

**DRAFT**

**CC/MIN/2007/2**

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

Minutes of the meeting held at 10.30am on Thursday 12 July 2007 at Royal Institute of Public Health and Hygiene, 28 Portland Place, London W1B 1DE.

Present

Chairman: Professor D Phillips

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

Secretariat: Ms F Pollitt (Scientific - HPA)  
Dr D Benford (Scientific – FSA)  
Mr J Battershill (HPA)

In Attendance: Dr K Burnett (DH Tox Unit, items 5 and 8)  
Dr P Edwards (HPA, item 3.2)  
Dr L Hetherington (HPA, minutes)  
Dr P Marsden (DWI, item 4)  
Dr K O’Leary (DH Tox Unit, minutes)  
Mr K Okona-Mensah (DH Tox Unit, item 6)  
Ms M Singh (FSA, item 3.1)

Assessors: Dr S Dyer (DH)  
Dr D Gray (HSE)  
Mr Mark Hosford (EA)  
Dr Scott Samuels (PSD)

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

1. Apologies for absence were received from Professor R Roberts, Dr C Allen, Dr B Viegas and Dr H Stemplewski (MHRA).

### Announcements

2. The Chairman welcomed Dr K O'Leary, Dr K Burnett, Mr K Okona-Mensah, Dr L Hetherington, Dr P Edwards, Dr M Singh and Dr P Marsden to the meeting.
3. Members were reminded of the need to declare any relevant interests before discussion of items.

## **ITEM 2: MINUTES OF THE MEETING OF 1 March 2007 (CC/MIN/2007/01)**

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

## **ITEM 3: MATTERS ARISING NOT COVERED BY LATER AGENDA ITEMS**

### **Item 3.1: Folic acid (CC/07/13)**

5. Dr Carthew declared a personal, specific interest and did not participate in the discussion.
6. The committee had requested that this issue was discussed further. CC/07/13 contained recent publications on folic acid, including two editorials from the British Medical Journal and two further papers. An abstract of a randomised clinical trial with folic acid supplements for the prevention of colorectal adenomas had been seen by the committee when it considered this topic last year; the full paper had now been published (Cole et al, 2007). A paper by Murtaugh et al (2007) reported a study on dietary intake of folate and co-factors in folate metabolism. Members were asked to keep in mind in the discussion the distinction between administration of folic acid by supplements and administration in the diet, because the toxicokinetics in each case are likely to be different. It was also noted that mandatory fortification of food with folic acid had been introduced in the US while the Cole et al study was in progress. Following the introduction of mandatory fortification, voluntary fortification had continued without any controls on permitted levels. Thus, total intake of folic acid would have exceeded the guidance level for upper intake of 1 mg/day recommended in the UK by the Expert Group on Vitamins and Minerals (EVM).
7. The committee was reminded of its recommendation at its meeting in July 2006 that there should be a precautionary approach in considering mandatory fortification of flour with folic acid because of concern about possible deleterious effects of high folic acid intake. Subsequently, SACN had asked for further clarification of this advice and the Chairman had agreed that aiming to increase low level intakes whilst ensuring that high level intakes do not increase is consistent with a precautionary approach. As a result, the SACN concluded that mandatory fortification should only be introduced if it is

accompanied by action to reduce folic acid intakes from voluntarily fortified foods to ensure that the numbers of people with intakes above the EVM's upper intake level do not exceed current levels and there is no substantial increase in mean intakes or in the folate status of the UK population. In May 2007, the FSA Board accepted the advice of the SACN that mandatory fortification of a food with folic acid, with controls on voluntary fortification and guidance on use of supplements, should be recommended to UK health ministers. This combined approach, of mandatory fortification with limits on voluntary fortification, would deliver a significant reduction in NTD affected pregnancies without increasing the number of individuals with intakes of folic acid above recommended upper levels compared to the current situation. The approach should also have the additional benefit of reducing the number of people with folate intakes below the Recommended Nutrient Intake.

8. The committee noted that the study by Cole et al (2007) had failed to show any evidence that folic acid supplementation protects against colorectal cancer but that, in this study, there was an excess of prostate cancer cases in the folic acid group compared to controls (7.3% vs. 2.8%;  $p=0.01$ ). It was suggested that this might be due to promotion of pre-neoplastic lesions to neoplasms. Members were reminded that the study had not been designed to investigate the effect of folic acid supplementation on prostate cancer risk and that the authors of the study had themselves commented that this could be a spurious association. It was also noted that there may have been a differential rate of PSA testing between the two groups. The committee was reminded that, according to the SACN report, there was no clear change in the incidence of prostate cancer following mandatory fortification in the US. The committee discussed whether the European Prospective Investigation of Cancer (EPIC) study might provide further information on folic acid and prostate cancer but was informed that this was unlikely as the dose ranges in the EPIC study would probably be too narrow. Members also asked the secretariat to check whether any other studies had investigated the potential association between folic acid intake and prostate cancer risk.

9. In response to a question about whether people with coeliac disease would ingest sufficient folic acid if fortification was limited to wheat flour or bread, Members were reminded that the proposal was not to stop voluntary fortification but to reduce the high level in some foods. Also, supplements would still be available.

10. The committee concluded that, on balance, it was content with the proposals recommended by the FSA Board which includes monitoring of the folic acid intakes and status of the UK population and postulated risks, including cancer incidence, and a review of the data on the benefits and possible risks 5 years after introduction of mandatory fortification. Members asked to be informed of the outcome of the 5 year review.

### **Item 3.2: Revision of OECD test guidelines 451, 452 and 453 for chronic toxicity and carcinogenicity (oral item)**

11. Members were reminded that they were asked by e-mail on 15 May for their opinion on the key issues raised in the revision of these Test Guidelines and the draft UK response, and that the deadline for comments was 12 July 2007. Any members still wishing to comment were asked to contact Dr Edwards during the COC meeting.

#### **ITEM 4: EPIDEMIOLOGICAL STUDIES OF CHLORINATED DRINKING WATER AND CANCER (CC/07/11)**

12. The COC has reviewed the available data on chlorinated drinking water and cancer on a number of occasions and the most recent COC statement was published in 1999. Further studies have continued to be published and the COC was asked to consider new epidemiological studies. These comprised:

- 8 studies on bladder cancer, comprising two new studies on cancer incidence, one meta-analysis and two pooled analyses, two studies on micronuclei in urinary bladder cells, and one study on cancer mortality (which also investigated other cancer types). Seven of these studies were positive (three in men only); four of them, including both pooled analyses and the meta-analysis, were by the same authors.
- 2 studies on colorectal cancer, comprising one case-control study which was positive for colon cancer in men only but not for rectal cancer risk, and the mortality study above which was not positive for either.
- 2 papers on a case-control study on childhood acute lymphocytic leukaemia (ALL). The parent study showed no statistically significant increased risk but a subset of cases examined for polymorphisms in enzymes involved in the metabolism of trihalomethanes (THMs) gave some positive responses.
- 2 studies on leukaemia in adults. One showed an increased risk for chronic myelogenous leukaemia (CML) but significantly decreased risks for other leukaemias; the mortality study was not positive for any type.
- Two studies on brain cancer. One showed a positive association in men but not in women, the mortality study was not positive.
- Two studies on pancreatic cancer, neither of which showed an increased risk.

13. The committee considered that the information in Annex B to CC/07/11 about the extent to which the studies had controlled for confounders such as social status and smoking provided insufficient information on this point. It was not clear if the same disinfection byproducts (DBPs) were under study in all cases, neither was there any information on the number of comparisons carried out in each study, which might influence the number of positive associations reported. In 1999, the committee statement mentioned the

difficulty of obtaining adequate exposure assessment. Members reiterated this point and commented that different methods of exposure assessment were used in different studies, which made comparison difficult. For example, it was not clear that the same DBPs were studied in all cases and the studies used different exposure ranges. However, it was pointed out that if the exposure assessment had been completely inadequate, a study would be less likely to report an increased relative risk. The committee was informed that while there are good data on trihalomethane (THM) concentrations in drinking water from 1990 onwards, information on concentrations prior to this date would be held by individual authorities, and that there are no stored water samples which could be used for historical analysis. There are no publicly available data for other countries.

14. Members considered that the retrospective cohort study by Vinceti et al (2004) was of poor quality. The study by Cantor et al (1999) appeared to be of good quality and reported an increased risk of brain cancer in men. However, it was not clear why this relationship should be sex-specific. In the studies on bladder cancer, there was limited evidence of a dose/response relationship. However, there was a possibility of residual confounding and it was questionable whether the association was biologically plausible given the low exposures. It was considered that there was limited evidence for an association with bladder cancer, but it was difficult to be certain because of the small relative risks and the problems with exposure assessment and confounding described above. In conclusion, the committee considered that any association between cancer and exposure to chlorinated by-products would be small. However, efforts to minimise exposure to CBPs should continue.

15. A draft update statement will be presented to Members for consideration at the next meeting.

#### **ITEM 5: TOXICOGENOMICS: A SELECTIVE UPDATE OF THE LITERATURE SINCE 2004 (CC/07/12)**

16. This paper was prepared for COC following a review of the literature, published from 2005 until the present, which utilised gene expression profiling methods to investigate chemically induced carcinogenesis. Members were informed that a large number of papers was retrieved, many of which appeared in isolation (i.e. the only paper of its type in the period reviewed) and, therefore, the selection of papers for review was intended to group papers together and enable more generalised conclusions to be made. The largest group of papers retrieved compared the effects of genotoxic carcinogens to non-genotoxic carcinogens, or carcinogens to non-carcinogens. Members were informed that, although many of the papers were apparently robust, containing a large amount of relevant data, including the identification of signature genes and fingerprints, it was difficult to compare them to arrive at overall definitive conclusions. Mechanistic investigations also provided large data sets which are likely to contribute to mode of action evaluations. Members were informed that, as methodologies appeared to vary across studies (i.e. microarray, statistical and analytical methods), it was again not possible to readily compare one paper with another. Furthermore,

in discussing results, it was not always clear why the authors of papers had focussed on certain changes in gene expression and ignored others which are more significantly altered.

17. The committee commented that toxicogenomics is a difficult and emerging area. Studies tended to be heterogeneous and no consensus had emerged as yet. Members considered that the studies varied in terms of cell lines and methods used, and concentrations of test compounds, and many of the studies relate to levels of gene expression and not mechanistic or biological effects. It was noted that pathway analysis software packages tended to provide many solutions but these may be based on changes in a very small number of genes. Looking at pathways and networks may be more productive than studying changes in individual genes. Members concluded that the results of studies should be considered as part of the weight of evidence for a chemical and that it would be useful to include them in the evaluation of a chemical by the COC, although it was probably too early for toxicogenomic data to impact on the assessment of carcinogenicity. It would also be useful to see good overview papers as they were published, e.g. interlaboratory comparisons and comparisons of genotoxic and non-genotoxic chemicals.

18. Members agreed that the COC statement should be updated in the light of the information presented, particularly as the previous statement was based on a workshop discussion. The Committee asked to be kept informed of developments in toxicogenomics by means of mini reviews of generic issues rather than general overviews.

#### **ITEM 6: NON-HODGKIN'S LYMPHOMA – OVERVIEW PAPER (CC/07/07)**

19. The COC asked for a review of the epidemiological data on the possible chemical aetiology of Non-Hodgkin's Lymphoma (NHL) in view of the increasing incidence of this neoplasm. CC/077 provided a general overview of the available studies published in the last 10 years. It includes a general summary of incidence rates and reported trends (temporal and geographical), and summarises the non-chemical aetiology of NHL. The final section focused on possible chemical risk factors and comprised a detailed review of studies published from 1 January 1997 which report on the possible relationship between NHL and certain occupations and chemical risk factors.

20. The committee was reminded that, among the chemicals cited in this paper, it had reviewed the possible NHL risk associated with occupational exposure to the organic solvents tetrachloroethylene and trichloroethylene (TCE) in 1996. The committee was unable to draw any conclusions based on the available evidence. The Committee also considered the health effects associated with exposure to tetrachlorodibenzo-*p*-dioxin (TCDD) in 2001 and concluded that TCDD should be regarded as a probable human carcinogen on the basis of all the available data. However, it also commented that any increased risk of cancer at background levels of exposure is likely to be extremely small and not detectable by current epidemiological methods.

21. The paper concluded that, overall, the quality of many studies was limited for a number of reasons and that the available data do not provide strong support for a causal role for any of the chemicals studied.

22. Members considered that there were issues relating to changes in diagnosis and classification in recent years, e.g. cause of death was more frequently being given as malignancy rather than infection. Nevertheless, death certificates were an unreliable source of information on cause of death. In addition, there had been changes in the categorisation of leukaemias and lymphomas which would impact on incidence rates. The committee was informed that animal lymphomas are not good models for human lymphomas although there was some evidence of similar pathways. It could not be assumed that, if a chemical caused lymphomas in mice, it would do so in humans. The committee noted the decreasing trend in death rates with NHL given in the CRUK (2007) paper. No explanation was given in the paper and the committee considered that the trend could not be attributed to changes in diagnostic practice.

23. The Committee agreed that major causes of NHL were cytomegalovirus and Epstein-Barr Virus. Re paragraph 45 of the covering paper, Members considered that there was weak or conflicting evidence for an association with smoking, and with electromagnetic fields.

24. From the epidemiological studies presented, Members noted a good dose-response relationship between NHL and occupational exposure to polychlorinated biphenyls (PCBs) and referred to a new study in Cancer Research by Engel et al on PCB concentrations in peripheral blood and NHL. The committee agreed that the data on PCBs should be considered in more detail, preferably in the form of a meta-analysis or pooled analysis, although an association with PCBs would not explain the trends in incidence. The committee was informed that butadiene had recently been classified in Group 1 by IARC on the basis of human data on chronic lymphocytic leukaemias and NHL. Apart from PCBs and butadiene, there was no strong evidence for an association between exposure to any chemical and NHL and no evidence that chemicals were responsible for the reported trend in incidence. The committee was informed of a new study on benzene and NHL by Vineis et al in Cancer Epidemiology Biomarkers & Prevention and asked to see this. It was noted that there were a number of good reviews on organic solvents but they came to contradictory conclusions. There had been suggestions in the past that NHL may be associated with exposure to hair dyes. The committee was informed that the EU Scientific Committee for Cosmetics was currently reviewing ingredients of hair dyes. In many cases supporting evidence was not being provided by Industry and it was likely, therefore, that the composition of these products would change in the future.

#### **ITEM 7: FURTHER CONSIDERATION OF THE MOE APPROACH FOR COMMUNICATING THE RISKS OF EXPOSURE TO GENOTOXIC CARCINOGENS (CC/07/08)**

25. Dr Carthew declared a personal, non-specific interest.

26. At a previous meeting, Members broadly agreed that the Margin of Exposure (MOE) approach might be used to aid risk managers to prioritise the risks of genotoxic carcinogens and to communicate those risks to the public. CC/07/08 tried to advance the idea of banding of MOEs and that each band is associated with a certain description of the potential risk to health and makes some suggestions for these descriptions. The Committee was asked for its views on these suggestions.

27. Some Members considered that it was not the role of the COC to advise on risk communication but, in general, it was considered useful for the committee to express an opinion on this issue. Members recalled that the MOE was the ratio of human exposure to a chemical and the lower confidence limit of the Benchmark Dose corresponding to a Benchmark Response of 10% tumour incidence above the control incidence (BMDL10). It was noted that the EU Scientific Committee on Food (SCF) and the WHO/FAO Joint Expert Committee on Food Additives (JECFA) considered a MOE of less than 10,000 to be of concern and above 10,000 to be of low concern. Reservations were expressed about using an additional MOE banding value of 1 million but it was concluded that this would be useful for risk communication purposes. It was suggested that it would be useful to incorporate examples for each risk category and to carry out studies to assess whether use of the bands improved risk communication with the public.

28. The committee was reminded that the MOE approach was a hazard ranking tool and so the word "risk" should not be used in the description of the bands. In conclusion, the consensus view was that the suggestion in 5B in CC/07/08 could be adapted so that the bands were termed: "May be a concern", "Unlikely to be a concern", and "Highly unlikely to be a concern". The existing language describing the margin of protection could be used for additional explanation.

#### **ITEM 8: FORMALDEHYDE: AN UPDATE ON THE CURRENT ASSESSMENT OF CARCINOGENICITY (CC/07/09)**

29. Professor Harrison and Dr Carthew both declared personal, non-specific interests.

30. This item follows on from the horizon scanning exercise last year when the committee discussed a published paper which argued against the recent IARC conclusion of "strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde". CC/07/09 presented the conclusions of the review of systemic formaldehyde mutagenicity at the last COM meeting. In view of the COM advice, it appeared unlikely that formaldehyde would induce leukaemia by direct systemic mutagenicity.

31. It was noted that the COM considered that it was not possible to draw a conclusion as to whether there was a threshold for *in vivo* systemic mutagenicity. A key point considered was that inhalation exposure to exogenous formaldehyde would have no effect on the endogenous concentration of formaldehyde. Members therefore questioned how IARC

had concluded that there was a causal association between leukaemia and occupational exposure to formaldehyde, particularly in view of the metabolic data in the IARC summary.

32. The Committee noted that it had nothing to add to the data or conclusions in the IARC monograph on formaldehyde and, therefore, decided that it did not wish to review the epidemiological evidence in detail.

**ITEM 9: PAPER FOR INFORMATION: REVISED CODE OF CONDUCT FOR OBSERVERS (CC/07/10)**

33. The Code of Conduct has been revised and was provided to Members for information.

**ITEM 10: ANY OTHER BUSINESS**

34. There was none.

**ITEM 11: DATE OF NEXT MEETING**

35. 15 November 2007.