Committee on
CARCINOGENICITY

CC/MIN/2015/01

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

Minutes of the meeting held at 10.30am on Thursday 23rd April 2015 at Department of Health, Skipton House, 80 London Road, Elephant and Castle, London, SE1 6LH.

Present

Chair:	Professor D Phillips	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr J Doe	
	Dr P Greaves	
	Professor R Kemp	
	Dr D Lovell	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	
	Dr R Waring	
Secretariat:	Ms F Pollitt	PHE Scientific Secretary
	Ms C Mulholland	FSA
	Miss B Gadeberg	PHE
	Dr H Garavini	PHE Toxicology Unit, Imperial College
	Mr K Okona-Mensah	PHE Toxicology Unit, Imperial College
	Dr K Vassaux	PHE Toxicology Unit, Imperial College
Assessors:		
Officials:	Dr O Sepai	PHE
Observers:	Dr M Cush	Delphic HSE Solutions Ltd

Contents		Paragraph
Item 1:	Apologies for absence and announcements	1
Item 2:	Minutes of meeting held on 13th November 2014 (CC/MIN/2014/03)	4
Item 3:	Matters arising	5
Item 4:	Request from ACNFP for advice on the novel food ingredient cycloastragenol (CC/2015/01)	8
Item 5:	Alcohol and Cancer risk	18
5.1	Consumption of alcohol and oral cavity and/or pharyngeal cancer risk (CC/2015/02)	21
5.2	Consumption of alcohol and laryngeal cancer risk (CC/2015/03)	26
5.3	Consumption of alcohol and oesophageal cancer risk (CC/2015/04)	28
5.4	Consumption of alcohol and head and neck cancer risk (CC/2015/05)	31
5.5	Bagnardi et al (2015): Alcohol consumption and site specific cancer risk: a comprehensive dose-response meta-analysis: British Journal of Cancer 112, 580-593 (CC/2015/06)	33
5.6	Burden of Cancer attributable to alcohol consumption – Further details (CC/2015/07)	38
Item 6:	Annual Report 2014 (CC/2015/08)	43
Item 7:	Any other business	44
Item 8:	Date of next meeting	45

ITEM 1: Apologies for absence and announcements

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

2. Apologies were received from Professors J Peto and K Warnakulasuriya, Dr D Benford (FSA Scientific Secretary) who was represented by Ms C Mulholland, Professor T Gant (PHE) and Drs H McGarry (HSE), C Ramsay (Health Protection Scotland) and H Stemplewski (MHRA).

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

ITEM 2: Minutes of meeting held on 13th November 2014 (CC/MIN/2014/03)

4. Minor amendments were made to the minutes in paragraphs 8, 16, and 38. The Secretariat was requested to check the values in paragraph 40 against the 2004 COC statement "Consumption of alcoholic beverages and risk of breast cancer".

ITEM 3: Matters arising

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

5. This draft guidance statement would be discussed at the next meeting.

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

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

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

7. A final draft of this statement would be ready soon, and would be discussed with Dr Rushton, prior to clearance by Chair's action.

ITEM 4: Request from ACNFP for advice on the novel food ingredient cycloastragenol (CC/2015/01)

8. The paper presented a referral from the Advisory Committee on Novel Foods and Processes (ACNFP) which requested comments on the potential carcinogenicity of a novel food application for cycloastragenol-TA65, a compound extracted from plants intended for use in food supplements.

9. The Committee discussed the genotoxicity findings and queried whether any referral had been made to the COM. The data seemed to be negative or equivocal. There appeared to be some small trends in the Ames data which was reported as equivocal, and it was suggested that, given that cycloastragenol produces metabolites, a pre-incubation test would have been more helpful. However the experiments had been done to standard and were well reported. It was noted that the criteria for the results in the Ames test were set by the applicant and according to those criteria the results were negative.

10. In addition, it was noted that, overall, the in vitro cytogenetics results were not significantly different to the historical controls. It was suggested this lack of a

significant effect was due to damage in some cultures but not others. It was queried what that damage was and whether it had been due to non-specific solubility effects. The in vivo micronucleus assay results appeared negative even where bone marrow toxicity was observed. It was noted that an intra-peritoneal route of exposure was used although intake of the compound would be oral, but this was thought to be to ensure adequate bone marrow exposure. Overall, the Committee concluded that it would be useful to look at the raw data before judging the genotoxicity results.

Post meeting note: The COM considered the genotoxicity data at its meeting on 18th June 2015, and concluded that no further genotoxicity testing was required

11. Members noted the differences in metabolism between species, especially with regard to the profile of metabolites M3 and M5 in rats compared to humans. It was queried how, with rapid absorption and metabolism, the compound could also be stated to have low bioavailability. It was noted that, although there was little parent compound present after ingestion, there were no data on metabolite concentrations or longevity.

12. With respect to the paper by Bernandes de Jesus et al (2011)[a], the Committee was concerned that the age at death of the animals was not known, the tissues had not been studied in detail, tumours had been summed in mice of different ages and it was not clear whether other organs of relevance had been examined to ascertain whether the liver tumours were primary or secondary. The study was also too small to have sufficient power to show statistical significance and, with only 4 months administration, it was not considered to be an adequate carcinogenicity study.

13. The 13 week study was considered to be sound. However, the Committee was concerned that the increase in heart weight observed in that study had been dismissed by the applicant. It was also noted that the applicant claimed a cardiotonic effect therefore an effect on the heart should not be dismissed, though it was noted that this was outside the remit of the COC.

14. It was noted that the mode of action of telomerase is to produce genetic changes by increasing repeats at the ends of DNA and it was not known whether this effect might also occur elsewhere in the DNA. It was noted that the in vivo genotoxicity tests undertaken would not necessarily pick up such effects. The possibility of cycloastragenol stopping telomeres shortening was of concern as this could increase cancer risk if the compound was stabilising damaged cells that could then go on to be tumorigenic. There was concern about whether this meant that the effect might be more significant in younger people taking cycloastragenol compared to those who are older. It was queried whether telomerase may have other effects. Evidence was required to show whether or not this was the case and what those effects might be. It was also noted that there might be potential for differences in the effect of cycloastragenol in people with tumour precursors and those without. Given the animal and genotoxicity data provided, Members would recommend a conventional two year bioassay, or other suitable model (such as a study in a transgenic strain).

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[a] Bernardes de Jesus B, Schneeberger K, Vera E, Tejera A, Harley CB and Blasco M (2011) The Telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. Aging Cell, 10, 604-621.

15. The reported biological effects of cycloastragenol could be considered to be therapeutic, even though any health claims were likely to be carefully worded as TA-65 is being marketed as a supplement, and it was queried whether there was any precedent for referral of a novel food to either MHRA or EMA.

Post meeting note: The ACNFP Secretariat confirmed that consideration of health benefits to support nutrition or health claims would be subject to separate assessment by EFSA under the relevant regulations. The role of the ACNFP was to undertake initial premarket risk assessment of a new novel food for the UK. Primarily this is a safety assessment and the Committee should advise accordingly. Potential benefits or efficacy of a product are only considered if they relate to safe use of a product, if they would mislead the consumer or be nutritionally disadvantageous compared to products they are designed to replace.

16. The Committee noted that intakes of the product would be influenced by the perceived health benefits, so people might consume more than intended and younger people might also consume more than expected to obtain the benefits sooner.

17. The Committee had reviewed the submitted data and there remained general concern about the use of cycloastragenol. The Committee recommended that the raw data from the genotoxicity tests should be further considered, and another Ames test with pre-incubation would provide more weight to determine whether a full 2 year bioassay would be required subject to advice from COM. In the absence of such data and based on that provided, the Committee would recommend a two year bioassay, or other suitable study to show a lack of effect, in a strain prone to tumourigenicity.

ITEM 5: Alcohol and Cancer risk

18. 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.

19. Dr Rushton declared that she had helped with the drafts of a number of these papers. It was agreed that this was not a conflict and Dr Rushton could participate fully in the discussion.

20. The Committee noted the significant amount of work by the PHE Toxicology Unit at Imperial College for this topic and thanked the various members of staff who had contributed.

Item 5.1: Consumption of alcohol and oral cavity and/or pharyngeal cancer risk (CC/2015/02)

21. The International Agency for Research on Cancer (IARC) had previously concluded that alcohol is causally associated with cancers of the upper aerodigestive tract (oral cavity, pharynx, larynx, and oesophagus). This paper presented a review of the available epidemiological evidence published since the last IARC review in 2009.

22. Many of the studies presented data on multiple sites within the oral cavity and pharynx but there was consistent evidence of an association with these cancer sites

(apart from the nasopharynx) and a dose-response effect. This supported and added weight to the existing conclusions.

23. It was noted that the meta-analyses would have had to consolidate disparate results, some of which would have been categorical data and, therefore, pragmatic decisions would have been made on what to adjust for and how, based on the data collected.

24. Data on polymorphisms had been presented in many of the papers on alcohol and risks at cancer sites. It was agreed that the data should be presented in a summarised form for the draft statement. It was considered important to ensure these data reflected the diversity of the UK population.

25. The Committee concluded that no consistent association was found for cancers of the oral cavity and/or pharynx with any particular type of alcohol beverage. It was noted that many studies did not take into account the human papilloma virus (HPV) status of the participants.

Item 5.2: Consumption of alcohol and laryngeal cancer risk (CC/2015/03)

26. This paper presented the evidence on alcohol and laryngeal cancer published since the last IARC review in 2009.

27. The majority of new studies were meta-analyses and these added further weight to the causal relationship between alcohol and cancer of the larynx. The association was not observed with light drinking, but the risk estimates in some of the studies for moderate and high level drinking were much higher than for some of the other cancer sites. It was noted that the combination effect with smoking was marked and also that, on cessation of alcohol consumption, it was many years before the risk returned to the level of a non-drinker.

Item 5.3: Consumption of alcohol and oesophageal cancer risk (CC/2015/04)

28. This paper presented the evidence published since 2009 on alcohol and oesophageal cancer and, where possible, evidence was given separately for oesophageal squamous cell carcinoma (SCC) and adenocarcinoma (AC).

29. The evidence added further weight to the causal association between alcohol and oesophageal SCC. A clear dose-response was observed, and effects were evident with light drinking as well as moderate and heavy drinking. There was no evidence of an association between alcohol consumption and oesophageal AC.

30. It was noted that the evidence on cessation of alcohol consumption, which had also been considered by the COC in March 2014, showed that it took a long time before risks return to the level of the non-drinker. This was clearly different to the benefits of smoking cessation where the risk starts to decrease shortly afterwards. It did indicate that it could be important to communicate with younger people about the benefits of limiting alcohol intake at a young age on subsequent cancer risk.

Item 5.4: Consumption of alcohol and head and neck cancer risk (CC/2015/05)

31. This paper presented the new evidence published since the last IARC review in 2009 on alcohol consumption and head and neck cancer risk. The studies assessed in this paper contained data which grouped a number of cancer sites together rather than analysing them on a site by site basis. The sites did not include brain and eye.

32. The Committee noted that the different studies included or excluded a number of different cancer sites, and some reported on head and neck cancers while others used the description “upper aerodigestive tract cancer”. Despite this variability, a strong association of alcohol with head and neck cancers was observed.

Item 5.5: Bagnardi et al (2015): Alcohol consumption and site specific cancer risk: a comprehensive dose-response meta-analysis: British Journal of Cancer 112, 580-593 (CC/2015/06)

33. This paper presented a meta-analysis of alcohol consumption and risk of 23 different cancers and assessed the dose-response relationship between alcohol and cancer incidence at each site.

34. This was considered a useful analysis assessing light, moderate and heavy drinking for the 23 cancer sites. It was highlighted that, in drawing up the intake categories, data from individual studies had to be considered and allocated to the most appropriate category, sometimes combining data. While this was a helpful means of assessing whether a dose-response relationship was present, the Committee advised caution in investigating meta-analysis data for a continuous dose-response relationship due to the assumptions that would have been made. In that respect, it was more appropriate to consider individual studies.

35. The use of adjusted risk estimates in preference to unadjusted relative risks from the individual studies was noted with some concern as adjustments might have been applied differently between studies, e.g. one study may have adjusted for ever smoking while another adjusted by smoking categories.

36. Overall, the conclusions in the paper were similar to the Committee’s own conclusions on the sites it had considered. In some instances there was slight discrepancy between the IARC conclusions and those of the authors, which if IARC reconsidered alcohol again, might lead to some change in its conclusions. However, the Committee did not consider that these sites were a priority for consideration, as alcohol was already established as causally associated with cancers at multiple sites, unless cancer at these sites is common.

37. It was not considered necessary to have a separate discussion of this paper in the draft statement to be produced on the Committee’s consideration, as the relevant data had been reviewed in the COC papers on the individual cancer sites.

Item 5.6: Burden of Cancer attributable to alcohol consumption – Further details (CC/2015/07)

38. This paper presented a further analysis of the papers considered by the Committee in November 2014 in paper CC/2014/18.

39. It was noted that most of the papers were in broad agreement over the proportion of each cancer which was attributable to alcohol consumption. The paper from the EPIC study did show some differences but this was likely due to the use of the hazard risk ratios from the EPIC study and use of consumption data from WHO rather than UK specific data.

40. The paper was considered useful to decide which cancer sites showed the most significant effects from alcohol consumption, but without focussing on the exact alcohol attributable fraction for each. The Committee agreed that further statistical help should be sought to determine whether the approaches used were appropriate.

41. It was queried whether the data in this paper would help inform on the effect of reducing alcohol consumption at a population level. From the evidence on cessation of alcohol consumption on cancer risk, it was likely to be a long time before risks began to decrease, however no data had been identified on the effect of reducing alcohol consumption on cancer risk. It was also noted that for cancers with a latency period, it may not be possible to reduce risk. Also, from a population perspective, the alcohol attributable fraction of cancers might increase due to the aging population and the different profile of cancers between age groups.

42. At the end of the discussion of this item, it was agreed that the Committee would discuss a draft statement at the next meeting covering the various aspects of alcohol and cancer risk discussed since September 2013.

ITEM 6: Annual Report 2014 (CC/2015/08)

43. A few suggestions for changes to the draft annual report were made, and otherwise Members were content for the document to be published.

ITEM 7: Any other business

Vacancy for COC Member with epidemiology expertise

44. The Chair informed the Committee that interviews for a new Member with epidemiology expertise were being held this week and it was anticipated that the new Member would be in post by the next meeting.

ITEM 8: Date of next meeting

45. The date of the next meeting was 9th July 2015.