Committee on the Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their human carcinogenic potential at the request of UK Government Departments and Agencies. The membership of the committee, agendas and minutes of meetings, and statements are all published on the internet (http://www.advisorybodies.doh.gov.uk/coc/index.htm).

During 2007, the Committee provided advice on a range of interesting topics. It carried out a number of reviews and gave further consideration to the issue of folic acid fortification and carcinogenesis.

Among the generic issues considered by the committee, it gave further consideration to the issue of risk communication. In this context, it assessed the use of the Margin of Exposure (MOE) approach, which is being developed in international fora for risk communication and risk prioritisation of non-threshold carcinogens. At the request of the Health and Safety Executive, the committee provided technical guidance on the draft guidance for assessment of the carcinogenicity of chemicals in the context of new European legislation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

Chairing the COC continues to be a challenging but rewarding task. I thank the members and secretariat for their support during the past year and look forward to working with them on the challenges ahead.

Professor David H Phillips
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Assessing the risks of acute or short-term exposure to carcinogens

3.1 The Department of Health and the Health Protection Agency are occasionally asked to provide advice on the health risks of acute or short-term exposure to genotoxic carcinogens. In 2006, they sought the advice of the COC on how this might be done and, after discussion, members decided that it would not be appropriate to use an acute T25 approach. One member had also informed the COC that there were some papers in the literature which might indicate a way forward and three of these were discussed by the committee at a meeting in 2007.

3.2 An underlying principle in the approaches suggested by two of the papers was that tumour incidence is linearly related to the cumulative dose of a chemical. However, the COC disagreed with this principle, which it assumed had derived from observations about the relationship between radiation dose and cancer risk. In the case of chemicals, it was noted that DNA repair processes could be significant at low doses, a non-linear response could occur due to the complexity of the carcinogenic process, and genotoxic carcinogens may have different effects eg at high doses some genotoxic carcinogens could also promote cancer via a cytotoxic mechanism. The relationship could also be affected by latency. It was noted that there were few relevant epidemiological data on chemicals but it appeared that, for smoking, the risk was sublinear with time, at least for lung and bladder cancer.

3.3 One paper had considered whether exposure of 1-10 days to genotoxic carcinogens may contribute to tumour development and, if so, whether this contribution to cancer risk could be quantified. A pragmatic approach was proposed, which used the premise that tumour incidence is linearly related to the cumulative dose of a chemical and incorporated the principle of the Virtually Safe Dose (VSD) associated with an "acceptable" risk level. The approach then applied factors to scale up from low level exposure daily over 70 years to the dose which might be acceptable if exposure was only for 1 day, or 2-10 days. The COC noted that the paper was mainly theoretical and used mathematical modelling to develop risk estimates from animal carcinogenicity data (an approach that is not recommended by the COC). Although there were areas of uncertainty and a number of assumptions in the proposed approach, members considered that extrapolation from lifetime exposures to short-term (up to 10 days) exposures for low doses would probably overestimate the cancer risk. They considered that, although there was an assumption that certain subpopulations would be more susceptible than others, there was no suitable data to allow any quantitative estimation and associated adjustment to cancer risk estimates. However, it was suggested that it may be possible to adapt the method by using the Margin of Exposure (MOE) approach and that this might provide a pragmatic approach to the risk assessment of short-term exposures to genotoxic carcinogens, although there would be some associated degree of uncertainty.

Betel quid, Pan Masala and areca nut

3.4 This item was considered in 2006 but not included in the 2006 Annual Report.

3.5 Areca nut is an ingredient of betel quid or pan masala, which is chewed as an aid to digestion and as a stimulant. It also may have limited use as a food ingredient. The COC last considered the carcinogenicity of areca nut in 1994 but since then, a number of relevant new papers had been

published. Consequently, the FSA sought the view of the COC as to whether the new information was sufficient to warrant updating its previous advice, and whether any conclusions could be drawn about the use of areca nut as a food ingredient.

3.6 In the previous COC assessment, the Committee had considered a range of data and had concluded the following:

- There was evidence of mutagenic and carcinogenic activity of areca nut extracts and derived compounds in experimental systems. In particular, the potent carcinogenic activity of the areca-derived nitrosamine, 3-(methylnitrosoamino)-propionitrile (MNPN), had been confirmed and methyl and cyanoethyl adducts had been detected in the DNA of the target tissues in which the tumours developed. There was evidence that endogenous nitrosation of areca nut alkaloids can occur in animals and humans; and areca nut derived nitrosamines, including MNPN, have been detected in the saliva of betel quid chewers.

- There were very limited data from epidemiological studies on the effect of betel or areca nut products without tobacco, which did not allow any conclusion to be drawn. There was, however, sufficient epidemiological evidence of a link between the chewing of betel quid containing tobacco and cancer in humans.

- Use of these products without tobacco was possibly carcinogenic in humans.

3.7 In 2003, the International Agency for Research on Cancer (IARC) assessed the use of betel quid, and concluded that both the chewing of betel quid and areca nut should be categorised as Group 1 carcinogens (carcinogenic to humans). In its conclusions, IARC stated that there is sufficient evidence in humans to conclude that betel quid chewed without tobacco causes oral cancer. IARC also concluded that there was sufficient evidence in animals to confirm the carcinogenicity of betel quid and areca nut without tobacco. This followed a previous IARC review in 1985, which concluded that there was inadequate evidence for the carcinogenicity of betel quid chewed without tobacco.

3.8 The COC reviewed a number of epidemiology studies published since 1993 and new animal studies which attempted to identify mechanisms for the carcinogenic potential of areca nut extracts and agreed with the IARC (2003) conclusions. The committee considered that most of the evidence suggested that areca nut is a site of contact carcinogen acting by a genotoxic mechanism, and noted that there was some evidence that a non-genotoxic oxidation mechanism could also be involved. The carcinogenic mechanism was likely to involve the nitrosation of precursor chemicals present in areca nut. It was not clear why there appeared to be an increased site-of-contact cancer risk for those who swallowed the juice. The COC also considered that there was no clear evidence that the use of areca nut without tobacco caused primary liver cancer or other cancers at distant sites.

3.9 The COC concluded that there was now sufficient evidence for a causal link between the chewing of areca nut without tobacco and oral cancer and that, overall, areca nut should be regarded as carcinogenic to humans. Members also agreed that the use of areca nut as a food ingredient was potentially carcinogenic.

Folic acid fortification and carcinogenesis

3.10 In 2005, the Scientific Advisory Committee on Nutrition (SACN) asked for advice from the COC on whether dietary folic acid intake is associated with increased cancer risk. After reviewing the available data, the COC recommended a precautionary approach in considering mandatory fortification of flour with folic acid. Subsequently, SACN had asked for further clarification of this advice and the Chairman had agreed that aiming to increase low level intakes whilst ensuring that high level intakes do not increase is consistent with a precautionary approach. As a result, the SACN concluded that mandatory fortification should only be introduced if it is accompanied by action to reduce folic acid intakes from voluntarily fortified foods to ensure that the numbers of people with intakes above the EVM's upper intake level do not exceed current levels and there is no substantial increase in mean intakes or in the folate status of the UK population.

3.11 At its July 2007 meeting, the COC discussed further recent publications on folic acid, including two editorials from the British Medical Journal. An abstract of a randomised clinical trial with folic acid supplements for the prevention of colorectal adenomas had been seen by the committee when it considered this topic last year; the full paper had now been published. This had failed to show any evidence that folic acid supplementation protects against colorectal cancer but that there was an excess of prostate cancer cases in the folic acid group compared to controls. It was suggested that this might be due to promotion of pre-neoplastic lesions to neoplasms. Members were reminded that the study had not been designed to investigate the effect of folic acid supplementation on prostate cancer risk and that the authors of the study had themselves commented that this could be a spurious association. It was also noted that there may have been a differential rate of PSA testing between the two groups, and that mandatory fortification of food with folic acid had been introduced in the US while this study was in progress and total intake of folic acid would have exceeded the guidance level for upper intake of 1 mg/day recommended in the UK by the Expert Group on Vitamins and Minerals (EVM). According to the SACN report, there was no clear change in the incidence of prostate cancer following mandatory fortification in the US. A second paper reported a study on dietary intake of folate and co-factors in folate metabolism.

3.12 The committee concluded that, on balance, it was content with the proposals by the FSA Board to recommend to UK health ministers that there should be mandatory fortification of a food with folic acid, with controls on voluntary fortification and guidance on use of supplements, monitoring of the folic acid intakes and status of the UK population and postulated risks – including cancer incidence- and a review of the data on the benefits and possible risks 5 years after introduction of mandatory fortification. Members asked to be informed of the outcome of the 5 year review.

3.13 Following the meeting, Members were informed that the Chief Medical Officer had decided to convene a special subgroup of the Scientific Advisory Committee on Nutrition (SACN) to examine further two papers on the potential adverse effects of folic acid on the risk of colorectal cancer and that the Chairman had been invited to participate in this subgroup.

Formaldehyde

3.14 At the 2006 horizon scanning exercise, the committee was informed that the International Agency for Research on Cancer (IARC) had concluded that there is "strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde". This conclusion was tempered because it was not possible to identify a mechanism for leukaemia induction. A literature paper had argued against there being a causal relationship for formaldehyde and leukaemia risk on the grounds that there is no evidence to suggest that formaldehyde reaches any target organ beyond the site of contact, no indication that formaldehyde is toxic to the bone marrow, and no credible evidence that formaldehyde induces leukaemia in experimental animals. In 2007, it considered the conclusions of a recent COM review of formaldehyde and the extract from the recent IARC monograph on formaldehyde which summarises the epidemiological findings on leukaemia.

3.15 The COM advice is given in paragraph 2.17 of this document. The COC noted its conclusions and considered a key point to be that inhalation exposure to exogenous formaldehyde would have no effect on the endogenous concentration of formaldehyde. Members therefore questioned how IARC had concluded that there was a causal association between leukaemia and occupational exposure to formaldehyde, particularly in view of the metabolic data in the IARC summary. The Committee decided that it did not wish to review the epidemiological evidence in detail.

Quantitative structure-activity relationships (QSAR)

3.16 The COC considered two recently published papers on the use of QSAR to predict carcinogenicity. One paper, from the US Food and Drug Administration (FDA) described an evaluation of the performance of a particular software, MDL-QSAR predictive discrimant analysis modelling of rodent carcinogenicity, to estimate the carcinogenic potential of small, organic, naturally occurring chemicals found in the human diet. The predictive performance for this group of chemicals and a control group of 19 known syntheic dietary constitutents was 97% sensitivity and 53% specificity. The second paper, by Benigni *et al* (2007), described and discussed preliminary findings from a project on (Q)SARs for mutagenicity and carcinogenicity initiated by the European Chemicals Bureau and carried out by the Istituto Superiore di Sanita', in the context of the forthcoming REACH legislation.

3.17 Members considered that it would be useful to review the final results of the REACH project when this had been published and then to decide whether to undertake a full review of QSAR for prediction of carcinogenicity.

Risk communication

3.18 In 2005, the COC and COM decided that they should collaborate to improve the way in which the advice on the potential carcinogenicity and mutagenicity of chemicals is presented to the general public. In 2006 and 2007, the COC discussed the ways in which the carcinogenic risk of chemicals might be better communicated and put into context alongside other risks. Members noted that the primary role of the COC and COM was to provide advice to government departments and regulatory

agencies which were responsible for risk management and risk communication. However, it was agreed that a wider understanding of the low risks associated with exposure to environmental carcinogens was desirable.

3.19 One suggestion was that the risks of environmental carcinogenesis could be compared with other involuntary risks, using established risk scales such as the Calman risk scale or the "Risk It" game developed by the HPA for radiation. However, the committee considered that it would not be possible to develop such an approach for chemicals as selection of exposure scenarios would be very difficult. It suggested that a more suitable approach might be to compare closely connected risks e.g. those of natural toxins and synthetic pesticide residues in or on the same foodstuff. The COC also agreed that current approaches to drafting statements needed to be improved, with more information on the reasons for undertaking reviews and non executive summaries developed for all statements. It asked the secretariat to consider carefully the audience in any further paper for the COC.

3.20 As part of this item, the FSA asked the COC to comment on the potential usefulness of the Margin of Exposure (MOE) approach being developed by the European Food Safety Agency (EFSA), the World Health Organisation (WHO) and the International Life Sciences Institute (ILSI) as a way of prioritising the risks associated with unavoidable exposure to genotoxic chemical carcinogens in food. The MOE is the numerical value obtained by dividing a reference point on the dose response curve for carcinogenicity in experimental animals by estimated human exposure to the chemical. The preferred reference point of the above organisations is the lower limit of the confidence interval on the benchmark dose (BMD), although they have noted that the T25 could be used in cases where the dose-response data were not adequate to define the BMD or the lower limit of its confidence interval of the (BMDL).

3.21 The COC agreed that the use of the MOE to prioritise the risk of exposure to genotoxic carcinogens was consistent with the most recent COC guidelines and would also contribute to international harmonisation in this area. It discussed the relative merits of using the BMDL10 or T25 and noted that the BMDL10 takes the quality of the data into consideration, due to the use of confidence intervals, whilst the T25 does not. The T25 was usually derived from poorer data sets. Overall, it would be necessary to decide which to use on a case-by-case basis depending on the quality of the available data.

3.22 A system for banding MOE values was agreed and is given below in Table 1. This expands on proposals for the interpretation of the magnitude of the MOE that had been made by JECFA and EFSA, where there was a consensus that an MOE greater than 10,000 indicated low concern. It was hoped that the banding system might improve the communication of advice on genotoxic carcinogens to wider audiences.

Table 1: Banding of MOE values for risk communication

MOE Band	Interpretation
<10,000	May be a concern
10,000-1,000,000	Unlikely to be a concern
>1,000,000	Highly unlikely to be a concern

3.23 Having agreed the MOE approach in principle for the communication and prioritisation of risks, the committee considered in detail the methodology used to derive the BMDL10. It reviewed an illustrative exercise for 3 genotoxic soil contaminants (hexavalent chromium, benzo(a)pyrene and 1,2-dichloroethane) and advised on several aspects of the methodology which should be used. Members involved in the international fora recommended that the COC should review ongoing work on model averaging when published.

Technical guidance for derivation of DNELs and risk characterisation of non-threshold effects in the context of REACH

3.24 At the March 2007 meeting, the HSE made a short presentation to inform members about progress with the development of technical guidance for the risk assessment of substances under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals - a new European Regulation). This focused on the proposed guidance for dealing with "non-threshold" genotoxic carcinogens. Two approaches were proposed: one is based on linear extrapolation from animal bioassay data to a predetermined low level of risk and the other is based on application of a large uncertainty factor (UF) to a suitable reference point on the dose-response for carcinogenicity. The latter approach was included because the UK, unlike most other EU member states, does not use the linear extrapolation approach. Both approaches generate a Derived Minimum Effect Level (DMEL) which is defined as the level of exposure above which humans should not be exposed. Members were informed that both the predetermined low level of risk and the uncertainty factors were decided at policy level and were non-negotiable.

3.25 The COC considered that the UF and DMEL methods are essentially equivalent but differ with respect to risk communication. Members noted that the UF approach differed from the MOE approach in that, in the REACH methodology, a predetermined UF of 10,000 was to be used. Members were concerned about the derivation of an UF of 10 for 'the nature of the carcinogenic process' given the limitations of current knowledge about DNA repair.

3.26 There was discussion of the units chosen for the DMEL values with some members favouring the use of moles/micromoles rather than dose/weight/day, because the biological response is based on the interaction of molecules of a chemical, not the weight administered. However, it was pointed out that this could be difficult since the purity of the active ingredient is not always known and it would be difficult to assess substances, as opposed to single chemicals, on a molar basis. The committee also discussed the proposal that "biological criteria" should be used to assess the relevance of a carcinogenic response, rather than statistics alone. It was pointed out that all tumours are biologically significant but it is important to know whether they are compound related and this is, in part, based on statistical analysis.

3.27 The proposals included using the Threshold of Toxicological Concern (TTC) approach to setting DMELs for somatic cell mutagens with no cancer data. However, the COM considers it premature at present to set levels such as TTCs for mutagens with no cancer data, as no agreement had been reached about how to rank such mutagens.

3.28 HSE commented that the committee's comments would be reported to the EU working group drawing up this guidance.

Horizon scanning

3.29 The COC undertakes "horizon scanning" exercises at regular intervals to identify new and emerging issues which have the potential to impact on public health. After an extensive literature search, a number of topics were identified by the secretariat for consideration by the committee at the 2007 exercise. From these, and committee members' own proposals, the COC considered that the following topics should be taken forward, together with those outstanding from 2006:

- the carcinogenicity of mixtures
- further consideration of the Human relevance framework/Mode of action
- a further review of proteomics
- mutational spectra (jointly with the COM).

Ongoing topics

Chlorinated drinking water and cancer

3.30 During 2007, the COC reviewed a number of new epidemiological studies on chlorinated drinking water and cancer. A statement will be published in 2008.

Non-Hodgkin's lymphoma (NHL)

3.31 Incidence rates for NHL have increased in all age groups in Great Britain in recent years, particularly during the early 1980s and 1990s. A number of epidemiological studies have been carried out on the association between chemicals and NHL and the committee reviewed these during 2007 to see if there is any evidence that exposure to environmental chemicals could have accounted for the increase in incidence of NHL. A statement will be published in 2008.

Toxicogenomics

3.32 The COC, COM and COT are updating their review of toxicogenomics. The COC has focussed on two areas in particular: whether toxicogenomics is useful in distinguishing between genotoxic and non-genotoxic chemicals, and whether it is useful in testing the hypothesis for a mode of action or of help in proposing a mode of action for a chemical. A joint statement will be published in 2008.

Statements of the COC

Statement on Prostate Cancer and Pesticide Exposure

Introduction

1 In 2004 the committee published a statement on prostate cancer, in which we discussed the known and potential risk factors associated with this disease. The statement included an evaluation of the epidemiological and other data on occupational groups and chemical exposures for which an association with prostate cancer has been proposed. Two occupational groups were considered: rubber workers, for whom we concluded that there was no convincing evidence of an increased risk of prostate cancer, and farmers/farm workers/pesticide applicators. In the case of this latter group, we concluded:

> "...that there was some limited evidence to suggest an association between farmers/farm workers, exposure to pesticides and increased risk of prostate cancer. The possibility of such an association being causal could not be discounted and the published literature should continue to be monitored for further studies. The committee commented on the need for improved measures of exposure to pesticides and in particular herbicides. It was considered that the potential association between herbicide use by farmers and farm workers should be kept under review" (COC, 2004)

2 Recently, we were asked by the Pesticides Safety Directorate of the Department of the Environment, Food and Rural Affairs (Defra) to consider a report commissioned from the Institute of Occupational Medicine (IOM) entitled "Desk Study on Prostate Cancer and Pesticide Exposure"(IOM, 2006) and to advise on whether the report alters the conclusion of our 2004 statement. At the same time, we considered a newly published review and meta-analysis of cohort studies of prostate cancer risk in pesticide manufacturing workers (Van Maele-Fabry *et al*, 2006). We report here on our conclusions.

3 The IOM report is a narrative review of the epidemiology of occupational exposure to pesticides and the risk of prostate cancer, and of the potential mechanisms that might underlie any association. The report concludes that epidemiological studies of manufacturing workers exposed to pesticides have not reported an excess risk of prostate cancer. It also concludes that there are a large number of studies of agricultural workers exposed to pesticides but that, nevertheless, the results have been inconsistent: many have been negative or inconclusive, with a few showing positive results. We note that the report proposes that pesticides might cause prostate cancer through a potential endocrine-disrupting mechanism based on androgen imbalance. This proposal may be derived from data that suggest that low dose exposure to certain chemicals may lead to an increase in prostate gland weight in young mice (vom Saal *et al*, 1997) but these data are disputed by others (Ashby J *et al*, 1999) who were unable to reproduce these observations. Moreover, pesticides are not a generic group of chemicals but comprise compounds of different structures and biological activities. It is unlikely, therefore, that a single mechanism of action would apply to all pesticides.

4 The meta-analysis by Van Maele-Fabry *et al* (2006) was conducted on 16 studies of workers ever employed in pesticide manufacturing and with potential exposure to pesticides. The analysis combined relative risk estimates from both incidence and mortality studies to derive an overall meta-rate ratio of 1.28 (95% CI 1.05 -1.58). After grouping the data into specific chemical classes of pesticide, increased pooled rate ratios were reported for each class but statistically significant results were only reported for phenoxy herbicides contaminated with polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans. We note that there are some unresolved methodological issues in this analysis, for example, adjustment for confounding might have been unsatisfactory, as little is known about the risk factors for prostate cancer.

5 We consider that the individual studies to date of exposure to pesticides in farmers/farmworkers and in pesticide manufacturing workers provide no consistent support for an association with prostate cancer. A recent meta-analysis by Van Maele-Fabry *et al* (2006) provides some limited evidence of a weak association between pesticide exposure in manufacturing workers and prostate cancer. It is not uncommon that the more formal approach of meta-analysis differs in its conclusions from a narrative review based on individual papers. Causality cannot be inferred from the available data. We recommend that the literature on this topic is kept under review.

March 2007
Statement COC/07/S1

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2007 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

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Declaration of COC members interests during the period of this report

MEMBER	Personal Interest		Non Personal Interest	
	COMPANY	INTEREST	COMPANY	INTEREST
Professor D H Phillips (Chair)	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Servier Buller Jeffries (Solicitor)	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Honorarium Honorarium	NONE	NONE
Dr C Allen	NONE	NONE	NONE	NONE
Professor A Boobis OBE	Bank Santander Barclays Bank BG Group BT Group Centrica Halifax National Grid Transco Scottish Power Astellas Pharma	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy	GlaxoSmithKline ILSI HESI	Research Support Unpaid member of Board of Trustees
Dr P Carthew	Unilever	Salary	NONE	NONE
Professor P B Farmer	Santander Bradford & Bingley Foreign & Colonial Friends Provident Health Effects Institute Torotrak ILSI HESI	Shareholder Shareholder Shareholder Shareholder Research Committee Member Shareholder Committee Member	American Chemistry Council CEFIC	Research Support and Conference attendance expenses. Research support
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE

MEMBER	Personal Interest		Non Personal Interest	
	COMPANY	INTEREST	COMPANY	INTEREST
Professor D Harrison	The Forensic Institute University of Edinburgh Lothian NHS Response Genetics (University consultancy no fee payable.) University of Florida (University consultancy) University of Canberra (University consultancy)	Shareholder	PI Medical Research (Scotland) Chair EMMS Nazareth Member Scientific Advisory Committee, Yorkshire Cancer Research.	Non specific research funding from Cancer Research UK. Breakthrough, CSO & other grant agencies. Trustee (Healthcare Charity) Trustee
Ms D Howel	NONE	NONE	NONE	NONE
Dr B G Miller	Scottish Power	Shareholder	NONE	NONE
Professor R A Roberts	AstraZeneca HBOS P & O	Salary Shareholder Shareholder	NONE	NONE
Professor D E G Shuker	NONE	NONE	NONE	NONE
Professor P Vineis	NONE	NONE	NONE	NONE
Dr N Wallis	Pfizer	Salary Shareholder	NONE	NONE