Committee on CARCINOGENICITY

**CC/MIN/2016/01**

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

Minutes of the meeting held at 10.30am on Thursday 17th March 2016 at Department of Health, Wellington House, 133-155 Waterloo Road, London, SE1 8UG.

Present

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| Chair: | Professor D Phillips | |
| Members: | Dr G Clare | |
| | Dr J Doe | |
| | Dr P Greaves | |
| | Professor R Kemp | |
| | Dr D Lovell | |
| | Professor N Pearce | |
| | Dr L Rushton | |
| Secretariat: | Ms F Pollitt | PHE Scientific Secretary |
| | Dr D Benford | FSA Scientific Secretary |
| | Miss B Gadeberg | PHE |
| | Ms C Mulholland | FSA (Items 1-4) |
| | Dr K Burnett | Toxicology Unit, Imperial College |
| | Dr K Vassaux | Toxicology Unit, Imperial College |
| Assessors: | Ms L Dearsly | HSE |
| | Mr N O'Brien | VMD (Items 1-5) |
| | Dr O Sepai | PHE |
| Observers: | Dr Meera Cush | Delphic HSE Solutions Ltd |

## ITEM 1: Apologies for absence and announcements

1. The Chair welcomed the Members and Assessors to the meeting. Apologies were received from Professors J Peto, H Wallace and S Warnakulasuriya, Drs C Powell and R Waring, and Mr D Bodey. Mr S Fletcher (Veterinary Medicines Directorate assessor) sent apologies and was represented by Mr N O'Brien, as did Dr H McGarry (Health and Safety Executive assessor) who was represented by Ms L Dearsley. Apologies were also received from Dr P Cassanelli (Defra), Dr W Munro (Food Standards Scotland), Dr C Ramsay (Health Protection Scotland), Dr H Stemplewski (Medicines and Healthcare products Regulatory Agency) and Mr P Holley (Department of Health - DH).

2. The Chair welcomed Professor Neil Pearce to his first meeting since his appointment in May 2015, and the Members, Secretariat and assessors introduced themselves. Professor Pearce gave his apologies for being unable to attend the first two meetings following his appointment due to prior commitments.

3. The Committee were informed that Dr Ovnair Sepai had replaced Professor Tim Gant as the PHE assessor, and Dr Paola Cassanelli had replaced Dr Mike Roberts as the Defra assessor. Dr Will Munro was the assessor from Food Standards Scotland, which came into being on 1st April 2015 with responsibility for food safety and standards in Scotland.

4. The vacancy for the Chair of COC, arising at the end of Professor Phillips term of office on 31st March 2016, had been advertised and interviews were planned to take place at the end of March. The Committee would be notified when a Chair was appointed.

5. It was noted that DH had reviewed payment of fees and expenses and it had been decided that fees would no longer be paid on new Committee appointments, including the new COC Chair.

6. Members were informed that they would soon be receiving their appraisal forms for 2015/2016, and were requested to consider these with discussion with the Chair as necessary and, once agreed, return them to the Secretariat.

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

## ITEM 2: Minutes of meeting held on 12th November 2015 (CC/MIN/2015/03)

8. Minor amendments were made to the minutes in paragraph 15 and 21.

## ITEM 3: Matters arising

### *Item 4: Alcohol and cancer risk*

9. The third draft statement had been updated following the November 2015 meeting and prepared for publication. It had been agreed with the Committee by correspondence after the meeting to publish the statement in co-ordination with the CMOs' new guidelines on 8th January 2016. The COM statement on the mutagenicity of alcohol had been published at the same time.

10. The Chair had represented the COC at a stakeholder briefing on 7th January with Gina Radford, Deputy CMO for England, and Mark Petticrew, co-Chair of the Guidelines Development Group. The Chair had been interviewed on the ITV 'News at 10' broadcast on 8th January.

11. It was noted that the Secretariat would be giving a presentation on the COC's work on alcohol during the Oral Communications session of the British Toxicology Society Annual Congress in April 2016.

### *Item 6: Horizon Scanning 2015*

12. The paper on industrial exposure leading to cancer, which had been suggested for review, had been received by the Secretariat. As the Member who had suggested the paper was unable to attend this meeting, the discussion of this paper had been deferred.

### *Item 7: Any other business: Guidance statement G07: Alternatives to the 2-year bioassay, parts A and B*

13. This guidance statement was updated following comments at the last meeting and cleared by Chair's action. It was published on the COC website on 2nd February 2016.

### *Cycloastragenol*

14. The Committee was given an update the considerations of the Advisory Committee on Novel Foods and Processes (ACNFP) following the COC and COM advice in 2015 and the assistance of an independent expert. Although the COM had considered that the mutagenicity studies conducted were acceptable, it was unclear whether these were relevant to the compound given its proposed mechanism of action and the explanation for the possible increase in liver tumours was unknown. The company making the application had then provided some additional information but the ACNFP still had remaining concerns about the compound and the company withdrew their application for approval. Thus it cannot be sold in the EU as it is not an approved novel food. The product may still be available elsewhere, for example, in the US.

15. It was noted that the ACNFP was grateful for the support of the COC and COM, and this was a good example of Committees working together.

## ITEM 4: Possible carcinogenic hazard to consumers from insulin-like growth factor-1 (IGF-I) in the diet. Part 3: The potential association of IGF-I with colorectal cancer risk and with lung cancer risk (CC/2016/01)

16. This paper was a third part of the evaluation of the possible carcinogenic hazard to consumers from IGF-I in the diet. The first and second parts had been considered at the March and November 2012 meetings, and covered: identity and physiological control of IGF-I, human physiological levels of IGF-I, IGF-I in food and tissues, its use as a human medicine, toxicology and safety studies, association between blood levels of IGF-I and breast cancer, and association with prostate cancer. This paper presented data on potential associations between blood levels of IGF-I and colorectal cancer and lung cancer.

17. It was noted that these papers considered blood levels of IGF-I rather than dietary exposure. The next paper would discuss dietary intake and contribution to blood levels, as well as looking at the potential associations between blood levels of IGF-I and other cancers, including ovarian and endometrial cancer. Previously, the Committee had noted the importance of distinguishing between free and bound IGF-I in blood measures.

18. For colorectal cancer, there was general agreement to the summary and discussion on pages 38-39 of Annex B (paragraphs 61-67), noting that overall the findings of the studies are inconsistent, but the meta-analyses tend to show a positive association.

19. There was concern that many of the case-control and retrospective studies had a cross-sectional design with blood IGF-I levels measured at the same time as classification to case or control group, resulting in difficulty of interpreting these studies. For the prospective studies, only a few studies had longitudinal measures of blood IGF-I levels, and these did not describe any changes between the time points when measurements were taken. It was difficult to interpret studies where measurements of serum IGF-I had been taken at the start of the study and cancers occurred many years later. Without further information on other exposures during this time, it would be difficult to determine the biological plausibility of an association between IGF-I and cancer.

20. In addition, most studies did not adjust for dietary exposure, though one study that did, suggested the highest risk was associated with the lowest intake of IGF-I. The Committee queried whether there was any information on variations in IGF-I with a 'normal' diet or indication of daily variation. Recent papers on circadian rhythm were noted. Based on available animal studies, neonatal animals show substantial absorption of IGF-I, but there is variation across ages and the link with the diet has been explored more recently, and will be addressed in future Committee papers on IGF-I. If absorption was generally low, it would be difficult to perceive how a small change in circulating IGF-I could have a great effect on cancer risk. When this issue was initially raised it was suggested that partially digested (truncated) IGF-I was potentially absorbed, but few new data have been identified on this topic.

21. The Committee noted that a number of statements were made in the papers without the necessary supporting information provided. Some of this was as a result of considering the topic over a prolonged period, however often the supporting information was not available in the reviewed research papers.

22. In response to a question, Members were informed that some of the studies reviewed investigated IGF-I specifically while others considered the effects of binding proteins or growth hormones, in general.

23. The difficulty of drawing the available data together in a meta-analysis was noted, along with the need to choose which data to analyse. It was agreed that two Members would consider further the meta-analyses to review the studies selected, the data included from the studies, and to get a clearer impression of the data with respect to the size of the effect and range of the available estimates.

24. In considering lung cancer, a number of similar comments were made as for colorectal cancer, in terms of study design and the need to consider the meta-analyses further. It was noted that some studies reported high level of IGF-I within lung tumours, but blood levels were not reported. The presence of high IGF-I within a tumour was not unexpected because the cancer cells grow more quickly than the surrounding tissue. The Committee was also unclear as to whether IGF-I in serum could be influenced by smoking.

25. It was agreed that the consideration of the meta-analyses for colorectal and lung cancer would support the drafting of a statement. In addition, the previous COC considerations would be checked to ensure consistency of interpretation with the new studies. A check would also be made of whether the book which prompted the COC's consideration had been updated.

**ITEM 5: Guidance Statement G09 – Assessing the risk of acute and short-term exposure to carcinogens (CC/2016/02)**

26. This paper provided an updated first draft of the guidance statement on acute and short-term exposure to carcinogens. An underpinning discussion paper had been presented at the July 2015 COC meeting. A first draft statement had then been prepared for the November 2015 COC meeting, but there had been insufficient time to discuss the paper. A few comments had been received and thus an updated version was presented at this meeting. One change, in response to a comment, had been to change the title of the Guidance Statement to "Assessing the risk of less-than-lifetime exposure to carcinogens", to avoid having to define "short-term".

27. The Committee was concerned about using the proposed approach based on Haber's Law, for a single high dose exposure, when extrapolating from a lifetime approach, as practical thresholds e.g. for DNA repair or absorption might be exceeded, which could result in an irreversible effect. In addition, there was a need to protect against effects on other endpoints which might occur at doses lower than those identified by extrapolation. The Committee discussed the option of excluding chemical incidents or accidents from this guidance to enable the approach to be used for lower level exposures.

28. It was also noted that peak exposures often occur against a background of existing lower exposure, e.g. in a food contamination incident, and it would be helpful if advice could be provided on any specific methods for dealing with that. An important aspect for that would be to consider the effect of cumulative dose.

29. Overall, it was agreed that a second draft of this statement would be brought to the Committee, with the original discussion paper from July 2015, to discuss what is fit for purpose, what can pragmatically be used and when a case-by-case approach is required.

**ITEM 6: Proposed strategy for discussion of alternative paradigms for assessing carcinogenic risk (CC/2016/03)**

30. This paper presented a background and strategy for the Committee to discuss alternative approaches for assessing carcinogenic risk. This would support further drafting to Guidance Statement G07 – "Alternatives to the 2-year Bioassay".

31. Overall, this document brought together the potential issues and considerations to make. Members discussed the need to be clear on the objective and purpose of the paper, and to include a section on problem formulation. This was because there were a number of different aims for which approaches such as those discussed could be used. These included: undertaking a risk assessment of a chemical for cancer in humans without the information from a 2 year study, making a hazard assessment and predicting classification of chemicals as to their carcinogenic potential, and predicting the outcome of a 2 year animal study. It was considered sensible to provide guidance on the usefulness of short-term study data for predicting cancer effects in humans.

32. It was recognised that the regulatory framework under which a chemical is developed for use may determine what tests are required to be performed and that these vary between industry sectors.

33. It was noted that some of the schemes used endpoints from short-term assays to predict a chemical's potential to cause cancer. Where none of these endpoints or risk factors are identified in shorter assays, the data show that it is reasonable to assume a substance is not carcinogenic. However, if any one endpoint is present, it does not necessarily mean that the substance is carcinogenic in animals or humans, as these endpoints are not specific to the cancer pathway. Concern was expressed that a conservative, hazard based approach could be used to inform risk management without appropriate risk assessment, i.e. if an endpoint is present, the chemical would be classified as carcinogenic.

34. The Committee discussed the challenge of trying to undertake a risk assessment or identify a point of departure in cases where one of the potential risk factors is shown to occur. It was noted that, in general, an approach adopted to protect against a precursor or initiating event would also guard against cancer, as is the case for non-genotoxic carcinogens.

35. Depending on the data used, there was potential to make an assessment on a qualitative rather than a quantitative basis, though it would be useful to indicate when a quantitative approach should be considered. The growing interest in the field of genetic toxicology for quantitation was recognised, as was the move towards probabilistic assessment rather than the present positive or negative categorisation.

36. It was noted that a number of the approaches outlined were not validated and it would be important to emphasise the developing nature of the strategies available. In addition, a few further approaches were mentioned to add to the discussion. It was agreed that there was a role for the COC to provide guidance on risk assessment and interpretation of the available data in the absence of data from a 2 year bioassay, and also to provide guidance on the relative advantages and disadvantages of the different proposed approaches.

37. It was considered that it would be helpful to present the guidance statement series at the next meeting to determine how this would fit in, particularly with the overarching statement, and also to determine what the title of the guidance should be.

## ITEM 7: CMOs' consultation on the new alcohol guidelines (CC/2016/04)

38. This paper presented a draft COC response to the CMOs' consultation on new alcohol guidelines. Prior to the meeting the consultation documents had been circulated to Members for comment so the draft could be prepared as the deadline for the consultation was 1st April 2016.

39. Some amendments were made to the draft response, in particular providing more detail in the response to Question 2, where the Committee considered that there should be clearer separation of the beneficial and harmful effects of alcohol consumption.

40. It was agreed that the Secretariat would revise the response and it would be cleared by Chair's action.

## ITEM 8: Annual Report 2015 (CC/2016/05)

41. A few minor editorial amendments were suggested for the Annual Report for 2015.

## ITEM 9: Any other business

### *Professor David Phillips*

42. This was Professor David Phillips' last meeting as Chair, and the Committee thanked him for his hard work, both in his time as a Member from 2000-2006 and subsequently as Chairman from 2006. It was noted that the Committee had considered a diverse range of topics in that time and Professor Phillips had led the discussions in a calm and efficient manner. Professor Phillips thanked all the Members of the Committee, past and present, for their participation, as he had learnt a lot from everyone, and wished the Committee all the best for the future.

### *Ms Frances Pollitt*

43. This meeting was also the last meeting for Ms Frances Pollitt, PHE Scientific Secretary for COC, who would be retiring from PHE at the end of April 2016. The Committee thanked her for all the work she had put in to all three sister Committees over the last 25 years as part of the Secretariat. The Chair gave particular recognition of the work done behind the scenes and outside of the Committee meetings to support and guide the Committee's work.

### *Committee guidance*

44. The Committee was informed that a poster was being presented at the British Toxicology Society Annual Congress on the COC Guidance Statements, as it fitted in well with a number of the sessions on carcinogenicity to be held at the meeting.

## ITEM 10: Date of next meeting

45. The date of the next meeting was 21st July 2016.