CC/MIN/2017/03

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

Minutes of the meeting held at 10.30am on Thursday 16th November 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 P Greaves	
	Dr D Lovell	
	Professor N Pearce	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	
	Dr R Waring	
Secretariat:	Miss B Gadeberg	PHE Scientific Secretary
	Mr B Maycock	FSA
Assessors:	Mr R Hartwell	Defra
	Ms L Lawton	Defra
	Mr I Martin	EA
	Ms H Reeves	VMD
	Dr O Sepai	PHE
Other invited Experts and Contractors:	Dr S Bull	WRc NCET
	Dr R Bevan	IEH Consulting
	Dr K Burnett	WRc NCET

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ITEM 1: Announcements and apologies for absence

1. Apologies were received from Professors R Kemp and S Warnakulasuriya and Dr J Doe, Dr D Gott (FSA Secretariat) who was represented by Mr B Maycock, and Assessors Dr H Stemplewski (MHRA), Dr W Munro (Food Standards Scotland), Dr H McGarry (HSE) and Mr N O'Brien (VMD) who was represented by Ms H Reeves. Defra was represented by Ms L Lawton and Mr R Hartwell. Dr Michael Wilde (University of Kent) had been due to attend the meeting as an observer but was unable to come on the day and sent apologies.

2. The Committee was informed that Professor Julian Peto had resigned from the Committee on 15th October 2017. The Chair expressed the Committee's gratitude to Professor Peto for his contributions to the Committee over the past 5 years.

3. The Committee was informed that appointments and reappointments with effect from 1st April 2018 were being discussed by the Secretariat and Department of Health (DH). The Committee would be contacted when adverts were put up for new Members, and Members were requested to distribute the adverts to their contacts.

4. As stated at the last meeting following the review of fees by DH, Members who have been reappointed since May 2016 were no longer eligible to receive fees unless in exceptional circumstances. The Secretariat was awaiting formal guidance on how such cases would be dealt with but in the interim any Members who wished to be considered to receive fees were advised to contact the Secretariat who would forward the request to DH for consideration.

5. It was agreed that the discussion of Adverse Outcome Pathways, and the paper on Cancer etiology and Causal Inference would be substantive agenda items in their own right, and they are numbered as such in these minutes

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

ITEM 2: Minutes of meeting held on 20th July 2017 (CC/MIN/2017/02)

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

ITEM 3: Matters arising

Item 3: Synthesising Epidemiological Evidence subgroup

8. The SEES subgroup Secretariat and Dr Hansell had met and discussed the amendments to the report as agreed by COC and COT. The amendments are ongoing and the document would be finalised as soon as possible.

Item 4: Second draft statement on possible carcinogenic hazard to consumers from Insulin-like growth factor 1 (IGF-I) in the diet

9. A revised version of the statement and lay summary had been prepared and would be circulated to the Committee for comment after the meeting. Members were

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requested to provide any final comments by correspondence prior to approval by Chair's action.

Item 5: Guidance statements

10. It was expected that amendments to the guidance statements in light of the discussions at the July meeting would be undertaken soon.

Item 6: The toxicological evaluation of novel heat-not-burn tobacco products: First draft statement and follow up information from the joint Committee discussion (Reserved business) (CC/2017/16)

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

Item 8: Any other business – PHE Secretariat support contract

15. As had been reported at the joint COC, COM and COT meeting on 9th October 2017, the contract for provision of Secretariat support to PHE had been awarded to the National Centre for Environmental Toxicology (NCET) at WRc plc and IEH Consulting.

16. Dr Lesley Rushton declared a personal specific interest as part of the consortium, which had successfully bid for this work. Dr Rushton had not been involved in any of the preparation of the papers presented at the current meeting, and it was agreed she could take part fully in the discussions.

ITEM 4: Less than lifetime exposure to carcinogens – to incorporate margin of exposure for children (CC/2017/19)

17. No interests were declared for this item.

18. 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 horizon scanning topic regarding the adequacy of the margin of exposure (MOE) approach in children.

19. Paper CC/2017/19 provided a brief history of discussions by COC members and an up to date overview of the topic area, with a focus on the use of MOE-based approaches for adults and children. In addition, consideration was given to how children are defined for risk assessment purposes and whether they are at greater risk per se than adults from exposure to carcinogens. A set of principles were presented for consideration by the Committee.

20. The Committee was informed that any guidance would be used to underpin approaches used by Government Departments and Agencies for example in responding to incidents, although there would be considerable variation in the types of LTL exposure to be considered. Members considered that some examples of the types of LTL exposure to carcinogens would be useful to help define the type of guidance needed. General examples were suggested such as exposure of all age groups to a genotoxic carcinogen in food or water, over a period of up to 10 days; continuous exposure to chemicals from contaminated land during early life (0-6 years); and repeated (2-3 times daily) short duration (<30 min) exposures of children

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to atmospheric pollutants in urban areas, e.g. during the walk to school. It was recognised therefore that evaluations would need to be performed on a case-by-case basis.

21. The Committee noted that some experimental designs include intermittent administration, which may affect the toxicokinetics of the substance in question. Therefore, consideration of the available evidence should be part of the assessment of an LTL exposure scenario.

22. The use of Haber's rule for assessing LTL exposures was considered unsuitable for genotoxic carcinogens, as a single large exposure would be more likely to have an effect that long-term low dose exposure. This should be noted in the guidance.

23. It was agreed that a general set of principles or algorithm to consider when addressing LTL exposures would be an important part of the guidance. Suggestions included: consideration of the MOA to determine threshold or non-threshold DNA reactivity; information on the exposures within the available evidence for the substance in question; consideration of life-stage of the individual exposed to assess whether a specific exposure presents more, less, or even the same level of risk of a biological event occurring. For infants and children, the Committee proposed that a higher risk should be assumed unless evidence was available to show otherwise, and in all cases, it was emphasised that the use of additional UFs for all age groups should be supported with evidence.

24. The Committee concluded that guidance for assessing LTL exposures should be drawn up for consideration at the next meeting. For practical purposes, Members agreed that the guidance would also consider application of the MOE approach in children and infants, but that these would be separate parts of the document.

ITEM 5: Update to Guidance Statement G05: Points of Departure and Potency Estimates

25. Professor Heather Wallace declared that she had been appointed as the Chair of a new European Food Safety Authority (EFSA) working group on the Threshold of Toxicological Concern. Dr D Lovell declared the he is part of the ILSI Europe Task Force on Uncertainty in Risk Assessment: A Comparison of TTC versus Chemical-Specific Approaches.

26. The Committee had discussed the draft update to this Guidance statement at the July 2017 meeting, where it had been agreed that to undertake a full revision of the document would take some time. Instead it was agreed that the short update to the statement should be completed and that the topics to be considered in more detail should be brought to future meetings. This item provided more information on the benchmark dose modelling (CC/2017/20) and threshold of toxicological concern (CC/2017/21) approaches, and an amended version of the draft updated guidance document for agreement (CC/2017/22).

Item 5a) Update on benchmark dose modelling (CC/2017/20)

27. As part of the revisions to Guidance Statement G05 on points of departure and potency estimates, discussed in July 2017, the COC requested an overview of

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recent updates to benchmark dose (BMD) modelling, with particular focus on the EFSA, 2017[a] guidance.

28. Paper CC/2017/20 considered the use of dose-response data in risk assessment, the BMD approach, available software including a comparison of available dose-response models in each, and the use of model averaging for calculating the BMD confidence interval and quality criteria.

29. In terms of impact on the COC guidance, the use of a reference point (RP) derived using BMD modelling (e.g. BMDL) in risk assessment does not change the basic approach or assumptions. EFSA (2017) strongly recommended that the BMD approach, and more specifically model averaging, is used for the determination of RPs for use in: (i) deriving health-based guidance values; (ii) MOE approach for substances that are both genotoxic and carcinogenic; (iii) comparison of potencies; and (iv) probabilistic risk assessment.

30. Members suggested that as the EFSA (2017) guidance was currently considered the best available document on BMD modelling, it would be sensible to refer to this where possible, but not duplicate text.

Item 5b) Recent developments on the Threshold of Toxicological Concern (CC/2017/21)

31. Members were presented with a paper outlining recent developments in the evaluation and application of the TTC approach with view to updating the TTC section in Guidance G05. This included the updated guidance from EFSA (in conjunction with WHO 2016), a report of an ILSI meeting in 2011 and summaries of some publications recommending updates to the cancer potency databases used to derive the original threshold values.

32. The ongoing work of an EFSA working group on TTC was noted and overall, it was decided that a full revision of Guidance statement G05 should be deferred until the ongoing work at EFSA is complete.

33. Members requested some changes to the paper for clarification purposes. This included definitions of Cramer classes.

Item 5c) Update to Guidance Statement G05: Points of Departure and Potency Estimates (CC/2017/22)

34. A few further amendments were suggested for the update to this guidance statement. It was agreed that the amended update should be circulated to Members and could then be cleared by Chair's action.

35. A full revision of the document would then be undertaken at a later date.

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[a] EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen KH, More S, Mortensen A, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V, Solecki R, Turck D, Aerts M, Bodin L, Davis A, Edler L, Gundert-Remy U, Sand S, Slob W, Bottex B, Abrahantes JC, Marques DC, Kass G and Schlatter JR (2017). Update: Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2017;15(1):4658, 41 pp. doi:10.2903/j.efsa.2017.4658

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ITEM 6: Updated Guidance Statement G06: Cancer Risk Characterisation Methods (CC/2017/23)

36. No interests were declared.

37. The Committee has agreed to regularly review the published guidance statements to ensure they remain up to date. As part of this process, G06 on cancer risk characterisation has been updated. Members were presented with the draft updated document (CC/2017/23).

38. Members largely agreed with the proposed amendments.

39. Some changes to the section on the use of human studies were requested. Further comments would be sought from two Members after the meeting and the statement amended accordingly. It was noted that the guidance statement was written prior to drafting Guidance Statement G02; Interpretation of Evidence of Carcinogenicity in Humans: Epidemiology and Case Reports and it was anticipated that the section relating to use of human studies would be updated in light of discussions of G02 once available.

ITEM 7: Statement from a joint committee workshop on the use of epigenetics in chemical risk assessment – first draft (CC/2017/24)

40. No interests were declared.

41. A joint COT, COC and COM workshop on the use of epigenetics in chemical risk assessment was held in October 2017 during which delegates heard three presentations and were asked to consider a number of questions with regard to the inclusion of epigenetics in chemical risk assessment. This paper presented a first draft statement based on the presentations and on the outcome of the subsequent discussions.

42. It was considered that the presentation summaries could be more succinct but that overall, the statement captured the discussions and conclusions at the meeting. Some aspects required clarification including acknowledging a lack of understanding of epigenetic effects in humans and that the human data represented observations only and were not formally designed, reproducible experiments. With regard to a 'normal' spectrum of epigenetics, it was considered that this is of particular difficulty when examining data from humans.

43. It was also noted that little is known about the relationship between animal and human epigenetic responses to chemical exposure, and therefore extrapolation of results may not be relevant to a risk assessment. Furthermore, it was believed that the use of arrays was a flawed approach, given the lack of consistency across platforms.

44. Comments on the statement from the workshop presenters and participants would be sought after this COC meeting and the statement amended accordingly. The amended statement would then be considered by COT and COM at their respective February 2018 meetings.

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ITEM 8: Presentation on Adverse Outcome Pathways

45. No interests were declared.

46. Professor Heather Wallace gave an overview presentation on adverse outcome pathways (AOPs), introducing the AOP concept, the overlap with the mode of action framework, the linear structure of an AOP from molecular initiating events through key events to the adverse outcome, and how they are developed. It was highlighted that AOPs are not chemical-specific, they are modular, and a pragmatic simplification of biology. In use, networks of AOPs are likely to be needed as there are interactions between individual AOPs, and they will develop overtime as information on key events evolve and new key events are identified. The presentation concluded that currently AOPs have good potential for prioritisation, e.g. in drug development to determine compounds to progress, or for development of *in vitro* tests. However there are challenges with respect to the complexity of biology, quantification of dose-response relationships, how exposure assessment and toxicokinetic data are accounted for in AOPs, and how AOPs are evaluated.

47. In discussion, it was noted that epidemiology and toxicology can learn from each other, as epidemiology uses a relationship of cancer risk as x^{n-1}, where n is the number of steps in the cancer process, though it needs to be known which cancers this will work for. Probability can be associated with each step and if rates are available for each step as well then incidence can be estimated.

48. For the mode of action framework it was noted that human relevance was also considered. For AOPs, information would be needed on whether the pathway between the molecular initiating event and the adverse outcome were conserved between species. Where this information is available, AOPs would be useful for REACH applications, where *in vivo* data are not necessarily available for chemicals being considered.

49. Whether the pathways were reversible, and if adaptation could be captured in a pathway, were considered, as AOPs were appealing in their simplicity but represented complex biology that has in built redundancy.

ITEM 9: Papers of Interest on Cancer Etiology and Causal Inference (CC/2017/25)

50. No interests were declared.

51. This paper presented papers of interest that had been suggested at the March 2018 meeting.

52. The Committee discussed the topic of causal inference, which was part of an ongoing debate within the epidemiological field about balancing causality evidenced from randomized controlled trial that relies on the availability of an intervention for the disease of interest, and drawing together all the available evidence, often from other types of epidemiological studies, to infer causality of the disease in question. The example of obesity was used, where IARC have established that obesity causes cancer, but as obesity is a state of health rather than an intervention it is not possible to prove such causality by means of a randomized controlled trial.

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53. The relevance of the discussions about causal inference to the work of the COC was noted. The Committees draw together information from human, animal and *in vitro* studies, with toxicological studies providing additional important mechanistic information that cannot always be obtained from epidemiological studies. In addition, evidence is assessed not just by the nature of the experimental design but more importantly from the information contained in the studies considered. Diverse forms of evidence are encouraged including negative findings, and the Committee often needs to make an evaluation on limited data.

54. Overall the Committee agreed that disciplines working together, such as in the Committee structure, is important to draw together the available evidence on a topic and make an appropriate assessment.

ITEM 10: Horizon Scanning – including topics from July 2017 and joint COC, COM and COT meetings (CC/2017/26)

55. No interests were declared.

56. This paper presented the list of topics from the horizon scanned in 2016 as well as highlighting topics raised in at the July 2017 meeting and at the joint COC, COM and COT meeting on 9th October 2017.

57. It was noted that from the list at the end of 2016, the items on margins of exposure for children and epigenetics had been addressed.

58. There was interest in the influence of the microbiome on the health effects of chemicals. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) were holding a workshop on this in conjunction with the Interdepartmental Group on Health Risks from Chemicals (IGHRC) in the spring, and the Secretariat would discuss with the organisers the potential for COC members to attend.

59. A high priority for the Committee would be to consider the effects of immunological and stromal cell modulations on cancer risk. It was suggested that presentations from experts, covering both animal and human data, could be a useful means to start consideration of factors which influence the immune status and thereby affect risk.

60. For nanomaterials, it was noted that the MRC Toxicology unit had recently published a paper on carbon nanotubes and mesothelioma risk.

61. Following the discussion, the list of topics was:

- Immunological and stromal cell modulations relevant to cancer risk
- Nanomaterials
- Mechanisms incorporating genomics and the Cancer Genome Atlas
- E-cigarettes (if referral from COT) and effect of early life exposure to cigarettes
- *In vitro* systems - to be undertaken when resource allows

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ITEM 11: FSA Consultation on Declarations of Interest (CC/2017/27)

62. No interests were declared.

63. This paper provided the consultation which had been issued by the Food Standards Agency on guidance for dealing with declarations of interest, for Members awareness. It was queried whether consideration could be made of having means by which declarations only needed to be updated once rather than across multiple Committees.

ITEM 12: Any other business

EU Exit

64. Members queried progress on EU exit. The Chair of COM noted that this had been discussed at a meeting of Scientific Advisory Committee Chairs and Chief Scientific Advisors, where it was noted that this was at the top of the agenda for all Government Departments and Agencies, followed by covering usual business. Members highlighted concerns over participation at EU level meetings and whether the UK would continue to attend. It was noted that EFSA had recently put out a call for experts to sit on its Scientific Panels from July 2018, when the UK is still part of the EU. Defra noted that there would likely be more engagement with COC in place of discussions which were currently held at EU level.

Defra policy update on nanomaterials in REACH

65. Defra gave an update on REACH public consultation on nanomaterials which had closed in early November. Defra would be participating in a meeting in mid-December to discuss issues with respect to physicochemical properties, and appropriate tests for inhalation toxicity. The Committee noted that nanomaterials were on the horizon scan and Defra were keen to be kept informed of this work.

ITEM 13: Date of next meeting

66. The date of the next meeting was 8th March 2018, subject to any discussions on participation at the COT meeting on the Microbiome in February 2018.

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