

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

Minutes of the meeting held at 10.30am on Thursday 10 April 2008 at  
Department of Health, Room 136/7B, Skipton House, 80 London Road,  
Elephant and Castle, London SE1 6LH.

Present

Chairman: Professor D Phillips

Members: Professor A Boobis  
Dr P Carthew  
Professor P Farmer  
Professor D Harrison  
Ms D Howel  
Professor R Roberts  
Professor P Vineis  
Dr N Wallis

HPA Secretariat: Ms F Pollitt (Scientific Secretary)  
Ms S Kennedy (Administrative Secretary)  
Dr L Hetherington (Minutes)  
Mr J Battershill

FSA Secretariat Mr B Maycock (for Scientific Secretary)

In Attendance: Dr K Burnett (DH Tox Unit, item 8)  
Dr P Edwards (HPA, item 6)  
Ms E Idahosa (DH Tox Unit, item 5.2)  
Mr K Okona-Mensah (DH Tox Unit, item 7)  
Dr K O'Leary (DH Tox Unit, items 5 & 9)

Assessors: Mr H Brunt (NPHS Wales)  
Dr S Dyer (DH)  
Mr M Hosford (EA)  
Mr S Samuels (PSD)

Observers: Dr R Fayokun (DH Tox Unit)

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

92

93 1. Apologies were received from Dr C Allen, Dr D Benford (FSA), Mrs R  
94 Glazebrook, Dr B Miller, Professor D Shuker, Mr A Smith, Dr H Stemplewski  
95 (MHRA).

96

97 Announcements

98

99 2. The Chairman welcomed Mr J Battershill, Dr K Burnett, Dr P Edwards,  
100 Ms E Idahosa, Mr K Okona-Mensah, Dr K O'Leary, Dr R Fayokun and Ms S  
101 Kennedy.

102

103 3. Members were reminded of the need to declare any relevant interests  
104 before discussion of items.

105

106 **ITEM 2: MINUTES OF THE MEETING OF 15 NOVEMBER 2007**  
107 **(CC/MIN/2007/03)**

108

109 4. Paragraph 13 of the minutes was changed to reflect the decision to  
110 review a second draft working paper on chlorinated drinking water and cancer  
111 (CC/08/2) (item 4 below) instead of clearing it by Chairman's action. The  
112 secretariat was asked to check the wording of paragraph 16 with the member  
113 who made these comments. Subject to these actions, and minor editorial  
114 changes, the minutes were agreed.

115

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

117

118 5. The Chairman informed Members of the outcome of the recent meeting  
119 of the subgroup of the Scientific Advisory Committee on Nutrition (SACN) on  
120 folic acid and colorectal cancer which had been asked to reconsider the  
121 papers by Cole et al (2007) and Mason et al (2007). The subgroup had  
122 concluded that the recommendation in favour of mandatory fortification of  
123 bread should remain unchanged. However, subsequent to the meeting, the  
124 secretariat had discovered that other relevant studies were in progress and so  
125 the FSA had decided to delay a final decision until the results of these were  
126 available in 12-18 months time.

127

128 **ITEM 4: SECOND DRAFT WORKING PAPER ON CHLORINATED**  
129 **DRINKING WATER AND CANCER (CC/08/2)**

130

131 6. The Committee considered a first draft of this working paper  
132 (CC/07/12) at the meeting in November 2007 and asked for a number of  
133 changes, particularly quantification of the risks measured in the new  
134 epidemiology papers. Members reviewed the second draft paper, agreed  
135 further minor editorial changes and finalised the statement for publication on  
136 the COC website.

137

138 **ITEM 5: MODE OF ACTION/HUMAN RELEVANCE FRAMEWORK**

139

140 **ITEM 5.1 IPCS Mode of Action Human Relevance Framework (CC/08/3)**

141

142 7. Professor Boobis declared a non-personal specific interest.

143

144 8. The International Programme on Chemical Safety (IPCS) Mode of  
145 Action (MOA) Framework is a conceptual framework for considering data on  
146 the mode of action of chemical carcinogens. The COC considered aspects of  
147 the Mode of Action Framework in 1999 and, in 2004, considered in detail the  
148 Human Relevance Framework (HRF) developed by a working group  
149 sponsored by the US Environmental Protection Agency and the International  
150 Life Science Institute (ILSI) Risk Science Institute (RSI).

151

152 9. This paper summarised recent developments made by the IPCS in the  
153 continuing evolution of Human Relevance Frameworks to systematically  
154 consider the weight of evidence of hypothesized modes of action in animals  
155 and their potential human relevance for cancer. The IPCS HRF involves  
156 answering a series of three questions followed by a statement of confidence,  
157 analysis and implications.

158

159 10. This overview paper described three case studies that use the IPCS  
160 HRF as an approach for determining the sufficiency of evidence and the  
161 relevance of an animal MOA for humans. Three different MOA were  
162 considered: 1) sustained cytotoxicity and regenerative proliferation leading to  
163 nasal tumours following exposure to formaldehyde, 2) direct alkylation of DNA  
164 leading to tumours in multiple sites following exposure to 4-aminobiphenyl, 3)  
165 increased hepatic clearance of thyroxin leading to thyroid tumours following  
166 exposure to thiazopyr.

167

168 11. Members considered that the IPCS HRF was a valuable evolution of  
169 the work on this concept. Members commented that the U.S. is trying to  
170 evaluate dose-response to genotoxic carcinogens with a view to moving away  
171 from linear assessment and asked whether the UK should also be moving to a  
172 non-linear assessment approach. They gave the example of aflatoxin where  
173 cytotoxicity substantially influences tumourigenicity and the dose-response is  
174 non-linear. They suggested that the IPCS HRF approach should be used on  
175 a case-by-case basis. There might be overlapping key events between  
176 experimental animals and humans, but overall there is one MOA for tumour  
177 formation for a chemical in a particular tissue. Therefore, it would be  
178 necessary to carry out separate analyses for different tumour types. Members  
179 commented that each potential MOA could be considered using this  
180 framework, and dismissed if the evidence was against it. No specific  
181 comments were made about the IPCS case studies.

182

183 **ITEM 5.2 Presentation of Project on MOA/HRF**

184

185 12. Professor Boobis declared a non-personal specific interest.

186

187 13. Members heard a short presentation by Ms Idahosa, a second year  
188 PhD student under the supervision of Professor Boobis and Dr Rushton, on

189 the weight of evidence in framework approaches to cancer hazard  
190 identification. Ms Idahosa provided an overview of her research project which  
191 focuses on the evaluation of conventional and non-conventional evidence for  
192 use in the IPCS HRF. Specifically, she discussed the application of  
193 systematic review methods to assess human epidemiological evidence for use  
194 in evaluating a mode of action and the consideration of the potential uses of  
195 toxicogenomics data to identify the molecular basis of key events in the  
196 mode of action. Ms Idahosa provided an overview of her current  
197 methodological approach of carrying out pathway analysis of transcriptomics  
198 data, providing examples of different commercial and non-commercial  
199 analytical tools.

200

201 14. In response to questions, Members were informed that animal and  
202 human data obtained from the literature were being used for the study. The  
203 research focuses on the hepatocarcinogenicity of phenobarbitone as a  
204 prototypical example, using temporal data and, where data were available,  
205 species differences. Members commented that study and experimental  
206 variability is likely to be considerable and suggested that it would also be  
207 worthwhile to consider the effects of strain differences as there are known  
208 variations in the response of different mouse strains to phenobarbitone.  
209 Members were informed that dose response effects would also be considered  
210 in the analysis and that any evaluation of human data would rely on the use of  
211 toxicogenomics studies carried out using human liver hepatocytes, of which  
212 none had so far been identified.

213

214 15. With regard to the use of toxicogenomics data, Members were  
215 interested to know whether there was a limit to the number of genes that  
216 might be used and the criteria for a positive response. Members commented  
217 that small changes in the magnitude of response might be important. Ms  
218 Idahosa acknowledged that a limitation of the approach was the reliance on  
219 publicly available data which, in most cases, reported only on differentially  
220 expressed genes, usually with more than a 2-fold but, in some cases, only a  
221 1.5-fold, change in expression. Members were informed that the aim was to  
222 generate a statistical evaluation of the genetic pathways and to determine the  
223 relevance of any changes in gene response.

224

225 16. A request was made to Members for any relevant data on the  
226 transcriptomics or proteomics of phenobarbitone that could be used in the  
227 study.

228

229 **ITEM 5.3: Statistical Inferences about the Mechanism of Action in**  
230 **Carcinogenicity Studies. Sielken et al (2005). (CC/08/4)**

231

232 17. This paper described a dose-response modelling approach to provide  
233 statistical insight into the relative likelihood of different mechanisms of action  
234 in cancer dose-response studies. The paper provided two examples based  
235 on time-to-tumour data for mammary fibroadenoma and adenocarcinoma in  
236 female Sprague-Dawley rats exposed to a pesticide in the diet. The examples  
237 considered how 34 different dose metrics (i.e. a measure of exposure to the  
238 pesticide or a measure of the biological activity potentially generated by the  
239 exposure if a specific mechanism of action applies) related to the

240 fibroadenoma and adenocarcinoma incidence data and demonstrated how the  
241 maximum likelihood statistical methodology could be used to provide an  
242 indication of the mechanism of action of the pesticide. This process ranked  
243 the mechanisms of actions being evaluated and provided a quantitative  
244 indication of the relative strength of support for each one.

245

246 18. Members commented that it was unclear how the dose metrics and the  
247 different variables were identified and chosen for inclusion as no references  
248 were cited in the paper. They questioned the statistical robustness of the  
249 approach noting that numerous correlations were performed and it was  
250 possible that some statistically significant associations had occurred by  
251 chance.

252

253 19. Members also considered that, although the most likely mechanism of  
254 action for the unidentified pesticide in the above examples was found to be  
255 hormonal, no other data were provided to show that it acted through a  
256 hormonal mechanism and therefore the assumption made in the paper was  
257 unwarranted. Moreover, no data were provided on the other dose metrics  
258 used. They commented that there may well be potential value in the  
259 approach suggested, but that more work was required. Before applying this  
260 approach to a specific example, it would be necessary to have alternative  
261 endpoints linked to a MOA.

262

263 **ITEM 6: REVISION OF OECD TEST GUIDELINES FOR CARCINOGENICITY**  
264 **STUDIES (CC/08/9)**

265  
266 20. The Organisation for Economic Cooperation and Development (OECD)  
267 was currently revising its Test Guidelines for carcinogenicity and chronic  
268 toxicity studies. The COC and COT had previously commented on updated  
269 proposals by post. The OECD was also preparing a Guidance Document to  
270 accompany the revised guidelines and the first chapter, on dose selection,  
271 was circulated to COC members and the OECD UK Shadow Group prior to  
272 the meeting. Members were provided with a copy of the draft chapter (Annex  
273 1 to CC/08/9, pp 4-17) and a copy of the expert comments received (Annex 2,  
274 pp 18-20).

275  
276 21. In response to the question in CC/08/9 on the value of testing doses  
277 close to those of relevance from human exposure, Members commented that  
278 it was only practicable to consider human exposure in dose selection if likely  
279 exposures were known. Also, if the low dose was matched to human  
280 exposure, it might turn out to be an effect level, meaning that a NOEL could  
281 not be estimated. Although some regulatory authorities were moving to a  
282 benchmark dose approach, others still required a NOEL. It was noted that the  
283 original papers by ILSI, on which the chapter was based, were extensive but  
284 omitted discussion of routes of exposure other than oral. Members were  
285 informed that the Guidance Document would contain a separate chapter on  
286 administration routes.

287  
288 22. At a workshop held in February 2008, it was proposed that there should  
289 be further development of a number of chapters in the Guidance Document. It  
290 is anticipated that the OECD secretariat will be looking to a member country to  
291 lead on drafting each chapter. The UK had originally thought to propose  
292 leading on the chapter on MOA/HRF but the US was now doing this and  
293 Members were asked what other chapter the UK should undertake. Members  
294 considered that although much guidance already exists on histopathology, it  
295 would be important to bring it into an OECD context and agreed that the UK  
296 should propose leading on this chapter.

297  
298 23. Members were informed that no fundamental new design aspect was  
299 intended in the revised guideline for carcinogenicity studies (TG451). A  
300 Canadian review paper was in progress on transgenic animals and, once  
301 available, the OECD would consider whether to produce a new test guideline  
302 in this area. It was not intended to include prenatal/perinatal exposure in  
303 TG451 but Members were asked to inform the secretariat if they were aware  
304 of any work in the UK which would inform this area.

305  
306 **ITEM 7: NON-HODGKIN'S LYMPHOMA**

307  
308 **ITEM 7.1: 1,3-Butadiene and non-Hodgkin's lymphoma: review of the**  
309 **evidence for IARC's reclassification of 1,3-butadiene to Group 1**  
310 **carcinogen (CC/08/08)**

311  
312 24. When the Committee discussed this topic in July, a Member had  
313 informed the committee that IARC had reclassified 1,3-butadiene (BD) from

314 Group 2A to Group 1 on the basis of human data showing an association with  
315 chronic lymphocytic leukaemia (CLL) and non-Hodgkin's Lymphoma (NHL).  
316 The Committee had decided to consider the evidence that IARC had reviewed  
317 before any conclusions on BD were incorporated into the NHL statement.

318

319 25. The full report of the IARC meeting was not yet available. However,  
320 the secretariat reported that Grosse et al (2007), summarising the IARC  
321 reclassification, stated that it was classified in Group 1 'on the basis of  
322 sufficient evidence in humans of an increased risk to leukaemias'. Grosse et  
323 al (2007) noted two key studies, one of which observed an association  
324 between BD exposure and CLL, and one between BD and NHL (Graff et al,  
325 2005 and Ward et al, 1995, respectively). Enquiries had been made of Dr V  
326 Cogliano, head of the Carcinogen Evaluation Unit at IARC, as to whether the  
327 working group specifically concluded that there was an association with NHL  
328 in humans, but no reply had been received. Changes in classification of NHL  
329 (CLL is classified as a subtype of NHL under the WHO/Revised European  
330 American Lymphoma (REAL) classification scheme) might complicate the  
331 situation further. It was considered, therefore, that the Committee should  
332 reach its own conclusion on the basis of the available data.

333

334 26. The US EPA had also recently reviewed the human carcinogenicity  
335 data on BD and had concluded that excess lymphohaematopoietic cancers  
336 (including NHL) in monomer and polymer workers were causally associated to  
337 BD exposure.

338

339 27. CC/08/8 reviewed the epidemiological evidence and associated studies  
340 used to form the basis of IARC's reclassification. The secretariat highlighted a  
341 few points noted in the text. Para 9, second sentence should have read: "A  
342 total of eight [*not nine*] cohort studies were considered in detail (BD-monomer  
343 [4 studies (*not 5*)];..." [not nine since Cowles et al 1994 was excluded from  
344 further analyses]. Ward et al (1995) expressed the risk estimates as relative  
345 risks in their paper but called them SMRs (except in the abstract). Table 2  
346 expressed them as published in the paper but the main text of CC/08/8 had  
347 corrected them.

348

349 28. Members considered the studies in workers exposed to BD monomer  
350 and then those in workers in the styrene-butadiene (SBR) monomer industry.  
351 Members noted that there was a spectrum within the classification of NHL:  
352 some patients may present with CLL but, on examination, prove to have also  
353 a solid tumour; some may present with both NHL and CLL. Members  
354 commented that most of the studies were limited by potential confounding  
355 such as co-exposures and poor ascertainment of exposure. Further, there  
356 was no reason why individuals exposed to BD should have immunodeficiency  
357 as this is a rare condition and so unlikely to be a confounder.

358

359 29. Members commented that the IARC monograph was for BD and not  
360 NHL specifically. One of the Members who had been on the IARC committee  
361 commented that the upgrade of BD to Group 1 was made on the basis of the  
362 mechanistic information and he was not sure if there was an evaluation of  
363 specific tumour sites.

364

365 30. Overall, Members concluded that the available evidence did provide a  
366 convincing case for an association between BD and NHL in humans.

367

368 **ITEM 7.2: Second draft working paper on Non-Hodgkin's lymphoma**  
369 **(CC/08/7)**

370

371 31. The Committee agreed the text subject to minor editorial amendments.  
372 The text on BD (paragraphs 16 and 19ii) will be amended when the details  
373 about the IARC reclassification of BD are confirmed and the statement will  
374 then be cleared by Chairman's action.

375

376 **ITEM 8: INITIAL DISCUSSION PAPER ON THE ASSESSMENT OF**  
377 **MIXTURES FOR CARCINOGENICITY (CC/08/6)**

378

379 32. The Committee had expressed an interest in current developments in  
380 the assessment of chemical mixtures with regard to carcinogens and their  
381 modes of action and an initial discussion paper was provided. Other  
382 evaluations, such as that included in the WiGRAMP report, an ongoing ILSI  
383 initiative and an electronic version of the COM statement on this topic, had  
384 been emailed to Members.

385

386 33. The current paper gave a brief overview of approaches for assessing  
387 the toxicity of chemical mixtures and had drawn on a few areas pertinent to  
388 carcinogenicity. Firstly, the concept of common mechanism groups (CMG)  
389 and toxic equivalency factors were addressed in relation to dioxins. Although  
390 other toxic effects of the class of chemicals were more usually examined, one  
391 paper evaluating tumours as an end point had been retrieved. Estrogens may  
392 also form a CMG and some approaches using *in-vitro* screening were  
393 presented which provided some robust information on dose additivity. Not  
394 many examples of *in-vivo* approaches to the assessment of mixtures had  
395 been found; a few papers investigating contaminants in drinking water were  
396 presented.

397

398 34. Members asked for a definition of the term 'mixtures' and asked if it  
399 referred to mixtures of chemicals, mixtures of carcinogens, or multiple  
400 exposures e.g. aflatoxin and hepatitis B. Members were informed that the  
401 COM had looked at mixtures of mutagens alone and it was suggested that the  
402 COC followed this approach. They were also informed that the COM had  
403 found a number of putative mechanisms for interactions between mutagens  
404 which required further research.

405

406 35. Members commented that there were only limited studies exploring  
407 mixture effects with respect to carcinogenesis and that very few studies had  
408 used cancer as an endpoint. In comparison, the COM had examined over 90  
409 papers and had been able to derive a strategy to assess the mutagenicity of  
410 mixtures of chemicals.

411

412 36. Members stated that they concurred with the concept of dose additivity  
413 for CMGs but that the database for cancer *per se* was very limited. However,  
414 there are exceptions to the concept of dose additivity. For example,

415 oestrogens may act through either ER $\alpha$  or ER $\beta$  to produce either inhibitory or  
416 stimulatory effects.

417

418 37. Members suggested a number of possible ways to proceed in this area:

- 419 • to look at *in-vivo* data and whether or not it is supported by *in-vitro*  
420 data, for example, in the case of endocrine disruptors.
- 421 • to examine some initiation-promotion papers to study the endpoints  
422 separately, e.g. number of tumours or preneoplastic foci produced or  
423 time to tumour, with a view to defining the mechanisms which might be  
424 operating.
- 425 • to carry out pharmacokinetic modelling of pairs of chemicals and to test  
426 the outcome against the predicted metabolic profile, for example, using  
427 chemicals such as polycyclic aromatic hydrocarbons where metabolism  
428 in mixtures is unpredictable.

429

430 **ITEM 9: CARCINOGEN-DNA ADDUCTS AS A BIOMARKER FOR CANCER**  
431 **RISK. RUNDLE (2006). (CC/08/5)**

432

433 38. During the 2006 horizon scanning discussion, Members had expressed  
434 an interest in this paper which suggested that epidemiological studies which  
435 seek to establish an association between carcinogen-DNA adduct levels and  
436 cancer risk often fail to incorporate fundamental epidemiological principles into  
437 their study methods.

438

439 39. The author described a number of epidemiological studies which have  
440 investigated associations between DNA-carcinogen adduct levels and cancer  
441 (hepatocellular cancer, breast cancer and smoking-related cancer) and  
442 addressed a number of methodological issues common to these studies: 1)  
443 the use of target versus surrogate tissue and how this choice impacts on  
444 control selection; 2) disease effects on adduct levels; 3) the time period  
445 reflected by adduct levels; 4) the use of inappropriate statistical analyses and  
446 5) small sample sizes. Each of these issues was discussed in detail in the  
447 paper.

448

449 40. The author had made a number of suggestions to improve study  
450 designs to overcome these issues in the future. These included studies that  
451 clearly address the prospective temporal relationship between adducts and  
452 cancer diagnosis, allowing selection of a referent group that is comparable to  
453 the cases and which provides for sampling of target tissue.

454

455 41. Members commented that the paper considered the use of adducts  
456 from surrogate tissues, particularly lymphocytes, as not being entirely  
457 acceptable and ignored the fact that adduct levels measured in target tissue  
458 samples may also lack relevance, because only certain cell types in the tissue  
459 will be targets, and only a very limited number of adducts are causal, the  
460 majority occurring at non-critical sites or in non-critical genes. Hence, it was  
461 an over-simplification to argue that target tissue samples will overcome a  
462 major limitation of adduct determination, and inappropriate to dismiss the  
463 value of adducts in surrogate tissues. Researchers were aware of the  
464 limitations of using surrogate tissues.

465

466 42. Members stated that adducts measured at the time of diagnosis may  
467 not reflect exposure at the critical period, and may be affected by the  
468 pathology of the condition. Members suggested that the lymphocyte fractions  
469 of blood samples could be stored in biobanks and used for biomarker  
470 analysis.

471

472 43. With regard to the development of a structured approach to the  
473 evaluation of biomarker studies, one Member informed the Committee that the  
474 Environmental Cancer Risk, Nutrition and Individual Susceptibility  
475 programme (ECNIS) intended to produce a guidance document on  
476 epidemiological design, including the use of DNA adducts. He undertook to  
477 bring the document to the COC's attention in due course. In view of this, the  
478 COC decided not to develop its own guidance for the evaluation of biomarker  
479 studies.

480

#### 481 **ITEM 10: ANY OTHER BUSINESS**

482

483 44. The Committee was informed that the statistician, David Spiegelhalter,  
484 had been made the Winton Professor of the Public Understanding of Risk, a  
485 new Chair at the University of Cambridge.

486

#### 487 **ITEM 11: DATE OF NEXT MEETING**

488

489 45. 17 July 2008.

490