

**DRAFT**

**CC/MIN/2007/3**

**FOR MEMBERS USE ONLY**

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

Minutes of the meeting held at 10.30am on Thursday 15 November 2007 at Department of Health, Room 102/124A, Skipton House, 80 London Road, Elephant and Castle, London SE1 6LH.

Present

Chairman: Professor D Phillips

Members: Dr C Allen  
Professor A Boobis  
Dr P Carthew  
Professor P Farmer  
Mrs R Glazebrook  
Professor D Harrison  
Ms D Howel  
Dr B Miller  
Professor R Roberts  
Professor D Shuker  
Dr N Wallis

Secretariat: Ms F Pollitt (HPA - Scientific)  
Mrs F Hill (FSA – Scientific)  
Dr L Hetherington (HPA - Minutes)  
Mr K Mistry (Acting DH - Administrative)

In Attendance: Mr J Battershill (HPA, items 1-3)  
Mr K Okona-Mensah (DH Tox Unit, item 6)  
Dr K O'Leary (DH Tox Unit, item 5)

Assessors: Mr S Samuels (PSD)  
Mr M Hosford (EA)  
Dr D Gray (HSE)

Observers: None

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## **ITEM 1: APOLOGIES FOR ABSENCE/ANNOUNCEMENTS**

1. Apologies were received from Professor P Vineis, Dr D Benford (FSA), Dr H Stemplewski (MHRA), Dr Bruno Viegas (Defra).

### Announcements

2. The Chairman welcomed Dr K O'Leary and Mr K Okona-Mensah. The Chairman congratulated Professor Farmer on his re-appointment as Chairman of the COM for a third term from 1 November 2007 to 31 October 2011. He will remain a member of COC for this period.
3. Members were reminded of the need to declare any relevant interests before discussion of items.

## **ITEM 2: MINUTES OF THE MEETING OF 12 JULY 2007 (CC/MIN/2007/02)**

4. The minutes were agreed subject to minor editorial changes.

## **ITEM 3: MATTERS ARISING**

### **3.1: Formaldehyde (oral item)**

5. Professor Harrison and Dr Carthew both declared personal, non-specific interests.
6. The COC was reminded that, at the July meeting, it had considered a recent COM statement on formaldehyde and information from its evaluation by IARC. Post meeting, Professor Boobis expressed concern about the rationale used by COM to reach the view that it was not possible to conclude that there was a threshold for systemic mutagenicity. This concern was forwarded to COM members so they could consider whether any clarification of the statement was required and a revised conclusion was subsequently agreed. In short, the COM concluded that, for occupational and environmental exposure to formaldehyde, the pattern of metabolism and distribution of formaldehyde indicated that there is likely to be a threshold for direct *in vivo* systemic mutagenicity.

### **ITEM 3.2: FOLIC ACID (ORAL ITEM)**

7. It was noted that Members had been informed by email of the Chief Medical Officer's decision to set up a specially convened subgroup of the Scientific Advisory Committee on Nutrition (SACN) to examine further two papers on the potential adverse effects of folic acid on the risk of colorectal cancer. Further, Members were informed that Professor Phillips has been asked to sit on the subgroup. Professor Boobis was also asked but was unable to attend. A meeting would be held in January.
8. A Member repeated his concern that fortification of bread would mean supplementing the diet of all the population, not just the target group and that a study by Cole et al (2007) had shown an excess of prostate cancer cases in

the folic acid group compared to controls. He suggested that it would be preferable to await publication of a study by Muir before a final decision was taken. However, Members were reminded that the proposal by the SACN aimed to increase low level intakes of folate while not increasing high level intakes. The Chairman undertook to make clear the Committee's reservations at the meeting in January and asked for any further comments to be submitted to the secretariat as soon as possible.

#### **ITEM 4: DRAFT WORKING PAPER ON CHLORINATED DRINKING WATER AND CANCER (CC/07/19)**

9. The Committee was reminded that it discussed 13 new studies on chlorinated drinking water and cancer at the last meeting. A short working paper had now been drafted to update the 1999 statement on chlorinated drinking water and cancer. The working paper followed the style of the earlier statement.

10. Members were informed that the Drinking Water Inspectorate (DWI) had suggested that the draft working paper should state that disinfection of drinking water is fundamental to preventing the spread of waterborne disease and the Committee suggested that cholera was added as an example. DWI had also commented that the concentrations of the trihalomethanes should be expressed as "up to 100µg/l." The Committee asked the secretariat to enquire why bromoform was found in chlorinated drinking water.

11. Members considered each of the 13 new studies again and made a number of comments. They noted that none of the studies was carried out in the UK and that conditions of chlorination may differ in other countries. They asked that the odds ratios and confidence limits be included in the working paper. It was suggested that general points to be discussed included the sex differences in some findings, biological plausibility and publication bias.

12. Members concluded that any association between cancer and exposure to chlorination byproducts is unlikely to be large.

13. The redrafted working paper will be cleared by Chairman's action and the final agreed statement published on the COC website.

#### **ITEM 5: FURTHER CONSIDERATION OF THE MOE APPROACH (CC/07/14)**

14. Professor A Boobis declared a non-personal, specific interest and Dr P Carthew declared a personal, non-specific interest.

15. Members were reminded that, at the November 2006 and July 2007 COC meetings, they had supported an extension of the use of the Margin of Exposure (MOE) approach for prioritisation and communication of risks and broadly agreed that this could be achieved using a banding approach. To date, the Committee has discussed worked examples from a number of publications on food-borne genotoxic carcinogens. The HPA and EA are currently considering whether the MOE approach could be used in the soil contamination area, as an alternative approach to QRA. The Committee was

now asked to advise on certain aspects of the methodology used, including derivation of BMDL10 values, illustrated by the application of the MOE approach to three genotoxic soil contaminants, hexavalent chromium, 1,2-dichloroethane and benzo[a]pyrene. The paper demonstrated the MOE approach by applying it to these environmental genotoxic contaminants to take Members through the derivation procedure and to illustrate the use of the agreed risk communication 'bands'. Estimates of exposure from food, drinking water and air were taken from the literature for illustrative purposes.

16. Members congratulated the secretariat on the paper. A Member noted that toxicological studies are generally based on four data points only and that this number of points is insufficient to carry out a good test of fit. The answer is likely to be averaged to over-fitted models. Ideally, toxicological studies should have 7 to 8 data points for this purpose. Members commented that fewer animals could be used over a greater number of data points for a known carcinogen but that this approach would be unsuitable if the aim of the study was to determine whether a chemical was carcinogenic or not.

17. Members considered that it is better to use the BMDL for a chemical in an MOE assessment than the NOAEL. Members pointed out an error in paragraph 2 of the paper. The goodness of fit tests whether or not predictions differ from the observed data, not whether or not an observed frequency distribution differs from a theoretical distribution, as stated.

18. Members considered that, when it came to deciding which model to use for deriving a BMD, all the options presented in paragraph 4 of CC/07/14 were plausible. It was suggested that if the range of results varied by less than a factor of two, it did not matter which model was used. Results with a large confidence interval should, however, be rejected. It was recommended that the COC should review ongoing work on model averaging when published.

19. A member asked which endpoint should be used to generate the BMDL when a chemical produced tumours at multiple sites. It was noted that there was little site concordance between animals and humans for genotoxic carcinogens and therefore ideally all relevant animal carcinogenicity data would be used.

20. In response to the questions in paragraph 21, Members agreed that the current exercise has helped address the feasibility of banding MOE values, although it should be borne in mind that the MOE banding system is arbitrary. They supported extending the use of the MOE and banding approach to other environmental genotoxic carcinogens but, for soil contaminants, commented that the time of exposure should be considered eg lifetime or short-term. It would be appropriate to state the range and distribution of the data, identify outliers, and state a consensus risk phrase to describe the entire data set (eg if 9/10 results are in one range, this should be used).

## **ITEM 6: NON-HODGKIN'S LYMPHOMA**

#### **ITEM 6.1: PAPER BY VINEIS ET AL (2007) ON “EXPOSURE TO SOLVENTS AND RISK OF NON-HODGKIN’S LYMPHOMA: CLUES ON PUTATIVE MECHANISMS” (CC/07/16)**

21. At the last meeting, Members asked to see the above mentioned paper. The paper had been excluded from the review because it deals with mechanisms rather than simple associations between chemical exposure and NHL. The paper follows on from a previous study which showed an increased risk of NHL associated with exposure to benzene, xylene and toluene and examines the hypothesis that this effect is related to the chemicals’ immunotoxicity by analysing the interaction with a previous history of autoimmune disease. A significant increase in NHL was found among individuals with high-level exposure to benzene and a positive family history of malignant haematologic neoplasms.

22. Members commented that the majority of the data presented in the paper demonstrated no association between benzene and NHL and, although possible mechanisms for the induction of NHL were suggested, the paper did not advance knowledge of NHL induction in the general population. Members noted that the paper identifies a subset of individuals who may be at risk.

#### **ITEM 6.2: DRAFT WORKING PAPER (CC/07/15)**

23. Members requested minor editorial amendments to the draft working paper.

#### **ITEM 7: HORIZON SCANNING EXERCISE 2007 (CC/07/13)**

24. Members noted the suggested priorities set out in the paper and supported further work in the following areas.

Carcinogenicity of mixtures Members asked for clarification about what aspects would be considered under the topic of carcinogenicity of mixtures. It was noted that many groups were addressing this area. It was suggested that, initially, the committee should address chemicals acting by the same mechanism eg the recent NIEHS study on dioxins.

Breast cancer Members considered the review by Green Brody et al (2007) and did not consider that further work was required on exogenous chemicals and breast cancer. A member proposed that it would be useful to review the most recent data on how oestrogens cause cancer but this was not generally supported.

Human relevance framework/Mode of action Members agreed with this proposal and considered that more work on the Human Relevancy Framework could aid identification of areas of importance in cancer research.

Proteomics A further review was supported. It was noted that many new papers had been published on biomarkers.

Mutational spectra It was considered that this area should be subject to a joint review with the COM.

Members also asked to see the paper by Pyatt et al (2007).

25. Members also made a number of suggestions for further work. One member suggested that it would be interesting to review the role of endogenous carcinogens in human cancer with a view to estimating the risk from these chemicals, if possible. Another suggested the area of stomach cancer and its etiology, with a view to assessing why the incidence had decreased. However, these proposals were not generally supported.

## **ITEM 8: PAPERS FOR INFORMATION**

### **8.1 QSAR predictive models for carcinogens (CC/07/17)**

26. Two papers have recently been published on using QSAR to predict carcinogenicity. The first paper, by Valerio et al (2007), was sent to Members but it was not possible to distribute the second paper, by Benigni et al (2007), at this meeting for copyright reasons. CC/07/17 provided a short summary.

27. Members considered that it would be useful to review the final results of the REACH project when this had been published and then to decide whether to undertake a review of QSAR for prediction of carcinogenicity.

### **8.2 Website links to information papers (CC/07/20)**

28. Members were informed that this paper contained the website links to the report of the first part of the HSE project on 'The burden of occupational cancer in Great Britain' and to the FSA Chief Scientist's first report.

## **ITEM 9: ANY OTHER BUSINESS**

29. There was none.

## **ITEM 10: DATES OF MEETINGS IN 2008**

30. 10 April, 17 July and 20 November.