

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

Horizon Scanning 2010

Introduction

1. The Committee's Terms of Reference indicate that the primary role of the Committee is to advise on the carcinogenic risk of substances to man at the request of Government departments and agencies; particularly, but not exclusively, the Food Standards Agency and the Health Protection Agency. Therefore, the work of the Committee is primarily reactive and the agendas are set by the Secretariat based upon the need for advice from Government departments and agencies.

2. The Code of Practice for Scientific Advisory Committees (Office of Science and Technology, December 2001), specifies that:

“Committees should ensure that they have mechanisms in place that allow them to consider on a regular basis whether new issues in their particular areas of responsibility are likely to emerge for which scientific advice or research might be needed.”

Therefore, in 2001, Members agreed that it would be useful to have an annual agenda item where Members suggest areas/topics that needed further consideration in the light of new and emerging evidence relating to cancer risk assessment.

3. This paper presents a brief update on progress with items identified in last year's horizon scanning and also presents some suggestions for discussion provided by Members, the Secretariat, and Assessors. Annex A contains references for potential Horizon Scanning items.

4. As discussed at the July 2010 meeting, Members 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. This could be usefully done as part of the annual horizon scanning activity. A list of existing statements is included as Annex B. Members, the Secretariat and Assessors are asked to consider whether any specific statements would benefit from re-evaluation.

Update on 2009 Horizon Scanning

5. During last year's horizon scanning meeting, Members discussed and prioritised the following items:

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

Grey shaded items were carried over from 2008 horizon scanning. Those struck through have been addressed.

6. At the July 2010 meeting, a scoping paper on gene-environment studies and a presentation on carbon nanotubes were discussed. The paper on the outcome of the ILSI HESI meeting held in December 2009 on short term and intermittent exposure to carcinogens has not yet been submitted for publication. It will be discussed at a future COC meeting.

7. The DH ongoing review of tobacco toxicology has focused on toxicity/carcinogenicity/mutagenicity approaches used to evaluate tobacco products and other areas. A review of childhood exposure to ETS and cancer in adulthood will be undertaken in due course. Mononuclear cell leukaemia (MNCL) in the F-344 rat and mechanistic studies in Zebrafish were areas of interest, given medium or low priority. These will be retained on the Secretariat's work programme and brought to the Committee when resources permit.

8. Recent COM meetings have focussed heavily on revision of its guidance so it has not been possible to take forward discussions on endogenous DNA adducts. The views of the COM will feed into COC discussion of this issue. Similarly, there were insufficient resources to organise the additional joint COM / COC meeting on thresholds of genotoxicity.

2010 Horizon Scanning

9. As experts in their field, Members are encouraged to identify emerging and developing issues that affect carcinogenic risk assessment. These will be discussed within the Committee and taken forward if considered appropriate. The Secretariat and some Members have identified some potential emerging and developing issues that the Committee might wish to consider:

Is the 2-year rat carcinogenicity study still necessary?

10. A 2004 paper by Cohen [1] proposed that it was no longer necessary to perform a two-year rat carcinogenicity study to provide a rational basis for human cancer risk assessment for chemicals. The author proposed that this could be replaced by a screening assay following 13 weeks treatment, with an emphasis on mode of action (MOA) and focus on interpretation of findings in the rodent for their relevance to humans. A recent paper by the same author [2, see Annex A] provides additional details for this mechanistic approach based on a detailed examination of liver carcinogenesis, on the premise that, in rodent studies, the liver is the most common target organ.

11. The proposal builds on earlier work by Allen *et al* [3] which used data from NTP carcinogenicity studies to assess whether pre-chronic liver lesions could predict liver tumours. This found that all chemicals that produced liver tumours in mice or rats could be detected at 13 weeks using four indicators: hepatocellular necrosis, hypertrophy, cytomegaly, and increased liver weight. There were no false negatives but numerous false positives. For this reason, in his proposal, Cohen (2004) advises that, if one or more of the above changes are found in the 13 week screening assay, a mechanistic screen is performed to determine the MOA(s). If no MOA is identified, he suggests three options: (i) rely on margins of exposure to predict safety for human exposures, (ii) do the necessary research to identify the MOA, (iii) carry out a full 2-year carcinogenicity study.

12. Also, according to presentations from an *ad hoc* Carcinogenicity Working Group of a pharmaceutical industry committee, it should not be routinely necessary to conduct a 2-year rat carcinogenicity study for pharmaceuticals [4] [5]. This conclusion is based on a review of the data on approximately 200 chemicals tested in a large number of chronic toxicity and/or carcinogenicity studies in rats. The review assessed whether potential pre-neoplastic histopathological lesions in the chronic studies were predictive of neoplastic outcome in the carcinogenicity studies. It found that the data did not support a site based tumour prediction but that an integration of genotoxicity results, mouse carcinogenicity data, histopathology results from the chronic rat study on a whole animal basis, and chronic rat hormonal data demonstrated 85% sensitivity and 85% negative predictivity for rat carcinogenicity outcome. The Working Group predicts that, if these criteria were used as triggers for a 2-year rat carcinogenicity study, it would yield a reduction of 36% in rat carcinogenicity studies.

13. The false negatives in this assessment was negative for proliferative lesions in the chronic toxicity studies and positive in the rat carcinogenicity study. A detailed review of these determined that they were single species, and mostly single sex, single organ rat carcinogens and appeared to be of questionable human relevance.

14. Although there is no request as yet from Departments to advise whether modifications should be made to current carcinogenicity testing requirements, this could arise in the future. Do Members consider that the

Committee would be wise to review the proposals above and the supporting work in full, or do they think that are these proposals are unlikely to be taken up by regulatory authorities?

15. As an adjunct to discussions on the requirement for the 2-year bioassay, would Members like to see an update on short term tests as alternatives to the 2-year bioassay?

Epigenetics and cancer

16. The study of epigenetic mechanisms, heritable changes in gene expression or chromatin organization which are not associated with alterations to DNA itself, and their role in human conditions is a rapidly growing research field. The topic has been addressed previously by the COM and the COT. Initially, the COM looked at transgenerational effects of methylation following a request from the ACP to review a paper which reported the potential for vinclozolin to induce transgenerational effects via the male line (http://www.iacom.org.uk/papers/documents/mut0615_000.pdf)[6]. Transgenerational epigenetics was then examined in more detail by the COT at a one-day workshop in February 2008. It was concluded that there is reasonable evidence that epigenetic changes associated with environmental exposures during development can result in adverse effects, although it is not clear whether transmission of acquired epigenetic changes occurs across generations in humans (<http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cot200803>). The workshop did not address in detail epigenetic alterations in carcinogenesis

17. There is a significant body of data which indicates the importance of epigenetic modifications in every step of tumour development [7, see annex A] [8]. Alterations in DNA methylation (hypo- and hyper-methylation) result in changed expression of tumour suppressor genes or induce loss of imprinting and there are a large number of examples of aberrant methylation patterns in a wide variety of tumours. Histone modification is also considered to have a role in tumour progression; post transcriptional modification by histone deacetylases (HDACs) can alter the regulation of DNA repair or replication, splicing or chromosome condensation.

18. Most of the literature on cancer/epigenetics focuses on the altered epigenomes identified in tumours and also on the potential to use epigenetics in cancer therapy [8]. There is some information on environmental and dietary exposures which may affect epigenetic patterns contributing to carcinogenic modes of action. For instance, it has been proposed that inorganic arsenic causes depletion of S-adenosylmethionine and consequently impacts on DNA methylation status [9]. A number of studies have suggested a link between aflatoxin exposure and methylation of specific cancer-related genes [7]. It has also been proposed that the co-carcinogenic effects of alcohol may be related to the induction of hypermethylation of specific genes [7]. Therefore it is likely that epigenetics has a crucial role in the modes of action of some chemical carcinogens.

19. Do Members think that a detailed review of the topic of epigenetics and cancer is warranted? If so, are there any specific areas which merit particular attention?

Dose response modelling in epidemiology studies

20. Epidemiology studies often suffer from limited exposure assessment. However, when good exposure data are available, such as from some occupational epidemiology studies, they provide the most appropriate data for the quantitation of the dose-response in humans. A Member has suggested that the Committee considers whether and how the dose response might be modelled to derive a tolerable exposure level for humans. For example, with in animal carcinogenicity data, the COC has recently favoured modelling the data to derive a Bench Mark Dose (BMD) which can be used in a Margin of Exposure assessment (for example, as in its 2008 assessment of the carcinogenicity of pyrrolizidine alkaloids in food). Would such an approach be appropriate with epidemiology data?

21. There are varied examples of dose-response approaches in epidemiology. For example, a statistical modelling of exposure to lead moved away from using the standard linear dose-response function and the nonlinear form was considered to be more appropriate [10]. Recently, the European Food Safety Authority (EFSA) has modelled dose-response data from epidemiology studies on both lead and cadmium to derive BMDLs [11, 12]. However it is widely recognised that there are many problems associated with modelling of epidemiology data.

22. Do Members have an interest in assessing the use of dose response modelling methods in epidemiology? It is suggested that this would tie in to the current review of the Guidance and a potential Guidance Statement on the use of epidemiology data in the revised strategy.

Mode of action framework:

23. The COC reviewed the MOA and human relevancy frameworks in April 2005 <http://www.iacoc.org.uk/papers/documents/cc052.pdf> . It was agreed that the MOA and HRF approaches both provided a logical framework in which to set the information needed when assessing the relevance of chemical induced animal tumours to humans. Since then this framework has been utilized in a number of ways. Would Members like an update of the work in progress?

Further suggestions and prioritising

24. Do Members have any further suggestions for future work on chemicals and cancer risk assessment?
25. Do Members have any thoughts on prioritising the suggested topics for review, including those outstanding from last year?

Secretariat November 2010

References

1. Cohen, S.M., *Human carcinogenic risk evaluation: an alternative approach to the two-year rodent bioassay*. Toxicol Sci, 2004. **80**(2): p. 225-9.
2. Cohen, S.M., *Evaluation of possible carcinogenic risk to humans based on liver tumors in rodent assays: the two-year bioassay is no longer necessary*. Toxicol Pathol, 2010. 38(3): p. 487-501. **(see annex A)**
3. Allen, D.G., et al., *Prediction of rodent carcinogenesis: an evaluation of prechronic liver lesions as forecasters of liver tumors in NTP carcinogenicity studies*. Toxicol Pathol, 2004. 32(4): p. 393-401.
4. Sistare F D, *An analysis of pharmaceutical experience with decades of rat carcinogenicity testing*. 2009.
5. Morton D, *Rat false negative predictions and alternative models*. 2009.
6. Anway M.D., Cupp, A.S., Uzumcu, M., Skinner, M.K. (2005) Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308 1466-1469
7. Herceg, Z. Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. 2007 Mutagenesis 22 91-103 **(see annex A)**
8. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010 31(1):27-36.
9. Zhao, C.Q., Young, M.R. et al Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proc.Natl. Acad. Sci 1997 94 10907-10912
10. Rotherburg, S.J. Rothenburg, J.C. Testing the Dose reponse specification in epidemiology: public health and policy consequences for lead. 2005; EHP 9 1190-1195
11. EFSA. Scientific opinion on lead in food. 2010.
<http://www.efsa.europa.eu/en/scdocs/scdoc/1570.htm>
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<http://www.efsa.europa.eu/en/scdocs/doc/254r.pdf>

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Horizon Scanning 2010

Copies of papers from the reference list

[Note: For copyright reasons the papers in the Annexes are not included in the published version. The bibliographic details of the annexed material are listed above. The documents are all in the public domain and individuals can obtain them by application to appropriate sources.]

- Ref 2. Cohen, S.M., *Evaluation of possible carcinogenic risk to humans based on liver tumors in rodent assays: the two-year bioassay is no longer necessary*. *Toxicol Pathol*, 2010. **38**(3): p. 487-501.
- Ref 7. Herceg, Z. Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. 2007 *Mutagenesis* **22** 91-103

This is a draft paper for discussion. It does not necessarily represent the views of the Committee.

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Existing COC Statements

As discussed at the July 2010 meeting, Members 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. This could be usefully done as part of the annual horizon scanning activity.

- Members are asked to review the list of statements and consider whether they are aware of research or other scientific opinions that would enable the conclusions and advice within these statements to be extended or revised.
- Assessors are asked to consider whether updates of any of these statements would be of value to their department or agency, particularly for those topics that Members consider to have advanced since the statement published.

It is acknowledged that some statements were produced at the time to answer a specific question and, although the statement could be updated, it would not necessarily be a valuable use of Committee resources.

COC Statements

Shaded items are currently being reviewed as potential Committee Guidance statements. Copies of individual statements are available from the COC website (<http://www.iacoc.org.uk>).

2008	Areca nut and Betel Quid Statement on carcinogenicity of Betel Quid, Pan Masala & Areca Nut chewing.
2000	Accelerator mass spectrometry An aid to carcinogen risk assessment
2003	Air Pollutants Risks associated with exposures to low levels of carcinogenic air pollutants

2004	Alcohol and breast cancer
2000	Alcoholic beverages and breast cancer Update of information published between 1995 and 1999
2006	Aspartame
2005	Childhood Leukaemia Association between childhood leukaemia and residence near sources of traffic exhaust and petrol fumes
1998	Chrysotile-substitutes Carcinogenic risks of polyvinyl alcohol (PVA) fibres, p-aramid fibres and cellulose fibres
2008	Chlorinated drinking water and cancer - 2nd statement
1999	Chlorinated drinking water and cancer
1998	2-Chlorobenzylidene malononitrile and CS spray
1998	Coumarin (With particular reference to the possible mechanism of hepatocarcinogenicity in the rat)
2003	Dibenzo(a,l)pyrene
2004	1,3-dichloropropan-2-ol (1,3-DCP) and 2,3-dichloropropan-1-ol (2,3-DCP) Carcinogenicity of chloropropanols
2001	1,3-dichloropropan-2-ol (1,3-DCP) and 2,3-dichloropropan-1-ol (2,3-DCP) Carcinogenicity of chloropropanols
2004	Dieldrin, DDT and certain hexachlorocyclohexane isomers Breast cancer risk and exposure to organochlorine insecticides: consideration of the epidemiology data on dieldrin, DDT and certain hexachlorocyclohexane isomers
1999	Dieldrin, DDT and certain hexachlorocyclohexane isomers Breast cancer risk and exposure to organochlorine insecticides: consideration of the epidemiology data on dieldrin, DDT and certain hexachlorocyclohexane isomers
1998	Environmental tobacco smoke and cancer Advice produced for Standing Committee on Tobacco and Health (SCOTH)
2003	Environmental tobacco smoke (ETS) and lung cancer: Consideration of paper by Engstrom JE and Kabat GC (2003). British Medical Journal volume 326, 1057-1066
2002	The investigation of interaction between genotype and chemicals in the environment on the induction of cancer
2002	ILSI/HESI research programme on alternative cancer models
2002	Intrahepatic cholangiocarcinoma Evidence for an increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968-1996
2002	Joint Statement of the COT/COC/COM on the use of genomics and proteomics in risk assessment.

2000	Longevity in carcinogenicity studies in rats Analysis of a database prepared by Pesticides Safety Directorate of MAFF
2004	Malachite green and leucomalachite green
2003	Malathion Joint Statement of COM/COC
2003	1-methylcyclopropene (1-MCP) Carcinogenic impurities in the pesticide 1-methylcyclopropene
2010	Mixtures Risk Assessment of the Effects of Combined Exposures to Chemical Carcinogens
1999	3-monochloro propane 1,2-diol
2009	Municipal solid waste incinerators Cancer Incidence near incinerators in Great Britain Update statement
2000	Municipal solid waste incinerators Cancer Incidence near incinerators in Great Britain
2002	Minimum duration of carcinogenicity studies in rats Review of two selected papers published in 2000
2005	Nanomaterial toxicology Joint statement of COC/COM
1999	Neonatal rodent bioassay Reviewed in the context of the proposal by the ICH (International Conference on the Harmonisation of technical requirements for the registration of pharmaceuticals for human use).
2009	Non Hodgkin's Lymphoma
1999	Ozone Animal carcinogenicity data
2007	Prostate Cancer and Pesticide Exposure
2005	Proquinazid Statement on its mutagenicity and carcinogenicity (cholangiocarcinoma in the rat)
2006	Joint COT/COC statement on Royal Commission on Environmental Pollution: Crop spraying and the health effects of residents and bystanders
2005	The use of Target organ mutagenicity data in carcinogenicity risk assessment
2001	2,3,7,8-tetrachlorodibenzo-p-dioxin Review of the evidence on carcinogenicity
1999	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Consideration of 1997 IARC monograph.
2004	Tobacco Reassessment of the toxicological testing of tobacco products
2004	Toxicogenomics