

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

Minutes of the meeting held at 10.30am on Thursday 19th November 2009 at Department of Health, Room 102A, Skipton House, Elephant & 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 Dr P Greaves Dr D Lovell Dr B Miller Dr C Powell Professor P Vineis Dr N Wallis Dr L Wright	
HPA Secretariat:	Ms F Pollitt Ms S Kennedy Dr D Mason Mr J Battershill	(Scientific Secretary) (Administrative Secretary) (Minutes)
FSA Secretariat:	Dr D Benford	(Scientific Secretary)
In Attendance:	Dr L Hetherington Dr K Burnett Dr R Fayokun Dr H Garavini Dr K O'Leary Mr K Mistry	(HPA, item 4) (DH Tox Unit, item 5) (DH Tox Unit, item 7) (DH Tox Unit, item 4) (DH Tox Unit, item 9) (DH)
Assessors:	Mr S Samuels	(HSE)
Observers:	Dr R Dempsey Dr J Pritchard L Simms	(Philip Morris International, item 7) (Imperial Tobacco, item 7) (Imperial Tobacco, item 7)

Contents	Paragraph
Item 1: Apologies/announcements	1
Item 2: Minutes of meeting held on 23rd July 2009 (CC/MIN/09/2)	3
Item 3: Matters arising not covered by later agenda items	5
Item 4: Statement on the Assessment of the Carcinogenicity of Chemical Mixtures (CC/09/12)	6
Item 5: Systematic Review of Epidemiological Literature on Para-occupational Exposure to Pesticides and Cancer (CC/09/11)	21
Item 6: Horizon Scanning 2009 (CC/09/14)	28
Item 7: Discussion Paper on the Carcinogenicity Testing of Tobacco Products (CC/09/15)	38
Item 8: Krysiak-Baltyn et al (2009). Country-specific chemical signatures of persistent environmental compounds in breast milk. Internat J of Andrology 32, 1-9 (CC/09/16)	62
Item 9: RNA related effects as mechanism of carcinogenicity (CC/09/13)	67
Item 10: Any other business	70
Item 11: Date of next meeting	71

ITEM 1: Apologies for Absence & Announcements

1. Apologies were received from Mr H Brunt (Assessor, National Public Health Service for Wales), Ms A Gowers (Assessor, EA) , Mr P Holley (Assessor, DH), Dr A Smith (Assessor, HSE) and Dr H Stemplewski (Assessor, MHRA).
2. The Chairman explained that the Food Standards Agency (FSA) had provided advice to the CMO on folic acid fortification in October. One Member reported that he had been independently contacted by DH to provide advice on the recommendations, and was in the process of providing written comments.

ITEM 2: Minutes of meeting held on 23rd July 2009 (CC/MIN/09/2)

3. Members made several small edits to the text and provided some clarification of the conclusions reached during the discussion of insulin-like growth factor-1 (IGF-1) in the diet.
4. Members queried the accuracy of the statement in the draft minutes regarding the association between red meat and colon cancer, attributed to a member of the Scientific Advisory Committee on Nutrition (SACN), in Paragraph 9 (line 95):

“The EPIC study (Norat et al., 2005), did not show a significant association after adjustment for confounding.”

Post meeting, the Secretariat contacted the SACN member, who confirmed that there had been no significant association in the EPIC study after *full* adjustment for confounding. The minutes were amended to reflect this point.

ITEM 3: Matters arising not covered by later agenda items

5. None.

ITEM 4: Statement on the Assessment of the Carcinogenicity of Chemical Mixtures (CC/09/12)

6. Guidance on the assessment of the carcinogenicity of chemical mixtures had previously been discussed at meetings in July 2008, November 2008, April 2009 and July 2009. At the last meeting, Members commented on the second draft statement and requested substantial revisions and inclusion of additional discussion. A third draft of the statement was presented and comments were invited.

General Comments

7. The Committee was asked whether, in view of the protracted discussion on this topic and lack of firm conclusions, it would not be appropriate to draft a statement at this time, with the associated discussion recorded in the minutes. It was acknowledged that this is a very complex

issue, which makes it hard to provide clear advice. Similar difficulties were experienced by the COM when it drafted its statement on mixtures of mutagens. Members considered that there was increasing concern within Europe regarding mixtures of endocrine disrupting chemicals and that this was gaining political momentum, possibly at the expense of looking at mixtures of carcinogens more broadly. It was considered to be important to provide a UK view on mixtures assessment; thus, the Committee should persevere in drafting a statement.

8. It was considered necessary to clearly define the target audience. The statement should provide guidance on how to approach the risk assessment of combined exposures to carcinogens, particularly outlining the substantial uncertainties in this regard. It was acknowledged that there would need to be some discussion of study design principles in order to provide guidance on how these studies might be used in a risk assessment. However, the scope of the document was not to provide experimental guidelines on how to conduct mixtures experiments; such a document would require considerably more detail.

Specific Comments

9. It was noted that the title of the statement implies that it will provide guidelines on how to design studies to assess chemical mixtures. It was suggested that “Risk Assessment of Mixtures of Chemical Carcinogens” or “Risk Assessment of Combined Exposures to Chemical Carcinogens” might be more appropriate titles.

10. The third draft of the statement was a considerable improvement. It would be further improved if definitions (such as paragraphs 18 and 19) could be included in the initial section of the statement, which would help set out the context of the document. There should also be discussion of mode of action (MoA) and dose response. In particular, the term ‘mixture’ should be defined (as exposure to a defined mixture of chemicals, or combined exposure to more than one chemical simultaneously, or at different times). Also the use of the terms synergy and potentiation should be clarified as these should not be synonymous. Care should be taken when discussing interactions which occur as a result of reactions between the chemicals in the mixture, and biological interactions resulting from exposure to the mixture of chemicals.

11. There could also be a section which discussed the use of *in vitro* techniques to assess interactions between chemicals in mixtures. This could refer to *in vitro* genotoxicity studies discussed in the COM statement but should also include broader mechanistic studies including non-genotoxic (including epigenetic) mechanisms, which may be examined *in vitro*. These bespoke assays may provide an opportunity to study an interaction in detail, which would not be feasible in animals or by epidemiological methods. Furthermore, current ‘risk’ assessment advice for genotoxic chemicals is hazard based, i.e. that exposure to chemicals which are genotoxic and carcinogenic should be as low as reasonably practicable (ALARP). Therefore, exposure to a mixture containing both genotoxic and non-genotoxic carcinogens should still be ALARP, regardless of the modulation by the non-genotoxic carcinogen. The most likely scenario for which it would be

important to be able to assess the risk of a mixture would be exposure to a mixture of non-genotoxic carcinogens.

12. However, it was also considered important to recommend caution when conducting focussed *in vitro* studies because these only give *potential* mechanistic insights and it should not be assumed that they can be readily extrapolated to the situation *in vivo*. *In vitro* studies cannot provide a point of departure for risk assessment.

13. The last sentence of paragraph 5 states “...*large and complex studies ...would be hard to justify in terms of either expense or animals.*” Concern was expressed that this statement might appear to advocate not conducting a carcinogenicity study of mixtures, even if there were to be a major health need for such a study. It should instead be noted that such studies would require justification on ethical grounds in view of the large number of animals required.

14. When discussing the section on simple similar action, Members noted that one of the important elements of the Toxic Equivalency Factor (TEF) methodology is that an endpoint needs to be defined as the basis for risk assessment. There are suitable animal studies for dioxins and dioxin-like chemicals that can form the benchmark for the TEF approach. However, when considering the potential carcinogenicity of mixtures of endocrine disruptors, chemicals such as the phytoestrogens may activate or inhibit the oestrogen receptor at different concentrations. Therefore this approach should be used with caution.

15. The TEF approach was also discussed in relation to polycyclic aromatic hydrocarbons (PAHs), citing the European Food Safety Authority (EFSA) opinion on PAHs. This document does not recommend a TEF approach for PAHs and, instead, recommends using a group of PAHs as a surrogate marker of PAH exposure. Members did not consider it appropriate to include PAHs in the section on simple similar action. It was also noted that the advantage of the EFSA approach was that it *does* incorporate some assessment of interaction because it is based on a study which tested a PAH mixture where interactions could be reasonably expected. This should be corrected in the draft statement.

16. The section on dissimilar action was very short and required more discussion. The approach would be to use response addition with multiplicative correction.

17. The statement should also cover the issue of the validity of extrapolation from interactions at high dose to interactions at low doses typical of environmental exposure. It would be inappropriate to recommend high dose studies of mixtures. This point could be included with the text emphasising the importance of understanding the individual chemicals' dose responses before conclusions can be drawn regarding the evidence for interactions. There should also be some comment about the multistage nature of the carcinogenic process; the order of events and timing of exposure are likely to be important when assessing a mixture. A paragraph discussing the utility of computer modelling to predict interactions could also be included.

18. The comments regarding epidemiology studies in paragraph 20 needed to be enhanced. For example, there should be more discussion of the

reasons for false positives and false negatives. This section should include more discussion about investigation of potential interactions. Mathematical models to allow several agents to be studied are now available. The use of biomarkers (both of exposure and of effect) is also becoming practicable.

19. Members suggested that more information for Annex A might be available from the International Agency for Research on Cancer (IARC). The IARC discussion of alcohol and tobacco will be reported in monograph 100E. It is expected to contain an extensive section on interactions and conclude that there is sufficient evidence of carcinogenicity for acetaldehyde. This monograph was still being drafted but some information might be made available to the COC Secretariat. In addition, a summary of the discussion is available in *Lancet Oncology*^a.

20. Several specific editorial changes to the statement were requested which will be reflected in the next draft and several Members agreed to provide draft text for inclusion. It was agreed that further drafts would be circulated to the Committee by email for comment, with final approval by Chairman's action.

ITEM 5: Systematic Review of Epidemiological Literature on Para-occupational Exposure to Pesticides and Cancer (CC/09/11)

21. Professor Boobis declared that he had been a member of the UK Government's Advisory Committee on Pesticides (until 2002) and the European Food Safety Authority (EFSA) Panel on plant protection products and their residues (PPR) (until 2009). He had also been consulted on several pesticide active compounds but none that directly relate to the present review. It was agreed that this should not preclude full participation in the Committee's deliberations.

22. In 2005, the Royal Commission on Environmental Pollution (RCEP) published a report on the assessment of the human health risks associated with the use of agricultural pesticides, which set out its concerns about the exposure of residents and bystanders. The COC and COT were asked by Defra and the ACP to comment on the report and, in 2006, published a joint statement. As part of its response to the RCEP recommendation, the COT recommended that an epidemiological review of para-occupational exposure should be undertaken.

23. The COC was provided with a discussion paper which presented summaries from a systematic review of the epidemiological literature on para-occupational exposure to pesticides and cancer. Members were asked to consider the studies reviewed and to discuss whether the results can be extrapolated to exposure in the UK. They were also asked whether there is an association between para-occupational exposure and cancer, and, if so,

^a Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Coglianò V; WHO International Agency for Research on Cancer Monograph Working Group. (2009) A review of human carcinogens-Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 10(11):1033-4.
<http://www.ncbi.nlm.nih.gov/sites/entrez/19891056>

whether this conclusion could be extrapolated to bystanders and residents, who might be expected to have lower exposure to pesticides.

24. It was noted that some of the tables were missing from the copies of Annex 1 that had been sent to Members. These related to the conduct of the literature review and were not considered to be critical for the discussion. These were verbally summarised by the Secretariat.

25. Members acknowledged that a great deal of work had gone into this review, and good summaries of the studies were provided in the discussion paper. However, the individual summaries of the studies did not offer conclusions about what each study contributes to the overall weight of evidence, and Members considered that there was insufficient information for them to draw conclusions from the summaries provided.

26. In addition, there was concern that the discussion paper focussed on those studies claiming to show a positive association, which meant that it was not possible to comment on the contribution of the negative studies to the weight of evidence. It was explained that an initial view was being sought and that a balanced systematic review would be presented in the first draft statement.

27. It was acknowledged that there were too many studies for Members to scrutinize each individual paper, so the conclusions of the reviewer were requested. Some assessment of the quality of the publication (either in terms of a quality score or key reliability criteria) would also aid the evaluation, along with a sensitivity analysis to help interpret the effect of the most extreme studies. Funnel plots were requested to allow the assessment of publication bias. More detailed summaries would be needed before the Committee could comment on a potential positive association with non Hodgkin lymphoma (NHL) and lack of association with breast cancer. Evidence from occupational studies in agricultural workers could also be used to inform the present review.

ITEM 6: Horizon Scanning 2009

(CC/09/14)

28. Members were provided with a discussion paper containing updates on progress with previous horizon scanning items and suggesting new issues for consideration. An addendum had been tabled containing two additional issues for discussion.

29. Investigations into potential carcinogenic properties of carbon nanotubes had been raised in the 2008 horizon scanning exercise. Members noted that this area of research had advanced, with repeats of some of the key studies; therefore these should also be considered when this item is brought to the Committee.

30. The use of rainbow trout in low dose cancer studies, where large numbers of fish were used to improve statistical power, was discussed. The issue of ethical consideration / Home Office approval of studies involving large numbers of fish was raised. Rainbow trout were considered to be less appropriate as a screening species than rodents for potential human carcinogens, since they are more distant on the phylogenetic tree. Reservations were also expressed about whether it is appropriate to consider

the individual fish to be the experimental unit in the analysis, or whether it should be the tank. This was not considered to be a high priority for further consideration. The use of zebrafish in mechanistic studies was considered to be of more interest and should be kept on the horizon.

31. In 2001 the Committee reviewed a number of papers on the relevance for cancer of interactions between genotype and exposure to chemicals in the environment. The review considered 'low-penetrance' genes (these are genes which may have a high prevalence in the population but alone are not a substantial contributor to the increase in cancer risk). Key elements of this review looked at epidemiological studies of candidate susceptibility genes and genetic association studies of the category of genes.

32. It was noted that many of the early papers on this subject focussed on genes coding for components of detoxification pathways. In the 2001 statement, the Committee correctly predicted that there would be a rapid increase in the availability of genetic association studies, as the technology continued to develop. Members asked to be provided with a copy of the previous statement as a starting point to determine whether the conclusions could be extended in light of scientific advances over the last decade. If this seems necessary, a discussion paper reviewing this field will be prepared with a view to updating the 2001 guidance statement. It was also noted that several recent reviews had been published which provide good summaries of this area of research. Recommendations from HuGE^b (the Human Genome Epidemiology Network^b) on the assessment of gene-environment interactions might also feed into these discussions. It was noted that the consistent association between ALDH2 gene and alcohol/acetaldehyde for head/neck cancers is a good example of gene environment investigation, where consistent results had been obtained. However, studies investigating associations with DNA repair genes have not produced consistent results.

33. The Committee was in favour of a joint meeting between COC / COM to discuss recently updated COM guidance on thresholds of genotoxicity. This meeting would be taken forward if Secretariat resources permit.

34. An addendum to the horizon scanning paper presented recent work on humanised mice, where the murine Pregnane X (PXR) and Constitutive Androstane (CAR) receptors are knocked out, with transgenic expression of the human receptors. Members agreed that such models were sometimes useful when investigating mechanisms of carcinogenicity, but that there was no reason to investigate this model in particular. The Committee is aware of the availability of these models, their uses and limitations. Such studies should be considered on a case by case basis.

35. The addendum also raised the issue of interpretation of mononuclear cell leukaemia (MNCL) in the Fisher-344 rat. Whilst recently reviewing data on phthalates, the HPA Toxicology Unit identified inconsistency in views on the relevance of MNCL (also known as large granular lymphocytic leukaemia) to humans. Members commented that the usual approach was to discount this tumour type, although a weight of evidence approach would be more appropriate, assessing MNCL on a case by case basis, in the context of other pathology. It was agreed to examine a specific example where the

^b <http://www.hugenet.org.uk/>

interpretation of the relevance of MNCL is important for the risk assessment, such as the phthalates.

36. Members were invited to contribute additional horizon scanning items, and were reminded that items could be submitted to the Secretariat throughout the year. Reduction in cancer risk associated with the use of the anti-diabetic drug metformin was suggested; however, it was noted that this was outside the COC terms of reference.

37. It was noted that the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) will hold a workshop on intermittent/short-term exposure to carcinogens in December 2009. Members were keen to discuss the output of this workshop.

Overall Prioritisation

Topic	Rank
Gene-Environment Studies	High
COC / COM joint meeting on Thresholds of Genotoxicity	medium / high
Endogenous DNA Adducts (await COM view)	medium / high
Carcinogenic Risk Posed by Carbon Nanotubes	medium
ILSI/HESI workshop on Intermittent/Short-Term Exposure to Carcinogens	medium
Mononuclear cell leukaemia (MNCL) in the F-344 rat	medium
ETS Exposure in Childhood and Cancer Risk	medium
Mechanistic studies in Zebrafish	low / medium
Rainbow trout cancer assay	not a priority
Humanised mouse models	not a priority
Metformin and cancer risk	not a priority

Grey shaded items have been carried over from 2008 horizon scanning.

ITEM 7: Discussion Paper on the Carcinogenicity Testing of Tobacco Products (CC/09/15)

38. Both Dr Wallis and Dr Powell declared a non-personal specific interest since their respective employers market smoking cessation products. They were permitted to remain in the room but not to participate in the Committee's discussions.

39. In 2004, the COC contributed to a joint COC/COM/COT statement on the toxicity of tobacco products. The Department of Health has asked for an update of the statement because of the increasing literature in this area and a growing concern about the strategies used for the carcinogenicity testing of tobacco products. Since there is no internationally agreed approach to the hazard assessments of these products, DH requires scientific advice on the suitability of the tests used to evaluate the carcinogenicity of tobacco products. Furthermore, DH has no means of evaluating the suitability of the toxicological data used to support the claims made by manufacturers of new products which purport to reduce harm to users.

40. The Secretariat noted some minor errors in the draft discussion paper. Paragraph 55 refers to a list of e-cigarette manufacturers (Annex 9), which later had been removed as it was not considered relevant to

carcinogenic assessment. As a consequence, subsequent references to annexes (Paragraphs 59, 68 and 69) are incorrect. Page 18 provides a correct list of annexes. In paragraph 25, A13 mice should read A/J mice. Finally, in paragraph 47, the text should refer to the Eclipse product primarily heating rather than burning tobacco.

COM views (June 2009)

41. The COM discussed mutagenicity testing of tobacco products at their June 2009 meeting and the Chairman provided a brief outline of their conclusions. The Committee discussed the validity of the mutagenicity tests and agreed with the World Health Organisation (WHO) view that the rate limiting steps in tobacco carcinogenesis were unclear. Members reaffirmed their view that mutagenicity ranking could not be extrapolated to *in vivo* exposure. Mutagenic effects would be likely to be modulated by inflammatory responses in the target organ. Concern was expressed about data presentation, since compensatory increase in product usage may mean that it is more appropriate to report mutagenicity data per milligram of nicotine than per cigarette; this could also be relevant to the COC deliberations.

42. The development of tests for whole smoke rather than smoke condensates would be desirable. Testing pyrolysed ingredients, additives and flavours was not considered by COM Members to add to the risk assessment. The identification of biomarkers of effect would aid risk assessment. Urinary mutagenicity testing was considered to contribute useful information in the case of bladder carcinogenesis only, not in the case of other target organs. The COM agreed that the available data on Potentially Reduced Exposure Products (PREPs) indicated a detectable reduction in mutagenic activity in some *in vitro* assays, but that it is unclear how this translates into a reduction in harm due to the complexities of the mechanism of tobacco carcinogenesis.

General Comments

43. COC Members questioned the reference to new tobacco products “as healthy alternatives to conventional smoking”, which appears in paragraph 2 of the discussion paper. This phraseology should be discouraged as it implies there are health benefits. The Secretariat explained that this was the description given by manufacturers of new tobacco products and not by the Secretariat.

Carcinogenicity Testing

44. The Committee was asked whether the approaches currently used to evaluate the carcinogenic potency of tobacco and its products are suitable; particularly focussing on the use of animal models for tobacco carcinogenesis, and the inhalation and dermal carcinogenicity of tobacco smoke.

45. Members noted that the mouse lung carcinogenesis model is widely discredited as a risk assessment tool; this model is weak and quantitatively unpredictable, thus it is not a reliable basis for comparison of products. The A/J mouse model has been proposed by the tobacco industry as a short term carcinogenicity test; but it is technically demanding, variable and inconsistent, and also widely discredited. Based on the dose response data provided, this

test is relatively insensitive, so would not be good at detecting decreased activity. The B6C3F1 mouse may be a better model for lung tumours, but the duration of exposure would need to be much longer.

46. Lung sectioning is not straightforward and pathological examination of skin is considerably easier; however, it is questionable whether this is representative of other organs. In addition, dermal exposure protocols are generally limited to testing smoke condensate, rather than whole smoke. Members noted that, even for inhalation studies, delivery of whole smoke to the lungs is technically challenging because of difficulties in managing inhaled particle size.

47. Concern was expressed that carcinogenicity following dermal exposure would be principally driven by tumour promotion and would not necessarily adequately reflect other modes of action (MoA) which may be more relevant in other target organs.

48. At a recent International Agency for Research on Cancer (IARC) expert group meeting on monograph 100E, the number of target organs of tobacco smoking was increased to 15 by the inclusion of colon and ovarian cancer. Members also noted that a recent paper [Baris et al. 2009; JNCI 101 (22), 1553-1561] suggested that smokers are *increasingly* at risk of bladder cancer. It could be postulated that changes in cigarette formulation in recent decades could be responsible for this increase in risk.

49. Overall these studies might help to identify and characterise some aspects of the hazard posed by these products, but it is not possible to use these studies as a basis for comparative risk assessment.

Harm reduction

50. Members' advice was sought on the toxicological basis of claims of reduced exposure, harm or risk posed by existing and novel tobacco products. This discussion covered comparison/modification of products, PREPs, novel nicotine delivery systems (such as e-cigarettes) and smokeless tobacco products. It was noted that some organisations, such as the WHO, place great emphasis on the need to reduce harm in addicted smokers.

51. Members disagreed with the notion that the studies presented in the discussion paper demonstrating a reduction in exposure to harmful substances would necessarily result in a reduction in carcinogenic potential.

52. With regard to e-cigarettes, there was some uncertainty as to whether these products only deliver nicotine in a vapour, or whether users of these products are exposed to other chemicals. If these products only contain nicotine, they would not be expected to contribute to exposure to tobacco derived carcinogens.

53. The Committee was asked what approaches could be used to assess effectively the carcinogenic potential associated with the use of novel and existing products. It was noted that there may be a temptation to develop tests that are sensitive, but not necessarily predictive of the real risk. Using such tests would result in spurious claims. It may also be inappropriate to perform direct comparisons of products without taking into account changes in smoking behaviour that might be expected to occur once the use of the new

product has become established. The Committee was informed of a number of intervention studies where electrically heated cigarettes were used for up to 12 months; product use increased throughout the study with no apparent plateau [Roethig HJ et al J Clin Pharmacol, 48, 580-591, 2008].

54. Members concurred with the WHO position quoted in paragraph 56 of the discussion paper:

“The WHO does not consider these products to be legitimate cessation aids for smokers trying to quit because they have not been adequately tested, nor to be proven nicotine replacement therapy (NRT) products. At present, there is no evidence to confirm safety or efficacy and there are no peer-reviewed studies on these products. However, the WHO does not discount the possibility that they could be smoking cessation aids, albeit with appropriate clinical studies and toxicity analyses.”

55. Recent epidemiological evidence does not support the hypothesis that the relative risk associated with smoking is decreasing since the advent of newer ‘safer’ cigarettes (such as ‘low tar’); the strength of association stays the same or may get stronger. The only plausible way of demonstrating reduced harm is to let people ‘smoke’ these products, recording their usage, and investigate whether risk of disease changes; although the Committee did not recommend conducting such a study.

Added Ingredients

56. Members were asked about the suitability of the approach used to test the contribution of individual or mixed ingredients, or additives, to the overall toxicity of tobacco products. The Committee considered that the available studies are inadequate to assess the risks posed by conventional cigarettes, so it is not possible to assess the modulation of that risk resulting from inclusion of additives. The relationship between effect (increase in biomarker) and exposure is also poorly understood. Furthermore, it is possible that additives might alter smoker behaviour, such as to increase product use; this increased exposure would be likely to result in an increased risk.

Biomarkers

57. The Committee was asked what work needed to be undertaken to develop biomarkers of disease, harm or injury for tobacco products, particularly in relation to cancer. This was considered to be a laudable but an unrealistic goal; many researchers and clinicians want a biomarker that shows whether an individual is going to develop cancer. Existing strategies, including 8-Oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG), urinary adducts and sister chromatid exchanges (SCE) in peripheral blood lymphocytes, have only been of limited utility.

58. The ‘omics technologies identified by the tobacco industry might provide some alternatives but these would tend to be biomarkers of exposure, rather than effect. Metabonomics might be able to identify biomarkers of early effects of smoking in adequately designed prospective studies, although the Committee was sceptical about the likelihood of finding a suitable biomarker.

59. The mechanisms underlying tobacco carcinogenesis are very complex, and are likely to be different in the various target organs and tissues, so it will be very difficult to identify a suitable comprehensive biomarker of effect.

Cancer Risk Index(CRI)

60. Members questioned the aims of the CRI approach and how a list prioritising carcinogens in tobacco smoke would be used. As was said previously for tobacco additives, the available studies are inadequate to assess the risks posed by conventional cigarettes, so it is not possible to assess the risks posed following removal of a specific carcinogenic element of the product. It would be very difficult to infer reduced harm on the basis of studies examining a limited number of endpoints. Furthermore, it was noted that the cancer potency estimates used were usually derived from one or more animal models using a linearised multistage model. The COC does not endorse these estimates, as outlined in COC guidance^c; therefore, the Committee would have no confidence in the values used to rank tobacco carcinogens.

61. Overall, the identification and removal of carcinogenic components from tobacco products would be desirable, although it is not clear whether removing them would result in any reduction in harm.

ITEM 8: Krysiak-Baltyn et al (2009). Country-specific chemical signatures of persistent environmental compounds in breast milk. Internat J of Andrology 32, 1-9 (CC/09/16)

62. A Committee view on this paper had been sought because of the high level of interest in Europe on endocrine disrupting chemicals (EDCs) and mixtures of EDCs. The paper postulates that exposure to endocrine disrupting chemicals may be the cause of the higher incidence of testicular cancer in Denmark compared to Finland. It describes an ecological study comparing levels of endocrine disrupting chemicals in human milk taken from Danish women and Finnish women. After correcting for multiple testing, 6 out of 109 chemicals^d exhibited significant differences between the two countries and all were higher in Danes; of the 109 chemicals, without correction, 58 exhibited significant differences and 54 were higher in the Danish samples. Members are asked for comments on the methodology, findings and conclusions of the study.

63. It was suggested that other systematic differences between the populations might explain the effects seen in testicular cancer rates. Being a purely ecological study, it is not possible to determine whether any association was causal. It would strengthen the analysis if milk from other countries had been included. Members also suggested that comparison of cows milk from different countries might also give an indication of the variation in national environmental chemical exposure; such information might be available from European Food Safety Authority (EFSA) or the European Commission;

^c <http://www.iacoc.org.uk/publications/documents/guideline04.pdf>

^d 1,2,3,4,7,8-HCDD; PCBs 156, 157 and 209; dieldrin; and hexachlorobenzene

however, it was noted that the contaminant content of cows' milk would be highly dependent on cattle feed specification.

64. Concern was expressed at numerous omissions when describing the analytical methods. The Committee was surprised at some of the levels of significance ascribed to the analyses, given the large number of multiple comparisons. It would be reasonable to expect that 6 out of 121 chemicals might be different between two national populations by chance, if the tests were independent. However, given the classes of persistent organic pollutants that had been identified, it is reasonable to assume that there would be some correlation amongst many of the chemicals. Members noted that the two populations clustered very closely together in the principal component analysis, and that there was no discussion of the outliers.

65. The paper did not describe how the subjects were selected in the two countries and it was unclear whether the sample was representative of the respective populations. The high prevalence of cryptorchidism in the study population might indicate bias in study recruitment. There were also insufficient details of sample collection and processing and it should be noted that there was an 18 month difference in sample collection between the two groups.

66. The Committee concluded that, from the data provided, it might be possible to say that the chemical signature may be different when comparing the two sampled groups; however, it is not possible to infer that this signature is representative of the Danish and Finnish populations, thus any associations should be regarded with caution.

ITEM 9: RNA related effects as mechanism of carcinogenicity (CC/09/13)

67. This area of research was identified during the horizon scanning exercise in November 2008 and it was considered to be an appropriate time to review the area due to the substantial amount of emerging data in the scientific literature. The Committee was provided with a review of the role played by RNA mechanisms in cancer development; concentrating primarily on RNA editing, alternative splicing, non-sense mediated decay (NMD), RNA binding proteins and RNA interference and the role of miRNAs, as mechanisms that could potentially influence tumourigenesis.

68. Members praised the thorough and detailed review and considered it to be worthy of publication. Unfortunately, there was insufficient time remaining for a full discussion and Members asked that this item be discussed at a future meeting. When updating the review, inclusion of diagrams might help explain some of the more complex aspects of the field.

69. To date, there have been very few relevant papers published on chemicals such as environmental chemicals or known carcinogens although there are numerous papers discussing the influence of therapeutic drugs on RNA mechanisms. Members noted that this is a rapidly moving field. Inclusion of a review of any emerging papers on environmental chemicals interacting with RNA processes would be useful.

ITEM 10: Any Other Business

70. None.

ITEM 11: Date of Next Meeting

71. 22nd April 2010 at Department of Health, Skipton House, Elephant & Castle, London, SE1 6LH. [This meeting was subsequently cancelled and the next meeting was held at the same venue on the 22nd July 2010].