in spring 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 12th July 2018 (CC/MIN/2018/01)

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

ITEM 3: Matters arising

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Synthesising Epidemiological Evidence subgroup

6. The report of the SEES subgroup had been published.

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

7. Publication of the statement on IGF-1 had been delayed but 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

8. Final amendments to this statement were being made prior to approval by the Chairs of the COC, COM and COT.

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

9. The finalised minutes of the discussion in July would be presented to the COT at its December meeting.

Item 7: Guidance Statements

10. The guidance statements discussed at the previous meeting had been approved and were expected to be published on the COC website soon.

ITEM 4: Presentation on immunological and stromal cell modulations relevant to cancer risk by Professor Nigel Gooderham

11. No interests were declared for this item.

12. The Chair introduced Professor Gooderham from Imperial College, London and reminded members that this presentation was the first part of a wider scope for COC looking at the role of the microenvironment, inflammation and the immune system in cancer.

13. Professor Gooderham presented an introduction to metabolism and its interaction with the inflammatory system in cancer, in a presentation entitled 'Immunological and stromal cell modulations relevant to cancer risk'. Research into a possible link between the exposure of humans to heterocyclic amines (HAs) from cooked meat in the diet and colon cancer was the starting point from which consideration of metabolism and mechanisms of carcinogenicity had led to investigation of effects of HAs on the immune system.

14. Metabolism of HAs occurred via cytochrome P450 (predominantly CYP1A2), forming esterified HAs that could bind to protein and DNA. It was considered that if mis-repair of the DNA occurred, this might lead to tumour formation. However, the findings of a study of 500 incident colon cancer cases did not support the hypothesis that the genotoxicity of HAs was a major driver for colorectal cancer. Additionally, hepatic CYP activity in patients was depressed rather than increased, probably as a result of systemic infection and inflammation.

15. The findings of the study of 500 incident colon cancer cases showed increased expression of CYP1B1 and 2E1 in tumour tissue, both of which were involved in carcinogen metabolism. In addition, tumour tissue had a distinct inflammatory microenvironment, with a number of pro-inflammatory cytokines (COX-2, IL-1β, IL-6, NF-kB-p65) being elevated. IL-6 was known to induce tumour CYP2E1 via the activation of JAK2 and STAT3. Further, IL-6 mediated tumour CYP1B1 induction by reducing the expression of miR27b, which was an inhibitor of CYP1B1.

16. The tumour microenvironment contributed to dysregulation of miRNA in epithelial cancer cells and immune cells, which is achieved through cross-talk between these cell types, mediated by IL-6. This sustains chronic inflammation and promotes pro-metastatic cancer cell behaviour. Looking forwards it was suggested that there could be therapeutic opportunities for colorectal cancer around CYP1B1, 2E1, IL-6, the JAK/STAT pathway and IL-6-mediated miRNAs.

17. After the presentation, it was queried whether, for the mechanistic model presented, the cells would need to be in close proximity for the mechanism to be viable. As miRNAs were extremely stable and not broken down when released into the systemic circulation, this allowed them to reach non-adjacent cells. The miRNAs were indicative of a tissue-specific response, which was why they were a good biomarker and could be used for diagnostic purposes for a number of cancers and also other diseases including kidney pathologies (when monitored in urine) and polycystic ovary syndrome. It was not clear whether all cancers have a unique miRNA profile but a study of 800 cancer patients had shown key differences between tumour types, including distinguishing between 3 different types of

leukaemia. It was also queried whether miRNAs could be used to detect early stages of disease and it was thought that there would be a need for collaboration with epidemiologists to identify possible disease markers that could then be looked at mechanistically.

18. The potential for an effect of the gut microbiome was queried and while it was known that the gut microbiome had its own miRNAs, this hadn't been sufficiently studied to be able to associate them with a function. It was also questioned whether CYPs are elevated in pre-tumour tissue (as well as tumour tissue) which could help prove their involvement in a causal mechanism. This was considered feasible as the data showed the metabolic capability of tumours is different from normal tissue which offers therapeutic opportunities. The role of oxidative damage in inflammation around the tumour sites was discussed and it was noted that this differed between cancer types, for example, in prostate cancer oxidative effects had more of a role than for colon cancer.

19. The Chair thanked Professor Gooderham for the comprehensive presentation and noted that the discussion would also be useful in future work on the role of the microbiome in cancer.

ITEM 5: Development of a framework for consideration of risk due to less than lifetime exposure (CC/2018/08)

20. No interests were declared for this item.

21. Over the last few years, COC members have 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. This also links with a previous horizon scanning topic regarding the adequacy of the margin of exposure (MOE) approach in children. From discussions at the November 2017 and July 2018 meeting, a general set of principles was developed to form the COC guidance statement on the topic.

22. The paper presented an updated version of the document including a flowchart and two hypothetical case studies to illustrate the possible utility of the set of principles, as requested at the July 2018 meeting. Due to issues that had arisen during development of the case studies, members were specifically asked to consider whether the distinction of chemicals within the set of principles (Steps 2A/3A and 2B/3B), currently based on genotoxic status, would be better based on a threshold- or non-threshold basis; this would also be consistent with G06 on risk characterisation.

23. The Committee requested that a number of additional considerations should be highlighted in the paper, whilst ensuring that the set of principles should not be too prescriptive due to the general nature of the guidance being given. In terms of changing the basis of decision making in the framework, it was noted that for both case studies, it had been necessary to assess the chemicals on the basis of a threshold and non-threshold mode of action. The examples used were, however, data rich which had enabled that approach to be taken and many 'real-life' examples were unlikely to have information on carcinogenic mode of action. It was agreed that in practice any chemical for which there was genotoxicity information would be

treated on a non-threshold basis, unless there was a specific reason to use a thresholded approach. The importance of including consideration of other properties such as reversibility and potency, in addition to genotoxicity, was emphasised.

24. It was queried whether guidance should be included on the circumstances under which a life time exposure study should not be used for a risk assessment, particularly if potent carcinogens (either genotoxic or non-genotoxic) showed tumour formation at an early stage. It was agreed that information on the latency period was important to include, if known, as this flagged concerns for the overall LTL exposure risk assessment. Members also discussed the need to ensure that the paper did not stray from risk assessment into risk management areas as this was not within the remit of the COC.

25. It was agreed that the framework would be modified in light of the discussion and be presented to the Committee again.

ITEM 6: Risk assessment of the effects of combined exposures to chemical on carcinogenicity (CC/2018/09)

26. No interests were declared for this item.

27. The Chair introduced this item by reminding members that human cancers nearly always result from exposure to multiple substances, which could be experienced simultaneously or singly over time. The COC had considered developments in the field of the risk assessment of mixtures of chemical carcinogens since the publication of the COC's Guidance Statement G08 (in 2010) in July 2018 (CC/2018/03).The paper presented here (CC/2018/09) discussed the potential for a novel carcinogen-specific risk assessment paradigm for combined exposures to possible carcinogenic chemicals, based on a multistage model of cancer (i.e. Hallmarks of Cancer), as an Adverse Outcome Pathway (AOP). Two examples of known synergistic chemicals (alcohol and tobacco smoking; asbestos and tobacco smoking) that have previously been considered by COC, were discussed to show the utility of an AOP/Hallmarks of Cancer approach.

28. Members discussed how they wished to take forward the guidance statement on effects of combined exposure to chemicals on carcinogenicity. It was agreed that publishing a manuscript in a peer-reviewed journal reflecting the COC's thinking on new approaches to the risk assessment of the effects of combined exposures on carcinogenicity should be the next step.

29. It was considered that any published review from the COC should endeavour to offer sensible advice on framing the problem of considering the multifactorial nature of cancer and how different chemicals may interact when exposure may be both coincidentally or differing in time. This would involve the expansion of the AOP methodology to recognise the multistage nature of cancer such as suggested by Hallmarks of Cancer. It was queried that one of the authors of the 'Hallmarks of Cancer' paper, had commented that they are not appropriate for risk assessment, however, Committee considered their use appropriate if treated with caution.

30. It was agreed that a short discussion article would be prepared and submitted to a journal. The draft article would be prepared by the Chair and the Secretariat and circulated to members for comment prior to submission in the name of the COC.

ITEM 7: Horizon Scan (CC/2018/10)

31. No interests were declared for this item.

32. The horizon scan paper presented the topics agreed in November 2017, with an update on progress and suggestions for new topics. An additional new topic from the Secretariat on the microbiome was provided verbally at the meeting.

33. Following on from the earlier presentation to begin the discussion of the effect on cancer risk of modulation of the immune system and stromal cells, it was agreed that more work would follow on this, most likely as further presentations. The role of infection in disease was noted, but would be a separate aspect. It was noted that there was cross-over between epigenetic mechanisms in cancer and immune modulation. Capturing timing of the effect would also be relevant.

34. It was suggested that unusually potent non-genotoxic carcinogens should be investigated and examples such as BRAF inhibitors and pioglitazone could be used.

35. With respect to the microbiome, the Committee requested a presentation to give a starting background to this work.

36. Potential follow-up work to the Synthesising Epidemiological Evidence Subgroup report, integrating toxicological and epidemiological data was considered. It was not clear if there would be much more material available than had been mentioned in the SEES report, though it was acknowledged that there were papers available on Bayesian methods and examples of combining animal and human data. The COC considered that the work should be scoped and then a view could be formed on what could be done. Projects undertaken by Leicester University and by IARC, ICNIRP and WHO were suggested for further consideration. It was noted that at the joint horizon scanning session in October 2017, interpretation of evidence from regulatory studies compared to published research studies had been discussed and would also be relevant to follow up.

37. With respect to the balance of expertise of the Committee, Members were invited to contact the Chair or Secretariat if there were aspects that should be added. In addition if there were any professional groups or individuals, Members would recommend publicising Committee vacancies to they would also be welcomed by the Secretariat, and likewise Members were invited to discuss Committee roles with people they considered might be interested or appropriate for the role.

ITEM 8: Guidance Statement G07c – updated draft (CC/2018/11)

38. No interests were declared for this item.

39. This paper presented a third draft of part C: Omics, high-throughput screening and bioinformatics, of the Guidance statement on Alternatives to the 2-year bioassay (G07), alongside the other sections of the document which had previously been agreed by the Committee.

40. A few minor amendments were suggested, including a minor amendment to the conclusions about the maximum tolerated dose in Part D: Alternative testing strategies. Use of artificial intelligence was discussed and it was agreed that the additional text in this version was sufficient.

41. It was agreed that once these amendments were addressed the document could be approved for publication by Chair's action.

ITEM 9: Any other business

Update on FSA Scientific Advisory Committees (Reserved Business)

42. A short summary was provided on planned changes to the FSA Scientific Advisory Committees. This was discussed as reserved business.

Meeting venue

46. The Committee agreed it would be helpful to come to a decision on the location of meetings in the future, and the Chair would contact all Members after the meeting to come to a decision. It was agreed that it would be helpful to make the most of the travel to meetings and have a good full day of discussions, which could include meeting with staff members in the margins of the meeting.

ITEM 10: Date of next meeting

47. The date of the next meeting was 28th March 2019, and the venue would be confirmed in due course.