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CC/05/17

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

HORIZON SCANNING PAPER 2005

Introduction

1. Members will wish to consider horizon scanning topics identified by the secretariat and DH Toxicology Unit Secretariat. A limited literature search was undertaken using PUBMED which indicated over a thousand publications in 2004/5 on chemical related carcinogenicity (based on search terms; environmental carcinogenesis, cancer trends, carcinogen risk assessment) and related topics which might potentially be relevant. The literature search was scanned briefly to highlight potential chemicals and generic areas of carcinogenicity evaluation which might be of interest to members. A brief overview has been produced below (papers have not been subject to full evaluation). The horizon scanning exercise also provides an opportunity for members and advisers from Government Departments/Regulatory agencies to suggest topics for further work. A short overview of the 2004 horizon scanning review and outcome is given below.

Review of 2004 Horizon scanning paper

2. The subjects identified in the 2004 horizon scanning exercise and outcome are listed below;

Topic	Outcome
Target organ mutagenicity in carcinogen risk assessment	Joint meeting of COC/COM 9 June 2005. Short statement to be produced. Full write up in progress.
Transgenic animal models for assessment of carcinogenic potency	COC considered not a priority for 2004
Risk Assessment of non-genotoxic carcinogens	COC considered short review of Mode-ofAction (MOA) and the proposed Human Relevance Framework (HRF) assessments.
Single exposure to carcinogens	COC considered a summary of available epidemiological evidence and agreed this was not helpful in assessing potential single exposure situations.
Metals and carcinogenesis	COC considered not a priority for 2004
Epidemiological aspects	COC identified a review of oesophageal cancer as a priority. A general overview was considered and alcohol was selected as a priority for further consideration.
Testing of nanoparticulates for carcinogenicity	COC considered a general overview review (along with COM/COT) and a short statement

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is being produced.

Follow-up actions arising from 2004 horizon scanning review.

3. Government Departments/Agencies have expressed interest in undertaking a full review of single exposures to carcinogens. There have been limited resources available to take this forward. It is proposed to focus the review on single exposure to genotoxic carcinogens to see if a potency ranking could be undertaken. It might be useful to compare potential exposure found as a result of exposure via food, air, water or a combination of these routes with estimates of carcinogenic potency as a possible method for prioritisation for risk managers. Background information on likely exposure scenarios would be obtained.
4. The Committee has only briefly considered a limited number of MOA and HRF assessments. One key outcome of such assessments is a structured approach to identification of data gaps. What follow-up work would members consider appropriate?

Potential Topics identified in literature search

Further information on dibenzo(a,l)pyrene

5. Mahadevan B et al¹ have demonstrated a dose-related increase of DNA adducts in the lung of C57BL/6 mice given a gavage dose of 1,5, or 20 mg/kg bw. Members will recall the COC advised that the relative potency of DB(a,l)P which is a highly potent rodent lung carcinogen to Benzo(a)pyrene could be estimated in appropriate DNA adduct studies. The COC had recommended intratracheal administration in rats. Would a useful comparison be attainable if appropriate gavage studies of B(a)P in mice were available which presented data in a suitable form for comparison. It had been estimated that DB(a,l)P would be between 10-100x more potent than B(a)P?

Trends in historical control tumours in rats

6. Tennekes H et al 2004,² have evaluated time dependent trends in tumour incidence for a range of rat strains and concluded there was little evidence for any time dependent trends. It was suggested that tumour drift was not common but occurred more often in outbred strains of rat. It was suggested that chemical should not be classified with regard to carcinogenicity if; (i) the only neoplasms occurred at sites where they are well known to occur spontaneously and at high incidence with good evidence that this sensitivity cannot be extrapolated to man, (ii) the mechanism of tumour formation doesn't involve genotoxicity and (iii) there is a clear NOEL. The generic

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argument is proposed that non-genotoxic carcinogens modulate tumour predisposition through the genes affecting the variance of background incidence of tumours. What are members views, and should this paper be considered at a meeting?

Comparison of animal and epidemiology data

7. Members will recall that Sanner and Dybing described and evaluated the use of the T_{25} potency indicator for ranking animal carcinogens according to potency. In a recent paper they described the correlation between a variety of potency indices of in-vivo genotoxicity (e.g chromosome aberrations, micronuclei, DNA binding and ^{32}P -post labelling) and carcinogenicity. The COM considered this data during its horizon scanning exercise and were surprised that a correlation had been reported. In a further recent paper³ the same authors have reported estimates of animal and human potency for a limited number of carcinogens (benzene, benzidine, 1,3-butadiene, cadmium, nickel subsulfide and vinyl chloride). It was reported that difference between the estimated T_{25} and estimated lifetime cancer hazard of 10^{-3} varied by a factor of less than 3. The authors claim this as evidence for good hazard characterisation based on animal studies. As the T_{25} has gained general acceptance for use in potency comparison of rodent carcinogenicity data, would members wish to review this paper in more detail?

Age-related differences in risk of carcinogenesis

8. Mattis and colleagues have reported a quantitative likelihood-based analysis of the sensitivity of rodents to carcinogens (9 chemicals, of which 5 were reported to have mutagenic activity) across three life stages, foetal, birth to weaning and weaning to 60 days. Quantitative estimates of lifetime risks for a generic mutagenic carcinogen were approximately 2.8 fold higher than for adult only exposure. It was suggested that the additional Uncertainty Factors applied by EPA to 0-2 y and 2-15 y risk assessments might not be appropriate in all cases. Would members wish to review these two papers^{4,5} in more detail?

Position paper on ignored concepts of carcinogen risk assessment

9. Trosko and Upham published a commentary in Mutagenesis⁶ where they describe both mutagenic and epigenetic effects in carcinogenesis. With respect to PAHs they and propose that the focus on mutagenesis has diverted attention from away from research on non-genotoxic PAHs which might contribute to the carcinogenicity of PAH mixtures such as cigarette smoke. The paper is appended. What are members views on the proposal?

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Trends in cancer incidence

10. The Committee has previously recommended reviews be undertaken on prostate cancer and oesophageal cancer in order to ascertain whether there are any environmental carcinogens associated with the induction of cancers of these organs. One factor in triggering the request was evidence for increased incidence of these cancers in the U.K. Information from the Cancer Research UK site is appended at the end of this paper for members information. Members are asked whether any further review of a cancer target organ is warranted at present.?
11. Dabre PD has published an analysis of the incidence of Upper Outer Quadrant breast cancer in England and Wales from 1979-2000 and in Scotland from 1980-2001.⁷ There is evidence for a linear increase in the incidence of UOQ breast cancer. Do members consider this should be considered in further detail and what are members views on the likely reasons for any such increase?

Comparative risk assessment

12. The secretariat is keen to undertake a review of selected environmental carcinogens and attempt to compare risks with a clearly defined exposure (e.g consumption of smoke from a cigarette). One possible approach which has had only limited consideration would essentially consist of attempting to compare *in-vivo* mutagenic potential of the carcinogens with an estimate of the total mutagenic potential of a cigarette. Alternatively it might be possible to use carcinogenicity as an end point. (This could be done allocating potency bands for chemicals or using a reference compound as a descriptor of potency) There would be a considerable number of assumptions to be made. However the outcome is meant to be a crude indicator of relative potency which could inform dissemination of committee advice to the general public. One possible outcome is that exposure to carcinogen as a contaminant would be reported to represent exposure equivalent to approximately 0.1, 0.01 etc of a cigarette. It is noted that current DH guidance on comparative risk assessment suggests that acceptability should not be intended by any comparative assessments which are meant to aid in dissemination of information on exposures (DH guidance on communicating risk. Pointers to |Good practice, 1997)

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13. Members may wish to note that the COM recommended that a high priority be given consideration of wider dissemination of COM and COC advice. (see Annex 1 for COM priorities).

Discussion and priorities

14. Members will be aware that there are a number of publications on topics previously considered by the committee which have been published during 2005 (e.g. Hormesis (Calabrese et al⁸), modelling of the dose response curve at low levels of carcinogen exposure (Connolly RB et al⁹), down regulation of genes associated with genomic stability following exposure to Benzo(a)pyrene diol epoxide, (Thavathiru et al¹⁰), and transcriptomics applied to carcinogen mechanism (Hester et al¹¹). These are all selected examples. Members are asked to consider whether these topics and those listed below should be taken forward and to give advice on any priorities.
15. The COM identified a number of projects during its horizon scanning exercise. These are appended as Annex1 at the end of this paper for members information.
16. The overall recommendations without suggesting a priority for COC review are given below. DO members agree?
17.
 - i) Review of single exposures to carcinogens, focussing on genotoxic carcinogens.
 - ii) A comparative risk assessment linked with a project on wider dissemination of COC advice.
 - iii) A project to consider published literature on age related carcinogen risk.
 - iv) Consideration on new literature on potency indicators.
 - v) Consideration of any cancer target organs as identified by COC
 - vi) Any proposals from COC members?

Secretariat October 2005

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References

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2. Tennekes H et al. Regulatory Toxicology and Pharmacology, 40, 293-304, 2004.
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7. Dabre PD Anttancer Res, 25 (3c), 2543-50.
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Press Release from Cancer Research UK

New UK cancer statistics releases for year 2000

Release date: 7 January 2004

THE SHIFTING patterns of cancer diagnosis over recent years are revealed by new figures released by Cancer Research UK and compiled by the UK Association of Cancer Registries.

Latest figures show that there were over 270,000 cases diagnosed in the UK in 2000, 3,000 more than in the previous year and 14,800 more than five years previously.

But Scotland, which has higher rates of cancer than the rest of the UK, has bucked the trend with a fall in cases, thanks to success in curbing the country's high smoking rates.

Across the UK, there were big increases in [malignant melanoma](#), [uterine cancer](#) and [prostate](#) cancer, partly offset by falls in the numbers of [stomach](#) and [cervical](#) cancers.

As people live longer, more and more are developing cancer, with numbers in the UK increasing steadily since the early 1970s, to the current all-time high. Certain cancers are increasing particularly sharply. The number of cases of [malignant melanoma](#) leapt to 7,000 in 2000 – an increase of 16 per cent in a year and 24 per cent over five years – providing a stark warning of the dangers of [over-exposure to the sun](#).

Cancer of the uterus also increased sharply to 5,600 cases, up eight per cent in a year and 22 per cent over five years. Cancer Research UK believes rising rates of [obesity](#) may be contributing to the increase, while hormone treatments like [tamoxifen](#) may also slightly increase the risk of [uterine cancer](#).

Cases of [breast cancer](#) increased by 12 per cent over the five years to 40,700, although between 1999 and 2000 there was actually a fall of 600 cases.

[Prostate cancer](#) increased by 25 per cent cases over five years to 27,200, but here the figures are influenced by increased use of the [PSA blood test](#), which often picks up cancers that will not be life-threatening. A 17 per cent rise in the number of cases of [non Hodgkin's lymphoma](#) is also partly likely to be the result of more sensitive diagnostic techniques.

Professor David Forman, Chairman of the UK Association of Cancer Registries, says: "Keeping track of cancer trends is vital for research on the [causes of cancer](#) and to help focus [prevention](#) strategies and treatment resources.

"Cancer mainly affects older people and as our population ages, we are inevitably seeing more cases. But it's important to pick out cancers where rates are increasing faster than we'd expect from changes in demographics, so we can gain clues about causes."

While some cancers are increasing, elsewhere there are success stories for

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cancer prevention strategies.

While concern remains over [smoking](#) rates in women, cases of many smoking related cancers are continuing to fall in men, whose smoking rates have been declining since the late 1970s. Success in cutting smoking is particularly noticeable in Scotland, which has for many years had the highest cancer rates in the UK, but which has now cut men's [lung cancers](#) by 15 per cent in five years.

Sharp falls in numbers of stomach and cervical cancers across the UK also reflect the success of cancer prevention. [Stomach cancer](#) has been decreasing for the last 30 years, as improved hygiene has reduced infection with [Helicobacter pylori](#) – one of the main causes of the disease – and the use of fridges has provided a more balanced diet throughout the year.

[Screening](#) has cut the incidence of cervical cancer, by picking up and treating [precancerous conditions](#). There were 2,991 cases of the disease in 2000, a fall of 13 per cent in five years.

Professor Robert Souhami, Cancer Research UK's Director of Clinical and External Affairs, says: "These statistics paint a detailed picture of the ups and downs of cancer incidence in the UK.

"The figures highlight the impact that cancer prevention strategies can make, with falls in smoking-related cancers, particularly in men, in cervical cancer, because of screening, and stomach cancer, thanks to improvements in food hygiene and preservation. It's particularly encouraging that Scotland's very high cancer rates are finally starting to come down.

"On the other hand, certain cancers are increasing more quickly than we'd expect simply by the ageing of the population. It's worrying to see that melanoma rates are continuing to rise unabated and we really need to hammer home the [< a >](#).

"It will also be important to understand the reasons for the increase in cancer of the uterus. It may be related to rising rates of obesity, which are pushing up the rates of a number of cancers in both women and men."

ENDS

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Annex 1 COM priorities from Horizon scanning for 2005.

Horizon scanning paper (COM asked secretariat to derive priority based on comments. Priority 1,2,3, 1= highest, 2= high, 3= low))

a) COM agreed that consideration of mitochondrial DNA was a priority for future work.(2)

b) COM agreed that consideration of nitropyrenes and Nitro PAHs a priority (2) COM didn't believe the positive with dermal application of paraquat (not prioritised)

c) COM wanted to look at mutagenicity of mixtures. After long consideration of potential mechanisms of interaction. com agreed to look at modulation of alkylating agent mutagenicity as a first start, to see if dose/effect addition rules were adequate.(2)

d) COM agreed evaluation of UDS v COMET was useful but noted the amount of data available in test houses and in public domain would be limited. In first instance secretariat asked to identify UDS positives and look for concordance with COMET (liver). Agreed there might be very little available. Some wider considerations of usefulness of comet to be considered after this.(1)

e) COM not too keen to look at potency indicators, were not convinced by Sanner/Dybing paper (not prioritised)

f) COM not too keen on looking at hprt assays. 3)

g) COM very keen on methylation status changes in transgenerational effects and suggested that broadening to effects on histones and RNAi as mechanisms for permanent changes to phenotype needed to be considered. COM agreed this was a major undertaking. (The original request comes from ACP/MTP, so Tom could consider this.) COM felt the current strategy would not address such compounds, there might be examples from MHRA (e.g antisense DNA products). (1)

h) COM keen to have presentation from David Kirkland on wider aspects of international validation of mutagenicity testing. (2)

i) COM requested some joint working with COC to improve presentation of advice to general public, to try to get over misconceptions, e.g all pesticides are genotoxic.(1)

k) COM agreed some additional work on generics of biomonitoring and perhaps with help of an expert statistical report on variance and determining minimum study level and criteria for positivity. (Priority 1, but would require some expert input by a statistician.