

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

Minutes of the meeting held at 10.30am on Thursday 2nd April 2009 at
Department of Health, Room 136B, 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
Dr P Greaves
Dr D Lovell
Dr B Miller
Dr C Powell
Prof P Vineis
Dr N Wallis
Dr L Wright

Co-opted member: Dr D Harrison

HPA Secretariat: Ms F Pollitt (Scientific Secretary)
Ms S Kennedy (Administrative Secretary)
Dr D Mason (Minutes)

FSA Secretariat: Dr D Benford (Scientific Secretary)

In Attendance: Mr J Battershill (HPA)
Dr K Burnett (DH Tox Unit, item 6)
Dr R Clarke (Oxford University, item 5)
Dr L Hetherington (HPA)
Mr K Mistry (DH)
Dr K O'Leary (DH Tox Unit, item 4)
Ms M Singh (FSA, item 5)
Dr A Tedstone (FSA, item 5)

Assessors: Mr A Browning (VMD)
Dr D Gray (HSE)
Mr M Hosford (EA)
Mr S Samuels (PSD)
Mr D Shillaker (PSD)
Dr H Stemplewski (MHRA)

Observers: Ms M Morrey (HPA)

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ITEM 1: Apologies for Absence & Announcements

1. Apologies were received from Professor P Farmer and Mrs R Glazebrook from the Committee and Mr H Brunt (NPHS Wales).

Announcements

2. The Chairman welcomed Dr P Greaves, Dr D Lovell, Dr C Powell and Dr L Wright to the Committee. He also noted that it had not been possible to appoint a suitable replacement for Prof D Harrison; therefore he has agreed to remain on the Committee for an additional term of service. The new Members were invited to introduce themselves.

3. Mr J Battershill, Dr L Hetherington, Dr K Burnett, and Dr K O'Leary were welcomed to the meeting. It was explained that Dr R Clarke of Oxford University would be attending to present data on an epidemiological meta-analysis of folic acid related cancer risk, and that Dr A Tedstone and Ms M Singh from the FSA's Scientific Advisory Committee on Nutrition (SACN) Secretariat would be in attendance for this item. The Chairman also welcomed Ms M Morrey, the new Head of the HPA's Chemical Hazards and Poisons Division, which provides the HPA COC Secretariat.

4. The Chairman explained that the meeting would be followed by an Interdepartmental Group on Health Risks from Chemicals (IGHRC) workshop on "Descriptive vs. Quantitative Risk Assessment of Genotoxic Carcinogens". Members not already participating in this meeting were encouraged to attend.

5. Members were reminded of the need to declare any relevant interests before discussion of items.

ITEM 2: Minutes of meeting held on 20 November 2008 (CC/MIN/08/3)

6. Members noted that Prof Roberts and Prof Shuker were both incorrectly referred to as Dr in paragraph 2. In Item 4, it was considered appropriate to state the time period covered in the study by Zambon *et al.*, rather than just the publication date; since the exposures at that time may not be equivalent to current exposures. With these revisions, the minutes were agreed to be an accurate record of the meeting on 20 November 2008.

ITEM 3: Matters arising not covered by later agenda items

7. The Chairman explained that the Update Statement on the Review of Cancer Incidence near Municipal Solid Waste Incinerators (COC/09/S2) had been finalised and would be posted on the website imminently.

ITEM 4: OECD Guidance Document for the performance of chronic toxicity and carcinogenicity studies. Chapter 3.6: Investigations including Histopathological Guidance (CC/09/3)

8. The Organisation for Economic Cooperation and Development (OECD) is currently developing a guidance document for the performance of chronic toxicity and carcinogenicity studies, to support Test Guidelines (TG)

9. It was explained that this first draft of the Chapter had been developed from existing OECD Guidance (GD 35), using Society of Toxicologic Pathology Guidance documents, standard texts and published literature. The UK was currently recommending that the new Guidance Document be drafted as a stand alone document that replaces the previous OECD guidance. Members agreed with this approach, expressing concern that unless all or part of the previous guidance was withdrawn, there could be confusion over those aspects of the new guidance that supersede those of the previous guidance. A Member questioned the relevance of section 3.6.1 in this part of the guidance document as it is more related to aspects of design. Members were informed that this section had been included to draw histopathologists' attention to aspects of study design, such as allocation, randomisation, study power and animal welfare. Members agreed that this section was important but it was considered that it should be moved further down the chapter and a more general introduction should be included at the start. The Secretariat explained that study design would be covered in a chapter elsewhere in the document. Members considered that there should be a reference to this chapter within the histopathology text. Members asked to see the sections on study design and animal welfare, when available.

10. Members offered to provide recent publications which would be more appropriate references for some parts of the document. It was also recommended that a section on ophthalmoscopy be included in the chapter.

ITEM 5: Folic acid and cancer risk – Presentation by Dr Robert Clarke(CC/09/4) (Reserved Business)

11. Dr P Carthew declared a personal specific interest because his employer manufactures food products that are fortified with folic acid. It was agreed that he could remain in the room, but would neither participate in the discussion nor in formulating conclusions.

12. The Scientific Advisory Committee on Nutrition (SACN) had been asked to advise the FSA Board on the mandatory fortification of flour with folic acid in order to improve the folate status of women most at risk of neural tube defect affected pregnancies. As part of this assessment, in 2006, the COC was asked by SACN for advice on the cancer risk of folic acid. Subsequently, SACN recommended that mandatory fortification should be introduced into the UK but with the proviso that it should be accompanied by controls on voluntary fortification, guidance on supplement use, measures for careful monitoring of emerging evidence on any adverse effects and a review after 5 years. The COC discussed additional evidence on the cancer risk of folic acid in 2007 and concluded that: *“on balance, it was content with the proposals regarding mandatory fortification recommended by the FSA Board which includes monitoring of the folic acid intakes and status of the UK population*

13. Subsequently the Chief Medical Officer (CMO) requested further expert advice on the potential adverse effects of folic acid on colo-rectal cancer (CRC) risk. An expert working group, which included two COC members, was set up to consider this further. The working group was presented with pre-publication data from a consortium of researchers conducting clinical trials on B-vitamins. The COC Chairman had asked Dr Clarke, the consortium co-ordinator, if the COC could be given an opportunity to consider these data ahead of publication and, Dr Clarke had agreed to provide the data to the Committee as pre-publication information. The presentation and discussion were therefore taken as reserved business.

14. [The minutes of the discussion will be published when the work has been published in the scientific press]

ITEM 6: First draft statement on the assessment of the carcinogenicity of chemical mixtures (CC/09/2)

15. Members were presented with a draft statement that drew together the discussions on the carcinogenicity of mixtures from previous meetings. It was noted that few conclusions had been reached in those discussions, and that this had hindered the drafting of the statement. Members were asked to provide further thoughts on the assessment of mixtures; particularly whether conclusions can be drawn from mechanistic studies or whether interactions can only really be investigated using carcinogenicity studies performed to established guidelines. The Chairman emphasised that the Committee must give some guidance on the principles and feasibility of evaluating the effects of mixtures of carcinogens. Since time was limited in the meeting, Members were encouraged to send comments by e-mail.

16. It was considered important to discuss whether there are appropriate test methods available and to discuss further the concept of dose additivity. It was suggested that it may not be possible to demonstrate dose additivity for the carcinogenic response since toxicokinetics and metabolism will affect the dose response, and may be subject to interactions that are independent of those that occur at the site of action. The dioxins and dioxin-like compounds were noted as a good example of where the toxicokinetics and metabolism are unlikely to greatly influence the interaction; however, the polycyclic aromatic hydrocarbons (PAHs) were cited as an example where potency equivalence factors are an oversimplification of the interactions.

17. Members considered that the document would be improved if structured with sub-headings. The document should discuss the difference between concomitant exposures to more than one chemical in a mixture and the interaction between exposures to more than one chemical but not necessarily at the same time. The International Agency for Research on Cancer (IARC) publication on complex mixtures and cancer risk^a was cited which states that “Even when some agents in the mixture are characterized

^a Vainio H, Sorsa M, McMichael AJ. Complex mixtures and cancer risk. IARC scientific publication no.104, 1990, Lyon

and the effects of those single agents are known, the sum effect cannot be predicted with any degree of certainty". Members considered that the potency of mixtures may not be explained by the potency of the components because of the relative timings of exposures and associated impact on pharmacokinetics.

18. The Committee was asked whether it was possible for testing to give an indication of the cancer risk posed by a mixture and if not, whether such a conclusion might be appropriate for the statement. The Committee noted that there was a significant data gap in the evaluation of cancer risk posed by mixtures. Mechanistic studies, such as the initiation/promotion studies discussed at the last meeting, are very limited in scope and it is not currently possible to extrapolate from these studies the implications for cancer risk assessment in the human population. It was suggested that there should be more discussion of potential epigenetic modification in the carcinogenicity of mixtures.

ITEM 7: COC Annual Report for 2008 (CC/09/1)

19. The Committee had been presented with the draft text for the 2008 annual report; however, there was insufficient time for discussion. The Secretariat asked Members to provide corrections and comments by e-mail.

ITEM 8: Any Other Business

20. The Secretariat was asked to provide Members with the papers for items 6 and 7 in electronic form, so that comments could be made directly onto the text.

ITEM 9: DATE OF NEXT MEETING

21. 23rd July 2009 at Wellington House, Waterloo.