CC/MIN/2014/03

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

Minutes of the meeting held at 10.30am on Thursday 13th November 2014 at Public Health England Colindale, 61 Colindale Avenue, London, NW9 5EQ.

Present

Chair:	Professor D Phillips	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr P Greaves	
	Dr D Lovell	
	Dr B Miller	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	
	Dr R Waring	
	Professor K Warnakulasuriya	
Secretariat:	Ms F Pollitt	PHE Scientific Secretary
	Dr D Gott	FSA
	Miss B Gadeberg	PHE
	Dr K Burnett	PHE Toxicology Unit, Imperial College
	Dr K O'Leary	PHE Toxicology Unit, Imperial College
Assessors:	Professor T Gant	PHE
	Ms S Thomas	HSE
Officials:	Dr O Sepai	PHE
	Mrs F Hill	FSA (Items 1-5)

ITEM 1: Apologies for absence and announcements

1. The Chair welcomed the Members and Assessors to the meeting.

2. Apologies were received from Professors R Kemp, J Peto and Dr J Doe, Dr D Benford (FSA Scientific Secretary) who was represented by Dr D Gott, and Dr H McGarry (HSE) who was represented by Ms S Thomas, Drs C Ramsay (Health Protection Scotland) and H Stemplewski (MHRA).

3. Dr B Miller was thanked for his contribution to the work of the Committee in the last 9 years as this was his last meeting before his period of appointment ends on 31st March 2015.

4. Gill Fisher, Committee Administrator, had left PHE and the Chair thanked her for the support she had provided to the Committee. Future correspondence on the Committee should be sent to the new dedicated email COC@phe.gov.uk where it would be picked up by the Secretariat and the new Administrator once appointed.

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

ITEM 2: Minutes of meeting held on 17th July 2014 (CC/MIN/2014/02)

6. Minor amendments were made to the minutes in paragraphs 9, 10, 17 post meeting note, 19, 27, 28 and 43.

ITEM 3: Matters arising

Item 3: Guidance Statement – G05: Points of Departure and Potency Estimates – 2nd Draft

7. This guidance statement had been published on the COC webpage on www.gov.uk.

Item 5: Consultation of the European Food Safety Authority on a Draft Scientific Opinion on Acrylamide in Food

8. The draft EFSA opinion was also discussed by COT on 2nd September 2014. A draft combined COC and COT response was circulated to COT Members, COC Chair and COC Secretariat on 5th September and the finalised version submitted to EFSA. The finalised response is available on the COT website: http://cot.food.gov.uk/sites/default/files/tox2014-36.pdf

Item 8.3: Draft feedback on reports provided to the CMOs' review of Alcohol Guidelines (Reserved Business)

9. The draft feedback had been revised following discussion at the last meeting and sent to DH for consideration as part of the CMOs' review of Alcohol Guidelines.

ITEM 4: Guidance statements

10. A list of the proposed COC guidance statements was tabled at the meeting for Members' reference.

Item 4a): G07 – Alternatives to the 2-year bioassay (CC/2014/15)

11. Dr Lovell declared an interest as he had worked with ECVAM on Cell Transformation Assays. It was agreed that he could fully participate in the discussion

12. This paper presented the first draft of this Guidance statement which had been provided for the July 2014 meeting but not discussed.

13. Members commented that the transgenic animal assays had been developed to be more relevant to humans by insertion of a transgene or deletion of genes. It was not clear whether improved human relevance had been achieved, and it was noted that data show that the genetic background of the transgenic mice has a role in tumourigenesis.

14. For the p53 mouse model, it was noted that, while the p53 gene was knocked out, there was no evidence that the remaining activated p53 protein was removed. Experiments on the positive control, para-cresidine, had given some unexpected results, showing there were still many unknowns in the use of a transgenic animal model, as there were in using wild-type animal models. There was a view, predominantly coming from the US, that the p53 model was not reliable for detecting non-genotoxic carcinogens. While the EU was not so clear on this, it was considered unlikely that much further data would be generated on non-genotoxic carcinogens in the p53 model given the lack of regulatory acceptance in the US.

15. The Tg.AC skin model had been shown to give positive responses with compounds that were slightly irritant. As a result, use of the model had not been widespread due to concern about the potential for positive responses in the placebo vehicle control group. In addition, a positive control group was often used with this model to confirm presence of the transgene. In the event that a poor response was seen in this group, the value of the results for the test substance was queried. Likewise many IARC Class 1 carcinogens had been shown to only respond at the maximally tolerated dose (MTD). Therefore, if a substance was not tested at the MTD, it was not clear what the results meant for human carcinogenicity, but testing at the MTD would raise questions over the physiological relevance of the results for test substance.

16. One use of transgenic animal models was when chronic toxicity studies have shown age related pathology. Use of the shorter duration administration with transgenic animals avoided any confounding by age related effects in a longer duration conventional carcinogenicity assay.

17. While transgenic animal assays had been suggested to reduce animal use, the Committee noted that this was not necessarily clear cut. Often a positive control group was used and, in addition, a high dose and a vehicle control group in the wild-type strain, resulting in a total of 7 test groups, rather than 4, or 5 with a positive control. Members were also concerned that the lower number of animals per group compared to the two year carcinogenicity study (often 25 rather than 50) would impact on sensitivity of the assay

18. A number of editorial suggestions were made in going through the document. In particular, the Committee agreed that the recommendations of the Carcinogenicity Alternative Mouse Models (CAMM) working group should not be replicated in the

COC guidance, though the reference to the review should remain. Instead, the COC should provide its own guidance on undertaking transgenic animal assays as part of the evaluation section. There were not known to be any OECD guidelines for transgenic animal assays that could be cited.

19. The *in utero* models were not considered to be useful for safety assessment, though they may be undertaken to provide information on mode of action. It was noted that *in utero* or neonatal metabolism could be very different to the adult animal. The Committee agreed that the discussion of this should be shortened.

20. The Committee also considered that the initiation promotion models were of limited use. While they could possibly be used to identify a promoter, they were not appropriate to risk assess an initiator. Therefore this section would also be shortened.

21. The timescales for preparation of sections C and D of the Guidance Statement were queried. It was noted that a number of initiatives on alternative testing paradigms (section D) were ongoing, including work by ICH. It was also noted that a number of developing methodologies and strategies (section C) were being used to support the paradigms. It was suggested that the ongoing processes and approaches sections could be presented without conclusions and then, once work was at a more appropriate stage, the COC guidance could be updated, but it was noted that this would in itself take time.

22. It was agreed that section A of the Guidance Statement should continue to be developed so it could be published and then sections C and D could follow later.

Item 4b): G03 – Hazard assessment and characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies (CC/2014/16)

23. G03 – Hazard assessment and characterisation: Conduct and Interpretation of Animal Carcinogenicity Studies is a short guidance statement providing advice on hazard identification and characterisation of chemical carcinogens. The draft guidance document referred extensively to existing references and other COC guidance statements rather than replicating information. Members agreed that this draft document was a reasonable overview of the area.

24. With reference to the conduct of carcinogenicity studies, little detailed information was provided in G03 as it was considered that this would duplicate the recent OECD guidance document published in 2012, to which some COC members contributed. For completeness, the guidance also referred to other publications such as the ICH guidance for Pharmaceuticals and US EPA guidance on carcinogen risk assessment. It was suggested that reference should also be made to the European Medicines Agency's Committee on medicinal products guidance on the conduct of carcinogenicity studies in animals. It offered detailed differences to the US guidance, which were important from an EU perspective.

25. Similarly, references were made to existing guidance on the statistical analysis of results and Members considered these to be appropriate.

26. Several editorial changes were suggested to the draft. It was suggested that reference should be made to the COM statement on thresholds of genotoxicity and

examples given of genotoxic chemicals for which a threshold may exist. The Committee agreed that the statement should be revised and could be cleared for publication by Chair's action.

ITEM 5: Third draft statement on vitamin E and the risk of prostate cancer (CC/2014/17)

27. The Committee had considered a review of the literature on Vitamin E and the risk of prostate cancer at its meeting in July 2012 and a draft statement was reviewed in September 2013 and July 2014. This work was prompted by the publication of the SELECT study[a] which found a positive association between supplementation with vitamin E and the incidence of prostate cancer. A further draft of the statement was presented for discussion at this meeting. Also, at Members' request, an executive summary and a lay summary had been drafted and were presented for comment.

28. Members had previously concluded that the placebo used in the study, soybean oil, was unsuitable because it was high in γ- and β-tocopherols in addition to containing small amounts of α-tocopherol, α-tocotrienol and β-tocotrienol, all of which were active ingredients of Vitamin E. At this meeting, Members asked whether the vehicle for the Vitamin E treated groups could also have been soybean oil. The Secretariat explained that this was difficult to ascertain as there were many different publications on this study and the information was fragmented.

29. A number of drafting comments were made on the main text of the statement, including:

- The unsuitability of the placebo should be mentioned in the Introduction.
- The first sentence of paragraph 44 did not make sense.
- It should be made clear in paragraph 89 when it was the opinion of the authors of the paper which was being quoted.
- Paragraphs 93 to 97 should be reordered.
- The end of paragraph 119 should explain that the increased risk of prostate cancer associated with vitamin E supplementation in the SELECT study may have been due to an inappropriate methodology.
- The Summary of Findings section and the Conclusions should be merged into a Conclusions section only and it should be made clear whether the Committee was considering the topic of Vitamin E and prostate cancer, or the SELECT study only.

30. Further drafting comments were made on the Executive Summary and the Lay Summary and it was considered that the brief section on the benefits of consuming vitamin E should either be in both summaries, or not be included at all. The Committee confirmed that it would be appropriate to publish both the Executive Summary to the statement and the Lay Summary.

[a] Klein EA et al. (2011). Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 306(14):1549-56.

ITEM 6: Alcohol and Cancer risk

31. Dr Clare declared an interest as a shareholder in Diageo. This was considered a personal, non-specific interest. It was agreed that Dr Clare would not participate in the discussion or conclusions of this topic.

Item 6a): Strategy paper for Calculation of Burden of Cancer attributable to Alcohol Consumption (CC/2014/18)

32. This paper presented a number of publications estimating the burden of cancer attributable to alcohol in the UK and others discussing methodological aspects of undertaking such an estimate. A number of areas had been identified for the Committee to consider for its work on burden.

33. It was queried how the Committee should proceed given the number of papers published on burden for the UK. The papers were considered to provide recent estimations and were either peer-reviewed or pieces of work commissioned by Government. Members agreed that a thorough review of the papers would be more appropriate than the COC undertaking its own estimation.

34. The literature presented used various approaches to adjust the available exposure data to address under-reporting in surveys and over-reporting of sales data (e.g. by compensating for spillage and also consumption by tourists). The in depth analysis presented by Meier et al[b] was useful in exploring the effect of different biases in the available data.

35. It was noted that the studies used for the risk estimate had changed over time, but many of the papers used similar ones. In addition, there was little variability between the population attributable fractions used. In considering the papers, it would be important to bear in mind whether there were any other data identified in the COC cancer site reviews that would be more appropriate to use. Members considered that dose-response information was important where it was available, and account should be taken of extra risk to heavy drinkers as well as the population as a whole.

36. It was noted that uncertainty should also be assessed, as few studies considered the confidence intervals in the reported values. It would be useful to evaluate the effect of different biases and assumptions. By accounting for uncertainty Members suggested that the statements of risk associated with alcohol might be different.

37. The Committee concluded that it would not undertake a calculation and therefore no subgroup would be required to discuss the topic further. Instead, the published papers presented should be re-visited and reviewed thoroughly by the Committee and the various aspects discussed in the cover paper should be tabulated for all the literature presented.

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[b] Meier PS, Meng Y, Holmes J, Baumberg B, Purshouse R, Hill-McManus D, Brennan A. Adjusting for unrecorded consumption in survey and per capita sales data: quantification of impact on gender- and age-specific alcohol-attributable fractions for oral and pharyngeal cancers in Great Britain. Alcohol and Alcoholism 2013 48(2):241-9.

Item 6b): Consumption of alcohol and female breast cancer risk (CC/2014/19)

38. As part of the proposed strategy to consider the role of alcohol consumption on cancer risk, it had been agreed that a review of the epidemiological literature published since the IARC review in 2009 on alcohol consumption and breast cancer might provide further insight into the causal association between breast cancer and alcohol consumption. This paper considered epidemiological studies (pooled/meta-analysis, cohort and case-control studies) published since the last IARC review. The cohort studies and case-control studies had been further divided into two categories: a) those examining breast cancer risk and b) those examining breast cancer mortality. Within each section, the studies were reported by geographical region (UK, European, US and others regions) and, within each region, in order of their Newcastle-Ottawa (NO) score, beginning with the highest scoring studies. It was highlighted that the relevance of the results from the case-control studies on breast cancer risk to the UK population required careful consideration. There had been an increase in the number of studies considering the relationship between alcohol and breast cancer by type of breast cancer (ductal or lobular) or receptor status since the last IARC review. The data were conflicting for tumour type to date. However, for oestrogen receptor (ER) status, there was increasing evidence to indicate a stronger association between alcohol consumption and ER-positive tumours. The paper also considered other risk factors for breast cancer.

39. A Member queried whether a case-control study was less reliable than a cohort study. It was explained that the study design was different, but case-control studies were not less reliable. Case-control studies often provide more data on exposure than cohort studies.

40. It was noted that, in 2004, the COC had evaluated all the available published research up to June 2003 on this topic and had concluded it prudent to assume that drinking alcoholic beverages may result in breast cancer in women. Research considered by the Committee had concluded that approximately 6% (3.2% to 8.8%) of breast cancers reported in the UK each year could be prevented if drinking was reduced to less than 1 unit/week. It was noted that this implied that one drink per day had a measurable effect. On the whole, the data in this paper were consistent with this. However, not all of the meta-analyses showed a positive association.

41. The Committee concluded that the views expressed in the paper on the recently available epidemiological studies on alcohol exposure and breast cancer risk were correct and that the studies added weight to the existing view that alcohol consumption is causally associated with the risk of breast cancer.

Item 6c): Consumption of alcohol and risk of colorectal cancer (CC/2014/20)

42. In 2007, IARC considered that there was sufficient evidence to conclude that cancer of the colorectum (CRC) was causally related to the consumption of alcoholic beverages and this was reaffirmed in their 2009 review. CC/2014/20 reviewed the epidemiological literature published since the 2009 review with additional data on the individual studies provided in Tables 1 to 3. The review identified one good quality meta-analysis by Fedirko et al (2010) which indicated an association between >1 drink/day and increased CRC risk. This meta-analysis included many of the studies which IARC had reviewed previously. It was noted that, among the meta- and pooled

analyses and systematic reviews, most indicated a positive association, although different factors such as heavy drinking, family history of CRC, young-onset CRC, and risk before and after food fortification with folate, were investigated. The pooled analyses by Nan et al. (2013) reported that alcohol consumption was associated with an increased risk of CRC in the pre-fortification period with folic acid but not in the post-fortification period.

43. The results from the cohort and case-control studies were generally inconsistent, with the majority of individual cohort or case-control studies showing no statistically significant positive association between alcohol consumption and CRC. The two UK case-control studies showed negative associations. It was queried as to how these inconsistent results would influence a meta-analysis of the data. Again, as was the case for other cancer sites reviewed by the Committee, Members highlighted uncertainties/limitations in the data such as the use of categorical groups and the appropriateness of the reference category. For example, the exposure categories of Park JY et al. (2009) corresponded to above one drink per day, below one drink per day or none for the analysis of type of alcohol, which was a relatively low dose cut off point. Members discussed the role played by the various polymorphisms of alcohol dehydrogenase (ADH) on CRC and how the generally accepted slow alcohol metaboliser (ADH1C*2/*2) was observed as the high risk genotype in three CRC studies. This conflicted with the generally accepted view, reported in Bongaerts et al (2011), that the fast-metabolising ADH1C*1/*1 genotype is the high-risk genotype in alcohol related diseases.

ITEM 7: Any other business

COT and COC Subgroup on synthesising epidemiological evidence

44. The COT had agreed to set up a subgroup to produce a document explaining how the Committee carried out narrative reviews of epidemiology data when data are insufficient or unsuitable for meta-analysis. It would also describe how toxicological data are integrated with the epidemiological evidence. The COT had agreed that the COC should also join the subgroup so the approach was one that both Committees agree, and two Members had been approached to participate. This work would also support the COC Guidance Statement series.

Horizon Scanning

45. It was noted that Horizon Scanning had not been presented as a formal agenda item at this meeting as it would have been normally. Members were reminded that horizon scanning was an ongoing process and if there were topics or issues that Members considered should be discussed by the COC then these could be raised with the Chair and Secretariat at any time.

ITEM 8: Date of next meeting

46. The date of the next meeting was 23rd April 2015.