CC/MIN/2014/02

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

Minutes of the meeting held at 10.30am on Thursday 17th July 2014 at Department of Health, Skipton House, Elephant and Castle, London, SE1.

Present

Chair:	Professor D Phillips	
Members:	Mr D Bodey	
	Dr G Clare	
	Dr J Doe	
	Dr P Greaves	
	Professor R Kemp	
	Dr D Lovell	
	Professor J Peto	
	Dr C Powell	
	Dr L Rushton	
	Professor H Wallace	
	Dr R Waring	
	Professor K Warnakulasuriya	
Secretariat:	Ms F Pollitt	PHE Scientific Secretary
	Ms C Mulholland	FSA
	Miss B Gadeberg	PHE
	Dr K Burnett	Imperial College PHE Toxicology Unit
	Dr K O'Leary	Imperial College PHE Toxicology Unit
Assessors:	Professor T Gant	PHE
Officials:	Dr L Kent	FSA
	Dr O Sepai	PHE
	Mrs F Hill	FSA (Items 1-6)
	Mr C Acton	DH Alcohol Policy Team (Item 8)

Contents		Paragraph
Item 1:	Apologies for absence and announcements	1
Item 2:	Minutes of meeting held on 27th March 2014 (CC/MIN/2014/1)	4
Item 3:	Matters arising	5
Item 4:	Second draft statement on vitamin E and the risk of prostate cancer (CC/2014/09)	7
Item 5:	Consultation of the European Food Safety Authority on a Draft Scientific Opinion on Acrylamide in Food (CC/2014/10)	14
Item 6:	Guidance Statement – G07: Alternatives to the 2-year bioassay – Introduction, parts a and b – First draft (CC/2014/11)	18
Item 7:	Presentation on zebrafish	19
Item 8:	Alcohol and Cancer risk	21
8.1	Consumption of alcohol and liver cancer risk (CC/2014/12)	24
8.2	Cessation of alcohol consumption and effect on liver cancer risk (CC/2014/13)	30
8.3	Draft feedback on reports provided to the CMOs' Review of Alcohol Guidelines (**Reserved Business**) (CC/2014/14)	37
Item 9:	Any other business	42
Item 10:	Date of next meeting – 13th November 2014	43

ITEM 1: Apologies for absence and announcements

1. The Chair welcomed the Members and Assessors to the meeting. A particular welcome was extended to Professor Warnakulasuriya who was attending his first COC meeting.

2. Apologies were received from Dr B Miller, Dr D Benford (FSA Scientific Secretary) who was represented by Ms C Mulholland, Drs M Roberts (Defra) and H Stemplewski (MHRA), and Messrs S Fletcher (Veterinary Medicines Directorate, Defra) and C Ramsay (Health Protection Scotland). Dr H McGarry (HSE) had been due to participate in the meeting but could not do so due to a problem with the teleconferencing facility.

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

ITEM 2: Minutes of meeting held on 27th March 2014 (CC/MIN/2014/1)

4. Minor amendments were made to the minutes in paragraphs 16 and 27.

ITEM 3: Matters arising

Item 6: Guidance Statement – G05: Points of Departure and Potency Estimates – 2nd Draft

5. This guidance statement had been amended as discussed at the previous meeting, and agreed by Chairman's action. It would be published in due course.

Reserved sections of minutes

6. It was confirmed that where agenda items are held in reserved session due to discussion of pre-publication results, the minutes of the COC's discussion would be made available once the data had been published.

ITEM 4: Second draft statement on vitamin E and the risk of prostate cancer (CC/2014/09)

7. The Committee considered a review of the literature on vitamin E and the risk of prostate cancer at their meeting in July 2012. This was prompted by the publication of the SELECT study[a] that found a positive relationship between supplementation with vitamin E and the incidence of prostate cancer. A draft statement on the topic was reviewed at the COC meeting in September 2013. This paper was a revised draft statement incorporating the comments and changes suggested at the September 2013 meeting. An updated literature search had been carried out for years 2013 and 2014 to identify any new publications since the previous draft statement was seen by the Committee and these studies were included in the paper. Members were asked to consider a new annex containing a table summarising the studies on vitamin E and risk of prostate cancer described in the statement. Three forest plots of the epidemiological studies (randomised

[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.

controlled trials, prospective cohort and case-control studies) were tabled at the meeting to illustrate the spread of the data.

8. The review was commended by Members and it was suggested that the paper should be published in the peer-review literature. Members provided a number of general comments on the current draft, including the need for an executive summary and a lay summary. It was also noted that there was a need for a clear introduction to the topic explaining why this review was undertaken.

9. Members discussed the incidence of prostate cancer and how it had increased over the last 30 years due to more screening, the aging population and greater awareness. It was noted that, despite the fact that the incidence of prostate cancer is much higher in the US, where regular screening occurs, compared to the UK, the mortality rate is the same in the two countries.

10. For the observational studies, it was not clear if the risk estimates had been adjusted for possible confounders. It was agreed that either an additional paragraph on confounders would be included in the statement or the tables would be amended to include a column stating the adjustment factors used for each risk estimate. It was noted that the uncertainties in the aetiology of prostate cancer made it difficult to accurately control for variables.

11. The tabled forest plots were discussed and it was suggested that the data on the different forms of Vitamin E be presented separately. Similarly the data on smokers and non-smokers should be presented separately. It was agreed that the forest plots were presented as illustrative diagrams and a pooled analysis would not be performed on the data.

12. The Committee suggested that the statement should clearly indicate what form of vitamin E was being referred to when the term was used. Similarly the doses used should be reported consistently, and information on the level of Vitamin E should be provided where it acts as a pro-oxidant in humans as opposed to an antioxidant. With respect to the animal studies, Members were concerned that the doses of Vitamin E used were very high, and clarity was needed on the relevance of these high doses to human exposures and what the effective dose would be in animals compared to in humans.

13. It was agreed that a revised draft statement would be brought back to the Committee at a later date.

ITEM 5: Consultation of the European Food Safety Authority on a Draft Scientific Opinion on Acrylamide in Food (CC/2014/10)

14. The European Food Safety Authority (EFSA) issued a Draft Scientific Opinion on Acrylamide in Food for public consultation on 1 July 2014. The Food Standards Agency (FSA) invited the COC and COT to submit a joint response to the consultation following discussion at the present COC meeting and September 2014 COT meetings. It was noted that the COM had previously assessed the genotoxicity of acrylamide and the EFSA conclusions were consistent with the COM statement. Also, the EFSA approach was consistent with the COC strategy for risk assessment of chemical carcinogens.

15. Members commented on the high quality and comprehensive nature of the scientific opinion and were broadly in agreement with the evaluation and conclusions reached. It was noted that there were limited epidemiological studies available compared to animal studies, but that the human data from dietary exposure did not demonstrate the risk of cancer identified in occupational and animal studies. It was suggested that this could be due to differences in metabolism between the inhalation and oral routes of exposure in humans (occupational and dietary exposure respectively). It was recommended that a detailed kinetic analysis be made between the inhalation and oral routes in humans and also between human and animal exposures to investigate further the differences in terms of susceptibility to tumours between species and following different routes of exposure.

16. The Committee agreed that the Harderian gland was an appropriate tumour to use for the BMDL derivations. Whilst not present in humans, it was well established that tumours in this gland were typically associated with genotoxic carcinogens and therefore it was difficult to exclude them from an assessment of carcinogenic potential. Members noted that it was not clear from Appendix K, why the Harderian gland had been selected as lower BMDL values were available which appeared to be equally appropriate to use. It was recommended that clarity should be sought on how the BMDL values had been selected. Comments were made about whether the use of the uncertainty factors (10 x 10) was sufficiently pragmatic.

17. Members commented that the overall conclusions on the occupational cohort studies did not accord with the IARC evaluation of acrylamide as Group 2A, probably carcinogenic in human.

Post meeting note: Further clarification on the Committee's position on the Harderian gland was sought after the meeting. The COC agreed with the EFSA assessment although, as noted by EFSA, the tumours were late onset which is not typical of a genotoxic carcinogen. Also, Harderian gland tumours were found in male mice not treated with acrylamide. In addition, comments were made about the involvement of CYP2E1 and glutathione-S-transferase in acrylamide metabolism and that the possible impact of polymorphisms of these enzymes in man had not been addressed in the review. It was also suggested that there could be more discussion about possible factors determining neurotoxicity and carcinogenicity in humans.

ITEM 6: Guidance Statement – G07: Alternatives to the 2-year bioassay – Introduction, parts a and b – First draft (CC/2014/11)

18. This paper provided a first draft statement following Members' comments on the discussion paper prepared for the November 2013 meeting. This item was not discussed, due to time constraints. Members were invited to review the paper and provide written comments by 12th September 2014.

ITEM 7: Presentation on zebrafish

19. Professor Heather Wallace gave a short presentation to the Committee on the use of Zebrafish (Danio rerio) in biomedical research. This topic had previously been raised during horizon scanning given the increased use of Zebrafish as a model in toxicological research and development. The presentation described the fish model, and the benefits of the fish: they are transparent and generate a large supply of eggs so that statistically meaningful studies are easily designed. Also, they are small in

size, easily manipulated and can be grown in 96-well or 384-well plates. The main disadvantages are that the fish lack some mammalian organs, are divergent from man on the evolutionary tree and ADME measurements are not possible as compounds are administered in the water. It was also noted that Zebrafish are prone to parasitic infections. The Zebrafish genome is sequenced and mutagenicity, transgenic and expression profiling studies are also possible. Preliminary trials have shown that they can be used to investigate toxicity endpoints - for example, there was good accord of LC50 values for 11 out of 18 chemicals from the NIH TOXNET programme. However, only general toxicity, not organ specific toxicity, can be identified. Zebrafish express some cytochrome P450s that are also found in humans. There are numerous other general uses, including in cancer biology, but in general they are considered useful for preliminary screening only.

20. The Chair thanked Professor Wallace for her interesting presentation.

ITEM 8: Alcohol and Cancer risk

21. 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.

22. Dr Rushton declared that she had helped with the first drafts of the two liver cancer documents. It was agreed that this was not a conflict and Dr Rushton could participate fully in the discussion.

23. The Chair welcomed Mr C Acton (DH Alcohol Policy Team) to the meeting.

Item 8.1: Consumption of alcohol and liver cancer risk (CC/2014/12)

24. The International Agency for Research on Cancer (IARC) has previously concluded that alcohol is causally associated with liver cancer. This paper presented a review of the available epidemiological evidence (pooled/meta-analyses, cohort and case-control studies) published since the last IARC review in 2009. The evidence presented had been evaluated using a scoring scheme to assess the quality of the studies.

25. It was noted that the majority of the studies used questionnaire based approaches for exposure assessment and there was no consistency between studies or countries as to how much alcohol was considered to be low, moderate and heavy consumption. It was noted that one UK unit is 10 millilitres or 8 grammes of alcohol.

26. The Committee discussed the biological plausibility of the apparent J- or U-shaped dose-response curve for alcohol and liver cancer. Concern was expressed that studies did not differentiate between never drinkers and former or ex-drinkers as many used a non-drinker category. This was of concern as it was not clear whether people had stopped drinking due to illness and, if they were former drinkers, how long they had abstained for. Members asked whether it was possible to investigate the differences between non-drinkers and drinkers, but while some aspects, e.g. religion, could be assessed it would be difficult to get all the necessary information. Overall, the Committee concluded that it was difficult to suggest a plausible mechanism for a U-shaped dose-response curve, there were shortcomings in the

data and it would be difficult to investigate the size of effect with the methods available.

27. The predominance of studies on Asian populations was highlighted, and the applicability of these studies to the UK population discussed. The higher incidence of liver cancer related to hepatitis in Asian countries, and that studies did not always adjust for hepatitis in the analysis, were noted. It was not clear whether this would affect relative risk estimations while it would be important in terms of absolute risk. In addition, it was noted that some of the studies were designed to investigate hepatitis rather than alcohol. The deficiency in alcohol dehydrogenase 2 (ADH2) in Asian populations was noted and it was not known what the prevalence of this deficiency is in the UK population but it was thought to be rare. It was also noted that the Asian population in the UK was not dominated by the populations studied in the literature. Finally, the difference in the types of alcohol consumed in Asia compared to types consumed in the UK, and the impurities within the alcohol, was also highlighted as limiting the applicability of the data to the UK population. The Committee noted that these limitations might not be as significant for other cancer sites.

28. For the estimation of burden, the Committee discussed how to best fit the data and whether it would be appropriate to assume a linear dose response. While data are available which show that in the UK heavy drinkers (22% of the population) consume 78% of the alcohol purchased, there was concern over focussing on the effects in heavy drinkers only due to the large number of people who consume smaller amounts of alcohol and the significant proportion of risk they could represent. It was agreed that there would need to be sensitivity analyses undertaken to show the differences between assuming a linear and a non-linear dose response. It was also suggested that comparison could be made between analyses using continuous or categorical exposure assessment to identify if there is a level above which there is an excess risk. It was unclear how the effects of drinking pattern could be assessed, especially as, for liver cancer, no studies had investigated the effect of binge drinking or the effect of having alcohol free days.

29. It was noted that it could be proposed that only studies scoring a certain number should be used for the burden estimation. For liver cancer however, it was noted that the studies focussing on the Caucasian population scored less than some of the Asian studies. In considering the scoring scheme overall, it was agreed that the Secretariat should continue to use the scoring scheme for further papers on alcohol and cancer risk.

Item 8.2: Cessation of alcohol consumption and effect on liver cancer risk (CC/2014/13)

30. At the March 2014 COC meeting, a paper on the effects of cessation of alcohol consumption on oesophageal and head and neck cancer risk was presented. It was agreed that the available studies of the effect of alcohol cessation on liver cancer risk should also be reviewed. This paper presented the available meta-analyses, and cohort and case-control studies on the effect on liver cancer risk of cessation of alcohol consumption.

31. It was noted that a number of the studies investigated special populations while the rest studied the general population. As had been found for the paper on

liver cancer risk, most of the studies were undertaken in Asia and only two European studies (Italian populations) were available. In addition, it was noted that the populations studied would change over time and the number of individuals who had stopped consuming alcohol many years ago could be much lower than those who stopped recently.

32. A Member asked whether the available data on alcohol cessation could be compared with the change in risk and relative risk following smoking cessation. It was also queried whether it had been possible to comment on the risk associated with a reduction in smoking but it was noted that this was difficult to analyse.

33. While liver cancer was rare in the UK, it was noted that the rate was increasing and there was conjecture about whether this could be due to alcohol consumption. It was noted that, in the UK, liver cancer due to alcohol is associated with cirrhosis, and it was queried whether alcohol could cause liver cancer without overt liver toxicity.

34. The Committee suspected that the apparent increase in liver cancer risk immediately after cessation of alcohol consumption was due to people who were already becoming ill, i.e. the sick-quitter phenomenon. It was considered plausible that there could be an increased risk of liver cancer due to regeneration of the liver on cessation of alcohol consumption resulting in damage or tumour promotion which had already begun prior to giving up alcohol.

35. It was estimated that it would take at least 20 years for the relative risk of liver cancer to reach the level of a non-drinker following cessation of alcohol consumption. The Committee queried whether it would be more helpful to express the risk of liver cancer after giving up in comparison to that associated with continuing to drink, rather than comparing with those who had never consumed alcohol.

36. It was suggested that big cohort studies such as the European Prospective Investigation into Cancer and Nutrition and the American Cancer Society study should be investigated to see if they could provide further information on the effects of cessation of alcohol consumption.

Item 8.3: Draft feedback on reports provided to the CMOs' Review of Alcohol Guidelines (Reserved Business) (CC/2014/14)

37. This item was discussed in reserved session as it included discussion of pre-publication research, which had been provided to the Committee on the basis that it was not disseminated further. The minutes for this item will be made available when the research is published.

ITEM 9: Any other business

42. The Committee was informed that its website had been migrated and was available at https://www.gov.uk/government/groups/committee-on-carcinogenicity-of-chemicals-in-food-consumer-products-and-the-environment-coc. Members asked whether electronic copies of the meeting papers would be available on the website for the next meeting, and it was anticipated that this would be the case.

Post meeting note: Members are able to request electronic copies of all papers (including reserved items) from the Committee Administrator.

ITEM 10: Date of next meeting

43. The date of the next meeting will be 13th November 2014 at Skipton House.

Post meeting note: This was subsequently moved to PHE Colindale.