

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

Minutes of the meeting held at 10.30am on Thursday 14th April 2011 at Department of Health, Room 102A, Skipton House, Elephant & Castle, London, SE1 6LH.

Present

Chairman:	Professor D Phillips	
Members:	Dr P Carthew Professor P Farmer Dr P Greaves Dr C Powell Mrs R Glazebrook	
HPA Secretariat:	Ms F Pollitt Ms S Kennedy Mr J Battershill Dr L Hetherington	(Scientific Secretary) (Administrative Secretary) (Item 6) (Item 6)
FSA Secretariat:	Dr D Benford	(Scientific Secretary)
In Attendance:	Dr K O'Leary Dr K Burnett	(DH Tox Unit, item 4 and 7) (DH Tox Unit, minutes)
Assessors:	None	
Observers:	None	

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ITEM 1: Apologies for Absence & Announcements

1. Apologies and written comments were received from Professor A Boobis and Professor P Vineis. Apologies were also received from Dr Lindsay Wright, Dr Brian Miller, Dr D Lovell, Dr Pip Edwards (HPA), Dr Ovnair Sepai (HPA) and Mr Andrew Smith (HSE).

2. The Chairman welcomed Dr Hetherington (HPA) for item 6, Dr K O'Leary from the DH Tox Unit, who had prepared the papers on Genome Wide Association Studies (item 4) and on microRNAs and cancer (item 7) and Dr K Burnett from the DH Tox Unit.

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

ITEM 2: Minutes of meeting held on 25th November 2010 CC/MIN/2010/2

4. Members made several small edits to the text, with revision required in paragraphs 19, 38, 41, 66, 71 and 74. In paragraph 47, the Committee suggested that the precise joint COC and COM items which had been delayed due to lack of resources be included in the sentence, namely papers on thresholds and on endogenous carcinogens. In paragraph 61, under the prioritisation of work programme for COC in 2011, clarification was sought on the exclusion of an update review on alcohol and cancer from the list entirely. In light of the recent publication on the role of alcohol in overall cancer risk, the Committee requested a copy of this publication for discussion at a future meeting.

ITEM 3: Matters arising not covered by later agenda items

3a – Dichlorvos – correspondence from AMVAC (CC/2011/04)

5. It was noted that Professor Boobis was not present but, in his written comments on this item, he had declared that he was a member of the Advisory Committee on Pesticides and Chair of the Toxicology Working Group of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR) of the European Food Safety Authority (EFSA) when dichlorvos was discussed in these committees.

6. The Committee was reminded of the previous discussion about dichlorvos at the last meeting and the presentation by AMVAC, in which it was argued that the forestomach tumours which occurred in a US National Toxicology Program (NTP) gavage study in B6C3F1 mice were due to a combination of the irritant properties of dichlorvos and the corn oil vehicle. The Committee was not convinced by the argument, but it was considered that the forestomach tumours were unlikely to be due to a genotoxic mechanism. Nevertheless, in view of the Committee on Mutagenicity (COM) conclusion that dichlorvos should be regarded as an *in vivo* mutagen at the site of contact, the COC confirmed that there needed to be clear evidence of a non-genotoxic mode of action for the tumours, before it could move away from the assumption of no threshold and the previous data requests were confirmed.

7. AMVAC then wrote to the Secretariat with a request that certain items are included in the minutes but the Secretariat considered that only those items mentioned during the presentation or discussion should be included. AMVAC subsequently submitted a technical note which makes a number of points and the Committee was now asked to consider these. The Secretariat noted that the 6th paragraph mentions a publication by Wooder and Wright which indicated that dichlorvos did not cause alkylation of DNA. This publication was considered by the COM in its initial review of dichlorvos and is referenced in its statement.

8. At the outset of the discussion regarding paragraph 2, a Member noted that there was an assertion that the Committee needed to determine if the positive response in the mouse forestomach observed with daily gavage dosing of corn oil is indicative of an oncogenic potential of dichlorvos. This was not the case. The COC had been asked for its views on whether there was a threshold for the carcinogenicity of dichlorvos.

9. With regard to paragraph 3, the Committee considered that, without the particle size distribution in the inhalation study by Blair, it is not possible to calculate what the dose is and, therefore, the exposure cannot be derived. Members could not be assured that the Maximum Tolerated Dose was achieved in the study.

10. With regard to paragraph 4, the Committee noted that there was a high incidence of hyperplasia in male controls (20 %) in this study. Moreover, the effect described was a standard response to corn oil gavage in NTP studies and therefore does confound the interpretation of the results. Nevertheless, these factors do not prove AMVAC's case.

11. With regard to paragraph 5, the Committee commented that the pathology data from the NTP data was "consistent with" rather than "supports" a lack of genotoxic mechanism for tumour development. In order to address paragraph 6, two Members agreed to review the Wooder and Wright (1981) paper. Members did not agree with the statement in paragraph 7 that forestomach tumours are not relevant to human risk assessment. Some changes in the forestomach were relevant and some not. However, Members commented that it was odd that these tumours were seen in the forestomach of mice but not rats and commented that a Mode of Action (MOA) study would be useful. A study by Benford *et al.* (1994) had previously shown an increase in S phase in the mouse forestomach with dichlorvos.

12. With regard to paragraph 9, it was commented that the Committee did not ask for the study described but said that, in the absence of a study to demonstrate a non-genotoxic effect, dichlorvos should still be assumed to have a genotoxic MOA. The Secretariat agreed to write to AMVAC once the minutes were agreed.

ITEM 4. Genome Wide Association Studies (GWAS)– Bladder Cancer and Colorectal Cancer (CC/2011/07)

13. At the COC meeting in July 2010, the Committee discussed a scoping paper on the interaction between genotype and chemicals in the environment on the induction of cancer in risk assessment (CC/2010/02). This detailed the major projects that have been initiated over the past decade in the fields of both genetics and exposure assessment and their contribution to understanding gene-

environment interactions and cancer risk. At the meeting, several Members indicated that a review of some examples of Genome-Wide Association Studies (GWAS) and cancer, namely bladder and colorectal cancer, would be useful.

14. Members commented that the paper provided an excellent summary of the main GWAS of bladder cancer and colorectal cancer currently available in the literature. However, Members commented that it is still not clear how these data will inform risk assessment generally for cancer susceptibility nor how the information could be used in the context of public health advice. It was considered difficult to understand what impact the potential genetic predispositions may have on the numbers of cancer. It was also noted that, even within the studies described, there were some discrepancies with regard to figures for tumours considered to be sporadic and those that may be associated with an inherited susceptibility. Members thought that it would be of interest to know whether a suspected genetic predisposition could identify high-susceptibility sub-groups and, if so, whether this could be used for avoidance or treatment strategies.

15. Members noted that, in general, there were few associations of known environment/genetic predispositions. Slow acetylators (NAT2) have a higher risk of bladder cancer but this was only flagged up because there was a previously established hypothesis as it was known smokers have a higher risk (i.e. you would need to know what you were looking for first). Some studies were described where there were strong associations between some Single Nucleotide Polymorphisms (SNPs) and genes for xenobiotic metabolising enzymes and certain cancer types. These may support the involvement of environmental chemicals in the cancer process. Members noted that, even when loci are positively identified, this does not provide information necessarily on function. For example, the loci 8q24 is known as a 'gene desert' i.e. gene regulation/expression by non-coding DNA is involved rather than the gene itself. Furthermore this locus has a pleiotropic action and is associated with a wide variety of cancers and other diseases such as diabetes.

16. Members addressed the questions given within the paper as follows:

16.1 In general, have the Committee any comments on GWAS?

Overall Members thought that GWAS have been useful but it would be difficult to use these data at this stage without clear understanding of the functional links and biological relevance. The research has now begun to focus on Exposure Wide Association Studies (EWAS) or the "Exposome".

16.2 Will information such as that described here be of help in assessments by the Committee and, if so, how?

The Committee was not yet clear how GWAS studies would inform the assessments of the COC other than on a case-by-case basis. For example, in a couple of studies, strong associations were found between SNPs in or close to genes for xenobiotic metabolising enzymes and certain cancer types. This would support the involvement of environmental chemicals in the cancer process. However, there are endogenous substrates for many of these enzymes, so the findings would have to be considered within the broader context of all available information. Such studies are likely to have most impact on the assessments of the COC if the specific genes involved in the associations observed can be identified, and their biological relevance

determined. The Committee agreed that further development of the studies is needed and some guidance on interpretation would be helpful to the Committee.

16.3 Do the findings of these GWAS shed any light on the environmental causes of colorectal or bladder cancer?

Currently, the Committee did not think so and considered that Exposure Wide Association Studies (EWAS) were likely to be more useful.

16.4 Do Members have any research or other recommendations with respect to GWAS?

Members were interested to know if GWAS could provide information about the epidemiology of cancer clusters. It was recommended that a watching brief was maintained on this area.

ITEM 5: COC Guidance statements – 2nd draft of the Overarching Guidance Statement (CC/2011/02)

17. Members were presented with a version of the statement which has been revised in accordance with the comments received at the previous meeting when only limited time had been available to review the document in detail. Members were asked to go through this draft, section by section, and provide detailed comments.

18. Members considered that the term 'genotoxic' should be used instead of 'mutagenic' and that the use of the term 'mutagenic or non-mutagenic carcinogen' may be confusing. Clarification can be given when an event is mutagenic (i.e. a heritable change). The former term was originally used in line with the new COM guidelines but it is not always appropriate in the context of the COC Guidance. A Member offered to assist the Secretariat when unsure of the appropriate term. Members considered that it should be made clear that the BMDL₁₀^a is a preferred method for potency estimation rather than the T25^b and TD50^c methods. It was stressed that the Committee recognises that the most precautionary approach for exposure to genotoxic carcinogens is zero tolerance but "As Low as Reasonably Practicable" (ALARP) is the widely accepted, pragmatic approach. Some sections did not refer specifically to the risk assessment of carcinogens, and this should be addressed.

19. Members identified a number of further general editing comments. Members also provided suggestions for updating the references and stated the need for a glossary of terms. It was decided that an updated version using track changes would be brought to the next meeting.

^a Lower 95% confidence limit of the benchmark dose for a 10% response

^b The chronic dose rate in mg/kg bw/day which will give 25% of the animal's tumours at a specific tissue.

^c The dose rate in mg/kg bw/day which, if administered chronically for the life-span of the species, will half the probability of remaining tumourless throughout that period

ITEM 6: Para-occupational exposure: Draft joint statement on the systematic review of epidemiological literature on para-occupational exposure to pesticides and health outcomes. (CC/2011/03)

20. The Committee considered a narrative review of the epidemiology literature on para-occupational exposure to pesticides and cancer in 2009. In the November 2010 meeting, it considered a meta-analysis of the case-control studies and a first draft of this statement. The Committee was informed that a similar statement on para-occupational exposure to pesticides and other health outcomes was under consideration by the COT, although that committee was using a narrower definition of para-occupational exposure. This difference in definition was the reason why the COT and COC were producing two separate statements rather than a joint statement. The Secretariat commented that it would ask the COC epidemiologists whether they agreed to the final version of the statement by correspondence, as they were not in attendance at the meeting.

21. A number of small editorial changes were suggested by the Committee. The Secretariat was asked to revise the references to reflect the use of numbers for the references. In paragraph 21, the Committee suggested that there was an explicit explanation for the scoring of the papers, indicating that 1 was the highest score awarded. In paragraph 26, it was suggested that the percentage contribution of the single papers to the overall meta-analysis should be expressed to only one decimal figure (i.e. 40.1% rather than 40.05%).

22. A Member questioned how the data considered in paragraph 27 was within the scope of para-occupational exposure. The Secretariat explained that there were cases of a mother carrying pesticides home on her clothes from work and exposing her children in this way.

23. The Secretariat was asked to seek clarification from the epidemiologists about whether each individual meta-analysis should be described in words in paragraph 28-29. The Committee commented that it would be interesting to see data on the level of effects in children following para-occupational exposure to pesticides when the parents did not have any evidence of disease following occupational exposure.

24. In paragraph 33, the Committee questioned the use of IARC terminology and the use of hyperlinks in HPA/DH documents to other international agencies. The Committee was advised that the COM intends to use links to other agencies' websites. It was noted that there is the practical issue of ensuring that URL links are still valid on a regular basis but that this would not be an issue for internal links.

25. In the conclusions, paragraph 37, the Secretariat was asked to clarify, and possibly to revise, point i. In point iv, the Committee agreed that "at this time" should be added to the end of the sentence. It was also noted that the COT conclusions differ from those of the COC.

26. In Annex 1, the Committee suggested that it would be helpful to include reference numbers and quality scores in the table.

ITEM 7: Role of miRNA Related Effects and Chemicals on Cancer (CC/2011/06)

27. At the November 2009 meeting, the Committee discussed a review of the role of RNA mechanisms in cancer development (CC/09/13). One area of particular interest was the role played by miRNAs in carcinogenesis. The Committee noted that literature was available on the effect of therapeutic drugs on RNA mechanisms and on how the manipulation of these processes could be exploited for therapeutic purposes. It indicated that a review of some examples of environmental chemicals influencing the miRNA processes involved in carcinogenesis would be of interest, if the data were available.

28. The current paper reviews a number of publications which have investigated the influence of environmental chemicals on miRNA expression in cancer and Members were asked for their views. Members commented that the paper provided an excellent review of the research area and that it is an interesting concept. The 25 studies examined give a good picture of the field although, at the present time, it is not clear how the role of miRNA and related effects can be incorporated into cancer risk assessments nor how it would be useful as a diagnostic tool. Members noted that it may be useful as an adjunct to molecular pathology studies. Members raised some uncertainties with regards to the interpretation of these studies. Firstly, it would be important to understand how a particular miRNA influences a specific gene expression and that more than one miRNA may impact on individual genes. It was not possible to determine whether the changes were simply a result of a homeostatic change or were associated with causality. Members thought that currently miRNAs would be less sensitive biomarkers of exposure than DNA adducts.

29. Members recommended that, as this was such an active area of research and potentially useful, the Committee should maintain a watching brief in this area.

ITEM 8: COC Annual Report for 2010 (CC/2011/01)

30. Members were asked for comments on the draft of the COC's annual report for 2010. It was suggested that, in view of the discussion of dichlorvos at this meeting, it would be necessary to move this item into "ongoing topics". A small number of editorial comments were suggested by the Committee but overall the draft COC report was agreed.

ITEM 9: Closed session: Paper for information: Length dependent retention of carbon nanotubes in the pleural space of mice initiates sustained inflammation and progressive fibrosis on the parietal pleura. (CC/2011/05)

31. The Secretariat was provided with this paper by Professor Ken Donaldson for information in response to the interest shown by the Committee in his work. The Committee were informed that this paper was "in press" and were asked to treat it accordingly [Post meeting note: the paper was published in the American Journal of Pathology Volume 178 (6), pp 2587-2600, June 2011]. Although it was provided for information only, Member's comments and views were sought on the work and/or on the implications of the findings for the carcinogenic risk of carbon nanotubes (CNTs) to humans.

32. Overall, the Committee considered this to be a very useful paper and discussed how it could help with the performance of risk assessments. In this regard, a Member noted another recently published paper by Professor Donaldson's group on genotoxicity testing of nanomaterial compounds (Nanotoxicology 4(4), pp 414-420, December 2010). The Committee expressed its gratitude to Professor Donaldson for providing the paper and expressed continued interest in this work.

ITEM 10: Any other business

33. Members were thanked for their helpful suggestions to a request from the Department of Health (DH) to the COC to provide advice on climate change and cancer. Members were provided with the consolidated response from the COC to DH.

ITEM 11: Date of next meeting

34. The date of the next meeting is 21ST July, 2011 at the Department of Health, Skipton House, Elephant & Castle, London, SE1 6LH.