

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

Minutes of the meeting held at 10.30am on Thursday 25<sup>th</sup> November 2010 at Department of Health, Room 124A, Skipton House, Elephant & Castle, London, SE1 6LH.

Present

Chairman:	Professor D Phillips	
Members:	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 Dr P Edwards Dr L Hetherington	(Scientific Secretary) (Administrative Secretary) (Minutes)  (Item 9) (Item 4)
FSA Secretariat:	Dr D Benford	
In Attendance:	Dr K Burnett Dr I Dewhurst Dr H Garavini	(DH Tox Unit, item 6) (Health and Safety Executive, item 5) (DH Tox Unit, item 4)
Assessors:	Dr C Pease Dr H Stemplewski	(Environment Agency) (MHRA)
Observers:	Mr I Chart Dr L Plunkett	(AMVAC Chemical Company, Item 5) (AMVAC Chemical Company, Item 5)

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### **ITEM 1: Apologies for Absence & Announcements**

1. Apologies and written comments were received from Professor A Boobis (COC Member). Apologies were also received from Dr C Allen (COC lay member), Mr H Brunt (Assessor, National Public Health Service for Wales), Mr P Holley (Assessor, DH), Dr A Smith (Assessor, HSE) and Mr S Samuels (HSE CRD).
2. The Chairman welcomed Drs Hetherington and Garavini, who had prepared the paper on para-occupational pesticide exposure (Item 4) and Dr Dewhurst (HSE), who had prepared the paper on Dichlorvos (Item 5). He noted that Drs Chart and Plunkett from AMVAC Chemical Company would join the meeting for Item 5; and Dr Edwards would join the meeting later to give a verbal update on OECD work (Item 9).
3. Members were informed that the HPA finance department had stipulated that, in future, first class travel would only be reimbursed in exceptional circumstances, in line with general restrictions on first class travel across Government. Therefore, Members were requested to use second class travel if at all possible. If this presents a problem, Members were asked to discuss it in advance with the HPA Secretariat.
4. It was noted that Dr D Mason (HPA) would soon be leaving the HPA to take up a position in Industry. He was thanked for his contribution to the work of the Committee.
5. Members were reminded to declare any interests they may have in an item before its discussion.

### **ITEM 2: Minutes of meeting held on 22<sup>nd</sup> July 2010**

[\(CC/MIN/2010/1\)](#)

6. Members made several small edits to the text.
7. With regard to the discussion of Genome-Wide Association Studies (GWAS), paragraph 38 of the draft minutes, it was explained that certain well respected scientific journals require authors to replicate their findings in several independent studies before a paper will be accepted for publication.

### **ITEM 3: Matters arising not covered by later agenda items**

8. The Committee was provided with comments on the Gene Environment Interactions Paper (Item 5 at the July meeting) from Professor Vineis, who had left the July meeting early. Members were content that these comments were adequately reflected in the minutes of the meeting.

### **ITEM 4: Para-occupational pesticide exposure**

#### **Additional evaluation of data from the systematic review of epidemiological literature of para-occupational exposure to pesticides and cancer** [\(CC/2010/04\)](#)

9. In November 2009, the COC evaluated a draft discussion paper detailing a systematic review of epidemiological literature which focussed on para-occupational exposure to pesticides and cancer. Members considered that further

analysis of these data were needed before conclusions could be drawn. To assist Members with their evaluation, an assessment of publication quality and bias, and sensitivity analyses (where appropriate), was presented in the [discussion paper](#).

10. Members agreed that the review was thorough and commended the Secretariat on the amount of work undertaken. They commented that it would have been useful for the numbers of cases to be included in the summary tables of case control studies. Similarly, the size of each cohort study is an important factor when considering the overall weight of evidence, and an accompanying narrative review would have been helpful since several of the study limitations can be lost in the tables, such as poor quality of exposure assessment. It was noted that there was no significant heterogeneity in the analysis, and funnel plots gave no evidence of publication bias (although the power to detect publication bias was low due to the small number of studies).

11. There would have been no value in conducting a meta-analysis on the cohort studies because only 2 cohorts of individuals were involved in the studies and there were no readily comparable exposure conditions where risk of disease was also reported.

12. A diversity of cancer types and exposure scenarios were reported in the case-control studies, which made comparison of these papers difficult in meta-analysis. Interpretation is also further complicated by the fact that the studies examine exposure to 'pesticides' as a whole; which comprises many different active chemicals, each with potentially differing modes of action and target organs. This could dilute any genuine associations seen in the study. It is possible that a high risk for a specific tumour type could be missed, although it was noted that, due to the extensive testing and toxicological evaluation of pesticides, high risk substances were unlikely to be in use today. A further complication is the fact that a proportion of past pesticide exposure would have been to substances whose use had been discontinued, thus would not be relevant to an assessment of current risk.

13. A meta-analysis was performed for a small group of studies reporting on 'haematopoietic cancers' in children. Although the pooled odds ratios (OR) were >1 in all of the meta-analyses performed, the confidence intervals suggested no significant association between the exposure and the occurrence of cancer. Members considered that, whilst confidence intervals which included the OR of 1 is a helpful tool for assessing the significance of the findings, the fact that all results were above 1 did provide limited evidence of a weak effect. The two highest quality studies reported negative findings and the remaining studies had limitations in study design and possible bias that cast some uncertainty on the conclusions. Together, the lack of significant effects, and limitations in study design and in the analysis of the studies mean that the strength of the findings is relatively weak; using International Agency for Research on Cancer (IARC) terminology, there is 'limited evidence' of an association.

14. It was noted that two recent meta-analyses of maternal prenatal occupational exposure also support an association between pesticides and childhood leukaemia ([Van Maele-Fabry \*et al.\*, 2010, Cancer Causes Control. 21\(6\):787-809](#); and [Wigle \*et al.\*, 2009, Environ Health Perspect. 117\(10\):1505-13](#)). Only 5 of the 25 studies included in the Van Maele-Fabry analyses and 4 of the 35 studies used in the Wigle analyses were also used in the COC review.

15. Members noted that there was some inconsistency in the study interpretation in the discussion paper; in paragraph 20, an OR above 1, with a lower 95% confidence interval of 0.94, was presented as providing some evidence of a positive association between mothers' occupational exposure to pesticides and the occurrence of haematopoietic cancers in children, which is different to the conclusion on professional pest control and haematopoietic cancers, in paragraph 26, which also yielded an OR above 1 and a similar lower 95% confidence interval of 0.98.

16. Members recommended that, although beyond the scope of the present review, studies investigating occupational exposure to pesticides would be of great benefit in interpreting the significance of the weak effect suggested by this meta analysis. Credence would be given to this finding if occupational studies, where exposure would be higher and better characterised, give rise to similar effects. However, one Member noted that even the occupational studies suffered from poor exposure assessment.

17. A major limitation of the available data is the pooling of all leukaemias, since the aetiology of such cancers is not necessarily the same. Grouping haematopoietic cancers could dilute the effects for specific types of leukaemia. Also, relatively little information was available for solid tumours. Some had been included as endpoints in the cohort studies and, if the actual numbers of cases had been provided, it would have helped to give an indication of the adequacy of the database ([Annex 2](#)). A further limitation of the available data was that no specific chemicals were identified as associated with increases in cancer risk.

18. Regarding extending conclusions from para-occupational exposure studies to bystanders and residents, Members considered this should be exposure driven; if bystander exposure is less than para-occupational then any effect is unlikely to be stronger. In general, it is not possible to extend the observations to residents and bystanders because the relative differences in the magnitude and profile of exposures are not yet known.

19. In summary, the Committee considered that there is limited evidence for a weak positive association with maternal para-occupational exposure to pesticides and childhood leukaemia. There is insufficient evidence to determine whether this is causal, nor which the likely candidate pesticides are.

20. In response to a question from the secretariat, Members considered that a good approach to take when conducting a review of cancer epidemiology studies for the committee was to provide a narrative review initially, followed by a targeted detailed meta-analysis.

**Draft joint statement on the systematic review of epidemiological literature on para-occupational exposure to pesticides and health outcomes. ([CC/2010/05](#))**

21. Members noted that COT had already offered comments on the sections relevant to it, and feedback was requested on those sections specifically relating the COC. In particular, the COT had clarified its definition of para-occupational exposure to be only exposure arising from occupational use of pesticides by a close family member. Members queried why the review should be limited to close family members, since there could be other long-term residents within the dwelling.

22. COC Members did not wish to limit the definition of para-occupational exposure in the same way as it would mean that several informative studies would not be included in the review. Since there would be a different scope to the COC and COT literature reviews, it would seem sensible to include separate headings to discuss the scope of each committee's review. It was decided that the COC would draft a separate statement, so that the COT can refer to the COC findings. The COC statement should give details of key study statistics (numbers of cases and controls, etc.).

23. Conclusions on mothers' occupational exposure to pesticides and haematopoietic cancers in children should be edited in line with COC discussions on the last item. Paragraph 28 should refer to "limited evidence of a *weak* association...". Paragraph 76 focusses on the limitations of the studies. This should include pooling of outcomes. Paragraph 77 discusses the relevance to exposure in the UK. It mentions that products may not be used / approved in the UK, or may be used differently. This should also state that none of the studies were conducted in the UK.

24. It was suggested that the conclusions should reiterate that the overall effect appears to be small. It would be helpful to include some information about when certain pesticides ceased to be approved, in relation to cancer latency period.

25. Conclusion ii) in paragraph 78 states that: "If there was an association between para-occupational exposure, cancer and specific pesticide active ingredients it would be small and difficult to investigate further." Members noted that the opposite could be the case, i.e. associations with specific pesticide active ingredients could be large, but masked by lack of association with all of the other active ingredients to which subjects were exposed.

26. Members were thanked for their comments. A second draft statement would be produced for further consideration in due course.

#### **ITEM 5: Dichlorvos**

**[\(CC/2010/06\)](#)**

27. Professor Boobis (who was absent but had provided written comments) declared a non-personal specific interest, because he chaired the working group that reviewed the carcinogenicity of dichlorvos for the European Food Safety Authority (EFSA). Dr Benford (FSA Secretariat) declared a potential interest, since she had been an author of the studies investigating the mode of carcinogenic action of dichlorvos, in 1991, whilst working for a former employer. The Chairman considered this to be a lapsed interest.

28. Members were informed that dichlorvos is an organophosphorus insecticide which, currently, has no agricultural or non-agricultural uses in the UK. Its use as a biocide is under review within the EU. The Health and Safety Executive (HSE) had requested COC advice as to whether a threshold can be assumed for the carcinogenicity of dichlorvos. This advice will be used when formulating a position for the ongoing EU discussions on the use of dichlorvos.

29. The mutagenicity of dichlorvos was evaluated by the COM in 2002 as part of a UK review ([COM, 2002](#)) which concluded that it showed evidence of site of contact mutagenicity in the skin, and in the liver following intra peritoneal dosing. The COM considered that, in absence of satisfactory evidence for an alternative

mode of action, it would be prudent to assume a genotoxic mechanism for the forestomach tumours seen in a US National Toxicology Programme (NTP) gavage study in the mouse (Chan, 1989; Chan et al, 1991; [NTP Study Report 342](#)) and oesophageal tumours seen in a dietary study in the mouse (NCI, 1977; Weisburger, 1982); thus, no threshold could be assumed for the mutagenic and carcinogenic effects of dichlorvos.

30. Subsequently, evaluations of dichlorvos have been performed by the US Environmental Protection Agency (EPA) and the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR) of EFSA. In its [opinion](#), the PPR Panel considered there to be a potential for site of contact mutagenicity *in vivo*. However, it accepted the conclusion of NCI (1977) that dichlorvos was not demonstrated to be carcinogenic in that study. Furthermore, the forestomach tumours were considered to be a high dose phenomenon which is subject to a threshold. The EPA review drew similar conclusions to the PPR Panel. The data, summarised in [CC/2010/06](#), was available to all 3 groups; no new data of any significance has been made available since the COM discussions in 2002.

31. Members were asked to consider the COM and PPR Panel reports, focussing on whether the tumours seen in studies with dichlorvos are likely to be produced by a threshold mechanism, and whether uncertainty about the mode of action means that it is still prudent to assume no threshold.

32. The Chairman had granted permission for representatives of AMVAC Chemical Company to give a short presentation of their interpretation of the mode of action for the forestomach tumours. Dr Plunkett summarised the findings of a review by Ishmael, *et al.* ([2006, Regul Toxicol Pharmacol. 44\(3\):238-48](#)), which evaluated the individual animal data from an inhalation study with negative findings by Blair *et al.* ([1976, Arch Toxicol. 35\(4\):281-94](#)). This had been criticised in the IARC review of dichlorvos ([IARC, volume 53, 1991](#)). Ishmael concluded that this study was adequately conducted for cancer risk assessment. A paper by Koutros *et al.* ([2007, Cancer Causes Control. 19\(1\):59-65](#)) considered the relationship between cumulative lifetime use of dichlorvos and cancer risk in the prospective US Agricultural Health Study cohort in 2004 and found little evidence of an association.

33. Dr Plunkett also discussed a report by Starr *et al.* (2008) entitled "Statistical analysis of the effect of corn oil gavage versus feeding on the incidence of mouse forestomach hyperplastic lesions: use of the National Toxicology Program database" which examined control group tumour incidence in corn oil gavage cancer studies, noting that female control mice from the NTP dichlorvos bioassay had the highest forestomach tumour incidence (5/49) in any of the 19 studies examined. In addition, corn oil gavage was associated with a significant increase in forestomach tumour incidence compared to dietary studies. Starr's analysis was extended in a subsequent report by Plunkett *et al.* (2009) (reference not located) which compared corn oil gavage with dietary and inhalation studies performed in multiple laboratories. This found a consistently increased incidence of forestomach tumours in corn oil gavage control animals.

34. Dr Plunkett suggested that the irritant properties of dichlorvos and the association between corn oil and forestomach tumours, together with lack of carcinogenicity by all other routes (inhalation, water gavage, drinking water, and diet), all add to the weight of the evidence that dichlorvos alone is not carcinogenic.

She considered that there is a threshold for tumour induction when dichlorvos is administered in corn oil.

35. The Chairman thanked Dr Plunkett for her presentation and invited comments and questions from the Committee. It was noted that, although the inhalation studies were negative, there is the potential for over estimation of the exposure level. The doses cited assumed 100% uptake but the actual level of uptake may have been as low as 10% of the administered dose. Dr Plunkett observed that the whole body exposure in the study meant that coat licking would be a substantial contributor to overall exposure, although she acknowledged that this would not contribute to a site of contact effect in the lung.

36. Members noted that there was a five-fold difference in response between male and female mice in the NTP study and it would be surprising if the proposed mechanism of dichlorvos irritation and a corn oil based mechanism for forestomach tumour formation was sex specific. They also noted the lack of a corresponding effect in the rat forestomach, where similar physiology would result in prolonged exposure of the forestomach epithelium. Dr Plunkett responded that physical injury of the forestomach epithelium may be more likely in the mouse gavage procedure, which could contribute to gastric irritation. The volume of the gavage dose and forestomach surface area may also be important factors in the different responses in the two species. The sex difference was difficult to explain, but was not observed in the other carcinogenicity studies on dichlorvos.

37. It was observed that, although the tumour incidence was increased in the highest dose group of female mice in the NTP study, there was no apparent dose-response in the incidence of forestomach hyperplasia in male and female mice.

38. Members asked whether there was any evidence of cytotoxicity in the pathological investigations following corn-oil administration. Dr Plunkett was not aware of any such analyses; however, Members considered it reasonable to expect that cytotoxicity would have been identifiable in the pathological specimens from the time-course used in the study by Benford *et al.* ([1994, Toxicology 92\(1-3\):203-15](#)), were it to have been present.

39. Members commented that, if one was to ignore the results from genotoxicity tests and consider the evidence from the range of carcinogenicity studies, the forestomach tumours bear all the hallmarks of a non genotoxic effect i.e. the effect is late onset and occurs at a single site, with no evidence of dysplasia in the polyps. It is likely that the carcinoma is relatively discrete, whereas genotoxic substances tend to lead to metastatic, invasive pathologies. Given the lipophilicity of the compound, administration in corn oil was likely to result in a higher level of gastric epithelium exposure than would be expected from equivalent doses in an aqueous vehicle. Members agreed that there seems to be some interaction between corn oil and test chemicals, so it is plausible that it has some influence on the results of the NTP study and that dichlorvos could cause cancer through a threshold based mechanism. However, there are not sufficient data to support the hypothesis, particularly given the results of the genotoxicity tests.

40. It was noted that the EFSA PPR Panel review had focussed on the physiological differences between humans and rodents, with regard to retention of the test material in the forestomach, which the PPR Panel considered not to be relevant to humans. Although the Panel did not rule out DNA interaction as a critical

step, it considered the forestomach tumours to be the result of high and sustained local exposure of the forestomach epithelium and, therefore, to be a thresholded effect. Similarly high levels of exposure for human tissues would be precluded by severe systemic toxicity as the result of acetylcholine esterase inhibition.

41. Members stated that, although rodent forestomach tumours should not be routinely disregarded; the uncertainties in this case mean that the weight of evidence for dichlorvos being a potential human carcinogen is not strong. However, the Committee's position on the risk assessment of carcinogens is that there needs to be clear evidence of a mode of action for tumour formation, before it can move away from the default non-threshold assumption for substances that are genotoxic and carcinogenic.

42. With regard to the specific questions posed in CC/2010/06, there is, at present, insufficient evidence to confirm a threshold mode of action for the female mouse forestomach tumours. One Member considered that, although dichlorvos appears to be a weak carcinogen and it is not possible to exclude a weak mutagenic effect from the available data, it might be possible to define a minimal risk level. For example, it may be informative to use benchmark dose modelling<sup>a</sup> to determine a BMDL<sub>10</sub>, and then consider whether the margin of exposure is acceptable at a worst case level of human exposure. However, it was noted that this approach is not used for regulatory authorisations. On balance, it was concluded that there is insufficient evidence to move away from the Committee's default approach for substances that are genotoxic and carcinogenic, which is that exposure should be as low as reasonably practicable (ALARP).

43. It was noted that key studies, exploring site of contact mutagenic effects using transgenic mice, DNA adducts and the comet assay would be of use in interpreting the relevance of the genotoxic mode of action. In 2002, the Advisory Committee on Pesticides had requested appropriate site of contact studies in the MutaMouse and investigation of site of contact gastric cytotoxicity in the mouse. Members agreed these studies would fulfil the data requirements for dichlorvos.

## **ITEM 6: Horizon Scanning**

**[\(CC/2010/07\)](#)**

44. The Committee was provided with a paper detailing progress with previously identified horizon scanning items and proposing some new suggestions of areas for consideration from Members, the Secretariat and Assessors. Members were invited to briefly discuss the former and new horizon scanning topics, along with any other topics that Members wished to raise; then to review the priorities for future work.

45. It was noted that the carcinogenic risk posed by carbon nanotubes and a paper on gene-environment studies had been discussed at the last meeting.

46. Members debated whether mononuclear cell leukaemia (MNCL) in the F-344 rat should remain on the list. It had previously been considered that it would

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<sup>a</sup> The Benchmark Dose (BMD) methodology is used to derive a point of departure from carcinogenicity study data for risk assessment purposes. The BMDL<sub>10</sub> is typically used, this is determined by fitting mathematical dose-response models to the data from the study, then taking the lower 95% confidence interval of the benchmark dose associated with a 10% response (e.g. tumour incidence).

be useful to have guidance on this, as there had been inconsistency in published expert views on the human relevance of MNCL. This tumour type is often routinely discounted but, when this issue was discussed under the 2009 horizon scanning item, Members considered that a weight of evidence approach would be more appropriate. It was also noted that the F-344 rat was not used so commonly for testing nowadays.

47. It was suggested that a better use of Committee time would be to consider the relevance of common strain-specific tumour types more broadly. It was noted that an International Life Sciences Institute (ILSI) group is looking into the relevance of different tumour types, and that the output of this group might be informative for Committee discussions. Often, these common tumour types do not yield the lowest point of departure arising from the study, so a risk assessment based exclusively on these tumour types is likely to be rare. The issue was considered to be of relatively low priority for the Committee.

48. The two joint COM/COC items, i.e. a joint meeting on thresholds of genotoxicity and an item on endogenous DNA adducts, had been delayed due to lack of resources. Members were informed that committee secretariat resources would not improve in 2011. These were considered to be important items that should remain on the work programme. The discussion then moved to the new topics suggested for inclusion in the work programme.

#### Alternatives to the 2-year bioassay

49. Members had suggested that the continued relevance of the 2 year bioassay should be included in the horizon scanning item. Attention was drawn to a recent paper arising from an ISLI HESI project to explore whether potential carcinogens could be detected by genotoxicity testing and precursor effects in 90-day studies ([Boobis \*et al.\*, Toxicol Pathol. 2009;37\(6\):714-32](#)).

50. It was noted that the debate is led by the pharmaceutical industry, where most of the 2-year bioassays are currently conducted. Although short-term assays are not well used at present, it was noted that presentations had been made to US and Japanese authorities, and there have also been suggestions that this proposal should be evaluated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

51. The premise is that short-term assays could identify early lesions, which predict a tumour endpoint that would have been detected by the 2 year assay; thus a sponsor could avoid conducting a 2-year bioassay if the results of a 6-month study were negative. Thus the methods would be predominantly hazard identification, and of little use to hazard characterisation or risk assessment.

52. Members were doubtful of the biological plausibility of being able to predict ovarian or testicular tumours on the basis of intermediate endpoints, such as liver or adrenal hyperplasia. There would need to be a huge range of intermediate endpoints to cover all possible modes of action. Even with a full range of intermediate endpoints, many lesions would be expected to develop long after these studies had concluded. Epigenetic changes are one area where the pathological consequences may not be evident in short-term studies.

53. A paper by Cohen ([2010, Toxicol Pathol. 38\(3\):487-501](#)) had been provided to Members. This proposed an alternative approach to the 2-year study,

based on a detection of 'key events' in cancer development and a mode of action (MoA) analysis. For this to work, it would be necessary to develop a specific and sensitive battery of acceptable tests that will always detect all the necessary key events. It was noted that an evaluation of toxicogenomic analysis of NTP studies was discussed at a recent US Environmental Protection Agency (EPA) meeting. It would be useful for the Committee to consider this paper when it is published.

54. Although Members had substantial reservations about the robust detection of carcinogenicity in short-term studies, it was considered that it would be a timely and valuable topic to review, particularly given that the COC guidelines are to be updated.

#### Epigenetics and cancer

55. Epigenetic effects are of increasing interest and are likely to further blur the boundary between genotoxic and non-genotoxic carcinogens (although this distinction is useful at present). The full implications of epigenetic changes are not always clear, for example, there is some evidence to suggest that low levels of air pollution causes a global hypomethylation of DNA. It is also important to understand how perturbation of one-carbon metabolism can result in epigenetic changes; this relates to certain types of dietary supplement, such as folate. It would be helpful to review information on any demonstrable role of epigenetics in experimental carcinogenesis. Thus, a review of this area would be useful.

#### Dose response modelling in epidemiology studies

56. Recent EFSA opinions have derived points of departure (PODs) from epidemiological studies using BMD methodology; these included the opinions on [cadmium](#) and [lead](#), where the PODs were based on non-cancer endpoints, and those on [arsenic](#) and [aflatoxin](#), where the PODs were based on cancer endpoints. The use of BMD modelling in this way is a contentious issue in several fora. There are concerns that applying a methodology directly to epidemiological data, when it has been designed to model experimental data, is likely to be inappropriate because the data are inherently different (dose spacing vs. continuous exposure, exposure uncertainty in epidemiology studies, etc.).

57. The criteria used in BMD modelling are not always clear in risk assessment reports. It was noted that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) had published guidelines on how to conduct and report modelling information ([JECFA, 2009](#)).

58. There may be some value in the COC considering the criteria that should be met when modelling epidemiological data; for example: whether or not the response should show a statistically significant trend with exposure, whether data should be constrained to a specific dose response, and how (or if) case-control data, which is not prevalence data, can be used. However, this was not considered to be high priority.

#### Mode of action (MoA) framework

59. The COC previously reviewed the MoA and human relevancy frameworks in [April 2005](#), and agreed that these approaches both provided a logical framework in which to set the information needed when assessing the relevance of

chemical induced animal tumours to humans. Members were aware of a number of developments in this area that would be worth reviewing.

### Alcohol and Cancer

60. A review of the association of alcohol and cancer was suggested, particularly in terms of exploring the acetaldehyde dose-response relationship and the MoA in animal studies. The COC had reviewed alcohol and cancer in 1995 and had issued a statement on [alcohol and breast cancer](#) in 2004. It was also noted that the evidence for the various tumour sites had been reviewed by the International Agency for Research on Cancer (IARC) and will be published in monograph 100E. The Secretariat questioned whether it would be a valuable use of Committee time, given that there is already a clear public health message regarding alcohol consumption.

### Short-term exposure to carcinogens

61. It was noted that a manuscript had been submitted for publication following an ILSI HESI workshop on short-term exposure to carcinogens. This would be shared with the Committee as soon as it is in the public domain.

### Prioritisation of Work Programme

62. Members considered the overall priority of former (shaded in grey) and new horizon scanning items:

<b>Topic</b>	<b>Priority</b>
Epigenetics and Cancer	high
Mode of Action Framework	high
Short-term exposure to carcinogens	high
Alternatives to the 2-year bioassay	medium - high
COC / COM joint meeting on Thresholds of Genotoxicity	medium - high
Endogenous DNA Adducts (await COM view)	medium - high
ETS Exposure in Childhood and Cancer Risk	medium
Dose response modelling in epidemiology studies	low - medium
Mechanistic studies in Zebrafish	low
Common strain specific tumour types (e.g. Mononuclear cell leukaemia (MNCL) in the F-344 rat)	low

### Existing COC statement review

63. At the previous meeting, the Committee had considered it appropriate to review all previous statements, in order to identify areas where the scientific thinking or evidence may have moved on since publication of the statement. Members were provided with a list of existing statements (Annex C of [CC/2010/07](#)) and were asked to consider whether they were aware of research or other scientific opinions that would enable the conclusions and advice within these statements to be extended or revised.

64. It was considered that non-experts visiting the site might be reassured that certain topics, such as chlorinated drinking water, have been periodically reviewed; however, it was noted that some statements, such as [environmental tobacco smoke](#), are more than 10 years old. It was suggested that perhaps the 10 oldest statements could be circulated to Members for consideration.

65. The Secretariat explained that the tobacco smoke statement was done at the specific request of the Department of Health, in order to shape policy. That policy has been implemented, so there would seem little need to revisit this topic. This emphasised that, although some topics may be out of date, this does not mean that it is necessary to revisit them; and the needs of the sponsoring department should be considered.

66. The Committee considered it important that out-of-date statements should not be left as 'current positions' as this could lead those visiting the site to believe that out-of-date concepts are the current view of the Committee. It was suggested that the Statements page could be divided into two sections, those which are still current, and an archive for statements that Members consider no longer reflect the current state of the science.

#### **ITEM 7: COC Guidance statements - update**

[\(CC/2010/08\)](#)

67. At the last meeting, Members supported the idea of providing COC guidance as a series of statements on specific topics, with a single overarching summary guidance statement to bring together the detailed advice. The draft presented at this meeting was a distillation of the previous 2004 guidance into the draft summary guidance statement G1 ([Annex 1](#)). Detailed discussion of specific topics (for example, low dose extrapolation of cancer models) had been removed and summarised, with the intention of retaining the detailed discussion in the underpinning guidance statements (a proposed list of these underpinning guidance statements was listed in [Annex 2](#)).

68. It was intended that the discussion should focus on the main issues that need to be addressed in subsequent drafts of the statement, rather than detailed drafting points. To this end, Members were provided with a series of questions to provoke discussion of the initial draft of the text. Unfortunately, due to a full agenda, there was little time available for a full discussion.

69. The 2004 guidance had presented the US National Academy of Sciences risk assessment paradigm as a four stage process. Whilst the four elements of the process were still emphasised in the draft, Members were content with the more flexible approach, given that there are other risk assessment strategies and frameworks that blur the boundaries between the elements in the classical paradigm. Risk assessors should be able to consider all the available information when evaluating the weight of evidence. It may be necessary to include other elements alongside the existing four components, such as *problem formulation* and *scope of the review*, so as to frame the question being asked of the COC or risk assessor.

70. There have been several highly relevant advisory documents published by national and international organisations, such as the EPA, IARC, WHO IPCS, ILSI HESI and publications from ECETOC on GHS. It was noted that the references from the previous guidance no longer relate to the current text. This was acknowledged by the Secretariat and would be rectified in later drafts.

71. There was considerable debate about the use of the term *genotoxic* carcinogen or *mutagenic* carcinogen. This had been prompted by COM discussions whilst revising its [guidance](#), where the distinction between mutagenicity and genotoxicity is made clear. There was some uncertainty as to what is meant by the

terms mutagenicity and genotoxicity, and whether clastogenicity is considered to be mutagenicity. The COM members present explained that mutagens include substances that cause point mutations, and clastogens and aneugens, but that genotoxicity is a broader term that does not necessarily result in heritable mutation. The definitions of these terms should be included in the COC guidance, and be consistent with those used in the COM guidance.

72. Members had substantial concerns about moving from referring to 'genotoxic carcinogens' to 'mutagenic carcinogens'. The distinction between genotoxic and non-genotoxic carcinogens is generally used to define whether a carcinogen should be considered to have a threshold of effect, and this is an established concept amongst most risk assessors. However, the distinction is becoming increasingly ambiguous. It was considered important to refer to the recent IPCS guidance ([Boobis et al., 2006, Crit Rev Toxicol. 36\(10\):781-92](#)).

73. Members were certain that it would be inappropriate to refer to mutagenic carcinogens at every point and, if there is a movement away from using the term genotoxic as a default, the correct term would need to be decided on a case by case basis. In most cases, mutagenic is probably correct, but there may be rare instances where this is not the case. Currently, many people incorrectly use the two terms synonymously, which means that the distinction could lead to confusion amongst risk assessors.

74. It was considered important to remove the text describing the requirement for a substance to be demonstrated to be an *in vivo* mutagen in order for it to be considered to be a genotoxic or mutagenic carcinogen; although the uncertainty associated with basing judgement only on *in vitro* data should factor into the weight of evidence evaluation. This is also important for the many environmental chemicals seen by COC that do not have a complete database of mutagenicity data. The draft COM guidance includes recommendations for evaluating the mutagenicity of substances with incomplete databases.

75. The title of the underpinning statement G5 should be changed to refer to points of departure and defining levels of (no) effect. It is also important to discuss the use of methods for the characterisation of hazard from mutagenic compounds separately for human and animal data due to the inherent differences in the modelling requirements of these types of data, as discussed in the previous horizon scanning [item](#).

76. It was acknowledged that the benchmark dose (BMD) methodology had been accepted by EFSA and WHO as the most appropriate available method for defining a point of departure from animal data, and that the T25 and TD<sub>50</sub> methods had been widely criticised.

77. With regard to potency ranking, it was considered necessary to remove the reference to Polycyclic Aromatic Hydrocarbons (PAHs) as this no longer considered to be an appropriate example.

78. It should be possible to use all points of departure as potency estimates, and for deriving potency equivalence factors, provided that the chemicals act by the same mutagenic mode of action and provided that there are no confounding toxicokinetic characteristics. It was noted that potency series are of questionable benefit, there being little evidence available to demonstrate that a potency series

from animal data is the same as that in humans, nor whether the relative potency at low dose is the same as that at high dose.

79. Members considered that criticism of mathematical modelling of cancer risk, expressed in the 2004 guidance, should be refocused on low dose extrapolation of cancer models, rather than modelling *per se*. As stated in the latest [EPA cancer guidelines](#), the key point is that, at present, there are no accepted biologically informative models. The shape of the dose response curve at exposures well below those at which there are observations cannot be determined empirically, because of the intrinsic lack of power.

80. Exposure assessment was considered to be an increasingly important aspect of carcinogen risk assessment, given the increasing use of the margin of exposure and Threshold of Toxicological Concern (TTC) approaches. Therefore, some broad and non prescriptive advice should be given about incorporating exposure evidence into a risk assessment. There may be some value in discussing the value of databases for estimating exposure.

81. Confounding due to measurement uncertainty should be included in the discussion of exposure assessment, and also in the epidemiology guidance statement. The error introduced by assessing exposure by some methods, such as food diaries or food frequency questionnaires, can demonstrate the value of using biomarkers of exposure; however, these can be of limited use in determining historical exposure.

82. It was considered that there should be more discussion of the margin of exposure approach. Members agreed that it is important for other toxic effects to be considered when assessing the risks posed by a carcinogen, both when following the Tolerable Daily Intake (TDI) approach for substances with an identifiable threshold of effect, and when using the margin of exposure methodology for characterising the risk posed by a non-threshold substance. This is because it is conceivable that a substance may cause toxicity at levels of exposure below its threshold of carcinogenic effect, or where its margin of exposure for a non-threshold carcinogenic endpoint is considered to be of low concern. It should be emphasised that, in most cases, evaluation of the overall weight of evidence on the toxicity of a chemical, including advice from COC, would normally be done by the Committee on Toxicity (COT).

83. There was some concern that Figure 2 in the overall summary recommends deriving many health based guidance values, then selecting the lowest. This is not current practice. The secretariat explained that it was presented in this way because simply selecting the lowest point of departure would not be appropriate, since different endpoints might warrant uncertainty factors of differing magnitudes. The wording should be changed so as not to refer to deriving a TDI in the 5<sup>th</sup> box down. It was noted that the consideration of the human relevance of the mode of action should come between determining whether there is a clear MoA and selecting a POD on the right of the figure.

84. The section on gaps and research needs was taken directly from the 2004 guidance. It was suggested that this be re-titled "Future developments". The first item, on the shape of the dose-response curve, could focus on mode/mechanism of action studies where, for example, key events can be "calibrated" against each other to determine the minimum perturbation necessary to trigger a downstream event.

There should also be some discussion of the utility of 'omics technologies to give clues as to mode of action.

85. There was brief discussion of Members' comments on the existing COC statements, presented in [Annex C](#). These would be taken into account when the underpinning guidance statements are drafted.

#### **ITEM 8: COM Guidance - consultation document**

**[\(COM Consultation\)](#)**

86. Members had now received an electronic copy of the COM guidance consultation. Professor Farmer (COM Chairman) explained that striking changes had been made to the guidance, including a reduced two *in vitro* test battery instead of the previous three test battery. The emphasis on *in vivo* studies has reduced, and guidance is also given on how to interpret compounds with existing or limited datasets.

87. In addition to posting the consultation document on the website, it had been e-mailed to many colleagues around the world, so it should be scrutinised by the broader expert community. The consultation period ends on the 12<sup>th</sup> February 2011 so that the comments can be collated and taken to the next COM meeting.

88. Given the overlap of Committee membership, the COC would not provide a formal response to the consultation; however, Members were asked to review the proposed strategy and are invited to submit individual comments via Secretariat.

#### **ITEM 9: Verbal update on progress with the OECD guidance for the performance of chronic toxicity and carcinogenicity studies – for information**

89. Dr Edwards reported that she had just returned from an OECD meeting to discuss the draft guidance on the conduct and performance of chronic toxicity and carcinogenicity studies. The UK-drafted chapter on "Investigations (including histopathological guidance)" had been very well received. One minor change had been requested, relating to the grouping/splitting of lesions because of overlap of the text with another chapter. Most of the remaining chapters would be edited relatively easily to take comments into account but there remained disagreement about the wording of the guidance on the duration of studies in which a high rate of premature deaths occurred.

90. The OECD meeting expressed some concern that the draft chapter on "Mode of Action" focussed on interpretation, not conduct and design, which is the purpose of the Guidance Document. A revised draft of all the chapters would be circulated to COC members for final comment in December and Members were encouraged to send comments directly to Dr Edwards. The Chairman thanked those Members who had contributed to the draft.

#### **ITEM 10: Any Other Business**

91. None.

**ITEM 11: Date of Next Meeting**

92. 14<sup>th</sup> April 2011 at Department of Health, Skipton House, Elephant & Castle, London, SE1 6LH.