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

Preface

The Committee on Carcinogenicity (COC) evaluates chemicals for their human carcinogenic potential at the request of the Department of Health and Food Standards Agency and other Government Departments including the Regulatory Authorities. All details concerning membership, agendas, minutes and statements are published on the Internet.

During the year 2003, the Committee provided advice on a wide diversity of topics including polycyclic aromatic hydrocarbons in air pollution (and in particular the highly potent compound dibenzo(a,l)pyrene), 1,3-dichloropropan-2-ol (a potential contaminant of drinking water), and impurities present in the pesticide 1-methylcyclopropene. The Committee also updated its view on intrahepatic cholangiocarcinoma, assessed the risks associated with exposure to low levels of air pollution and reviewed a paper by Enstrom JE and Kabat GC (British Medical Journal, volume 326, 1057-1066, 2003) on environmental tobacco smoke and lung cancer.

The Committee has an ongoing responsibility to provide Government Department's and Regulatory Authorities with advice on developments in procedures for the evaluation and risk assessment of carcinogens. During this year, the Committee provided advice on the proposed approach from the U.S. Environmental Protection Agency (EPA) on the supplemental data necessary for assessing susceptibility from early life exposure to carcinogens and on the hypothesis for the occurrence of "U" shaped-dose response curves (Hormesis). The Committee has commented on the proposed "Biobank" project.

The Committee discussed a number of proposals for greater openness and it is hoped to agree procedures for open meetings during 2004.

During 2003, the Committee also said farewell to three highly respected members. Professors Cooper, Renwick and Williams have given many years of highly valuable service to COC. I wish to record my thanks for the quality of their scientific advice and commitment to public health during their terms of office with COC.

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Dibenzo(a,l)pyrene in air pollution

3.1 In 1995, at the request of MAFF and the Department of Environment, the COC agreed a hazard-ranking scheme for the carcinogenicity of 25 polyaromatic hydrocarbons (PAHs). It was based on classification into one of 5 categories. The COC in 1995 had accepted the principle that the carcinogenicity of PAHs was additive. Advice on dibenzo(a,l)pyrene (DB(a,l)P) had not been requested in 1995. Since then, air pollution monitoring in the UK had detected the presence of dibenzo(a,l)pyrene in a number of samples. An assessment of the relative carcinogenic potency of DB(a,l)P compared to benzo(a)pyrene which claimed that this was about 100 times greater, had been published in an Environmental Health Criteria Document (International Programme on Chemical Safety).

3.2 The COC was asked to consider the mutagenicity and carcinogenicity data on dibenzo(a,l)pyrene and to consider to what category of the COC hazard ranking scheme of PAHs dibenzo(a,l)pyrene could be assigned. The COC agreed that the *in-vitro* mutagenicity tests and information on *in-vivo* DNA adduct formation was consistent with dibenzo(a,l)pyrene being an *in-vivo* mutagen. Members also agreed that dibenzo(a,l)pyrene was carcinogenic in mice and rats. Dermal application to mice produced tumours at a number of sites (including the skin, lung, and malignant lymphoma of the spleen and malignant lymphoma with multiple organ involvement) and intraperitoneal administration to rats produced lung tumours. Intramammary instillation in rats resulted in mammary tumours. Dibenzo(a,l)pyrene also acted as an initiator in mouse skin carcinogenicity promotion assays. The COC therefore considered that dibenzo(a,l)pyrene should be assigned to group A of its hazard ranking scheme for PAHs. This category includes chemicals for which 'there is a high level of concern about a carcinogenic hazard for humans because the compound is an *in-vivo* mutagen and/or a multi-site carcinogen in more than one species.'

3.3 Regarding potency, the Committee agreed that dibenzo(a,l)pyrene was a very potent genotoxic carcinogen and that potency varied depending on factors such as species, route of administration, dose and site of tumour produced. From the available data where a comparison could be made, members considered that the dibenzo(a,l)pyrene carcinogenic potency was likely to be in the range of 10-100 times more potent than benzo(a)pyrene depending on the tests system used. The measurement of DNA adducts (Time Integrated DNA Adduct Levels: TIDAL) following intraperitoneal dosing of DB(a,l)P showed that, in comparison to other PAHs, DB(a,l)P bound much more extensively to DNA, due presumably to the higher reactivity of its diol-epoxide metabolite(s). This might explain its greater carcinogenic potential.

3.4 The Committee agreed that there were insufficient data available on dibenzo(a,l)pyrene to draw any conclusions on the relative potency compared to benzo(a)pyrene by the inhalation route of exposure. The committee agreed to reconsider the topic of the relative carcinogenic potency of PAHs by the inhalation route of exposure at a future meeting. The Committee reached the following overall conclusion;

"Dibenzo(a,l)pyrene should be considered as a highly potent genotoxic carcinogen in experimental animals. There is a need for further consideration of the potential importance of exposure to dibenzo(a,l)pyrene and other highly potent carcinogenic polycylic aromatic hydrocarbons in air pollution."

3.5 A statement is appended at the end of this report.

1,3-Dichloropropan-2-ol (1,3-DCP):

3.6 1,3-Dichloropropan-2-ol (1,3-DCP) is a member of a group of chemicals called chloropropanols, which also includes 3-chloro-1,2-propanediol (3-MCPD) and 2,3 dichloropropan-1-ol (2,3 DCP). Chloropropanols are contaminants of some foodstuffs and of polyamine flocculants used in the treatment of drinking water. The COC considered the 1,3-DCP in 2001 and in particular a carcinogenicity bioassay in rats which had identified treatment-related tumours in several organs. Taking into account the advice of the COM on this compound, the Committee concluded that "*It is prudent to assume that 1,3 DCP is a genotoxic carcinogen and that exposures to 1,3 DCP should be reduced to as low a level as technologically feasible.*"

3.7 The COM considered two new in-vivo mutagenicity studies on 1,3 DCP namely a bone marrow micronucleus assay and an unscheduled DNA synthesis (UDS) assay during its 2003 meetings. In the light of these new data, the COM had now concluded that it would be appropriate to consider that 1,3-DCP was not an *in-vivo* mutagen.

3.8 The COC was asked to review its previous conclusions on the tumours induced by 1,3 DCP in rats. The Committee noted its previous opinion that the 1,3-DCP induced tumours of the kidney and thyroid could have been secondary to sustained cell proliferation. Members also agreed that there was evidence of a hepatotoxic effect at doses below those producing a significant increase in combined hepatocellular adenoma and carcinoma.

3.9 The Committee then considered possible modes of action of 1,3-DCP in inducing tumours of the tongue. Members agreed that a significant increase in the incidence of papillomas and carcinomas had been identified in the tongue at the high dose level in both males and females. It was noted that this dose level exceeded the Maximum Tolerated Dose level in that there was an increase in treatment related mortality and hepatotoxicity in this group of animals. The Committee agreed that 1,3-DCP was an irritant and had produced irritant effects in gastric mucosa of treated rats, but there were no suitable data on the potential for 1,3-DCP irritation of the tongue. Members noted that at the time of conduct of the bioassay (1986) it was not routine to examine the tongue histologically. It was agreed however, that since the compound had been given in the drinking water in the bioassay, chronic irritation was a plausible hypothesis for the induction of the tumours in the tongue. Members noted that there was evidence suggesting that bacteria metabolised 1,3-DCP to the genotoxic carcinogen epichlorohydrin. It was possible that bacteria present in the oral cavity might produce epichlorohydrin when exposed to 1,3-DCP and it was not known whether this would be rapidly detoxified in the oral cavity or tongue.

3.10 Members considered that although there was no precedent for site-specific tongue tumours arising from bacterial activation of a compound, the suggestion regarding 1,3-DCP was plausible. It was noted that chemical induction of tumours of the tongue in rats was relatively rare, the only examples that could be recalled readily were a variety of nitrosamine compounds. Members considered the possibility of further work to fully discount a genotoxic mode of action for the tongue tumours in rats. It was agreed that information on contact-irritancy, cell proliferation and formation of ^{32}P-postlabelling adducts in animals treated with suitably high doses of 1,3-DCP would provide appropriate information.

3.11 A revised statement would be drafted in due course.

Environmental tobacco smoke (ETS) and lung cancer: consideration of paper by Enstrom JE and Kabat GC (2003). British Medical Journal volume 326, 1057-1066

3.12 The COC undertook a detailed review of the evidence regarding the association between exposure to environmental tobacco smoke (ETS) and lung cancer during 1997. The review was requested by the Scientific Committee on Tobacco and Health (SCOTH). The full transcript of the COC statement can be found in the 1997 Annual report on the COC internet site(http://www.doh.gov.uk/coc/1997ar.pdf)

3.13 The Committee agreed there was evidence that exposure to ETS of individuals in the Cancer Prevention-1-cohort could not be adequately assessed and thus no definite conclusions could be drawn with regard to the study by Enstrom and Kabat.

3.14 The Committee reviewed a number of additional publications. Overall it was concluded that the study of Enstrom and Kabat should be reviewed with caution in view of inadequacies in assessment of exposure to ETS in the investigation.

3.15 A statement is appended at the end of this report.

Impurities in the pesticide 1-methylcyclopropene

3.16 1-methylcyclopropene (1-MCP) is a new pesticide active ingredient (growth regulator) being assessed by the Pesticides Safety Directorate (PSD) under EU Directive 91/414/EEC. 1-MCP blocks the effects of ethylene release in apples thus preventing over-ripening and softening. The Committee was asked for advice on the risks posed by the potential for exposure to two impurities present in the active ingredient namely impurities 1 and 2 which were presumed by the Advisory Committee on Pesticides (ACP) to be genotoxic carcinogens on the basis of published mutagenicity studies and life-time bioassays in rats and mice using oral administration. The Department for the Environment, Food and Rural Affairs (DEFRA) asked for advice on the carcinogenic risk posed by the impurities. The COC was not asked to evaluate the active ingredient and data on this compound have not been reviewed. The COC has not been asked to evaluate the other two impurities present in 1-MCP.

3.17 The COC was provided with published information on the mutagenicity, carcinogenicity and metabolism of impurity 1 and impurity 2 and with details of the manufacture of 1-MCP, information on the formulation and product to be used in the U.K and estimates of potential exposures to impurities present in 1-MCP during use. The data holder, Rohm and Haas company, provided an estimation of the 5% Bench Mark Dose for the most sensitive carcinogenic response for these two impurities which was for forestomach tumours.

3.18 The Committee's conclusions based on the questions posed by DEFRA are given below;

Whether a minimum risk levels for the impurities 1 and 2 can be derived

The COC concluded that pragmatic minimum risk levels could be established for impurity 1 and impurity 2. For impurity 1 this was equivalent to a daily oral does of 0.06 mg/kg bw/day. For impurity 2 this was equivalent to 1.28 mg/kg bw/day.

Whether exposures to the impurities 1 and 2 present any significant risks to consumers or operators

The COC noted that the maximum predicted exposures for operators and consumers will be below the proposed minimum by factors varying from approximately 3 to 5311. The risk of carcinogenicity posed by exposure to impurity 1 and impurity 2 is considered to be negligible.

Whether maximum levels of the impurities 1 and 2 should be proscribed

The COC agreed that maximum levels for these impurities should not result in doses exceeding the minimum risk level and restated that there was always a need to apply the "as low as reasonably practical" (ALARP) principle to genotoxic carcinogens.

3.19 A statement is appended at the end of this report.

Polycyclic Aromatic Hydrocarbons in air pollution

3.20 The COC has recently evaluated published carcinogenicity data on dibenzo(a,l)pyrene (DB(a,l)P) and had agreed that this compound was between 10-100 times more potent than benzo(a)pyrene depending on the test system used (see section 3.3 of the COC Annual Report). Thus a paper had been drafted which considered the potential impact of DB(a,l)P and other high carcinogenic potency PAHs on the existing approaches to risk assessment of PAHs in air pollution.

3.21 Three approaches to carcinogenic risk assessment have been advocated: the use of Potency Equivalency Factors (PEFs) (equivalent to Toxicity Equivalent Factors, TEFs, for general toxicity); the complete mixture method; and use of B(a)P as a surrogate carcinogen for all PAHs. It was possible that the B(a)P surrogate approach which is currently used to monitor for compliance with UK air pollution standard, might not be appropriate if high potency PAHs were present in air pollution and if the concentrations of these compounds varied significantly when compared to B(a)P. The COM had provided advice on the most suitable approach to measuring relative carcinogenic potency of PAHs using measurement of time integrated DNA adduct levels after intratracheal administration of low doses of PAH.

3.22 COC Members agreed with the suggested approach of using DNA adducts for ranking PAHs as a suitable surrogate for measuring carcinogenic potency by inhalation. It was noted that the potential for induction of PAH metabolism and differential repair of DNA adducts needed to be considered when interpreting results. However the approach represented a pragmatic method of providing ranking into broad groups. These results could be used with data on air levels (derived from a range of sites in the UK at different time intervals) to evaluate variation in carcinogenic potency of PAHs in air pollution. The outcome of this research would help review whether a PEF or B(a)P surrogate approach to the air quality standard was most appropriate for the risk assessment of PAHs in air pollution.

3.23 The Committee agreed that was important to find out the proportion and variation of high potency PAHs in the UK, as detected by air monitoring.

3.24 A paper is in preparation for submission to a peer review journal.

Update on consideration of Intrahepatic Cholangiocarcinoma

3.25 The Committee had considered this subject in 2000 and in 2001. Evidence for an increase in the mortality from intrahepatic cholangiocarcinoma over the period 1968-1998 had been provided by Professor Howard Thomas and colleagues (from the Department of Medicine at Imperial College of

Science Technology and Medicine). The Committee had advised that changes in diagnostic standards over time could have accounted for the reported increase and concluded that it was important to keep this topic under review. During 2001 more information was made available to the Committee including a prepublication report of additional investigations by Professor Thomas and colleagues. A statement had been agreed at the beginning of 2002. (http://www.doh.gov.uk/coc/intrahepaticst.htm).

3.26 Some additional information from Professor Thomas's group was considered by COC during 2003. This information was valuable in assessing the progress regarding the recommendations for research that had been identified by the COC in its statement. Members considered that the evidence for an increase in the incidence of IHCC was becoming more convincing, in particular, the evidence on trend now available from several countries. The COC considered the proposed case-notes study would not be useful in that it would only examine the accuracy of diagnosis as given on death certificates in the early 1990s and would not provide clarification on the possibility of diagnostic transfer.

3.27 Members commented on the published paper on DNA adducts (Khan et al, Gut (2003): 52, 586-591). This was considered to be a well-conducted study, although there was only a small number of controls. However, it was not possible to determine the cause of the adducts. They could be due to an exogenous genotoxic agent or an endogenous process, or they could be a marker of tumour development. Looking at tumour tissue and tumour-adjacent tissue from people with IHCC caused by liver fluke might help to clarify this. The Committee was unable to draw any conclusions about the relevance of the high levels of DNA adducts in tumour-adjacent tissue. The unpublished paper on P53 mutations was not considered to provide any support for causation by an exogenous genotoxic agent because the mutational spectra recorded showed no reproducible pattern.

3.28 The Committee will keep developments in this area under review.

Update on risks associated with exposure to low levels of carcinogenic air pollutants

3.29 At the November 2002 meeting of the Committee, Members considered a proposal to use the upper bound estimate derived from the one-hit model using data from epidemiology studies in exposed humans to set upper bounds of risk at low levels of exposure to air pollutants. Members were advised that the intention was to use this very conservative approach to advise on the practicality of risk management options for air pollutants and there was no intention to publish risk estimates based on this approach. The primary objective would be to assess the cost of reducing levels of air pollution to the exposures associated with the upper bound estimate of risk based on the one hit model. The COC was content with the approach provided that it was limited to chemicals for which there was good cancer epidemiology data and that data were used only as a guide when considering risk management options. Members felt, however that it was important to restate that extrapolation of risk estimates below the observed range was very problematic, as no model was completely satisfactory.

3.30 A statement on this topic was agreed during 2003 and is appended to this report.

Review of Committee Procedures

Horizon Scanning

3.31 The Code of practice published by the Office for Science and Technology (OST) on Guidance for Scientific Advisory Committees (http://www.ost.gov.uk/policy/advice/copsac/) encouraged Committees to develop strategies for the early identification of issues. This included i) "new issues", eg previously unidentified potential chemical mutagens/carcinogens which may represent a risk to public health and where advice is required, and ii) "new or unexpected developments in science."

3.32 The DH Toxicology Unit had provided a paper which updated the research priorities discussion and conclusions reached by COC in 1996 and also reviewed potential areas for further work such as cancers where there was evidence for an increasing trend in incidence (http://www.doh.gov.uk/coc/papers.htm). The chair thought that it would be valuable if the COC revisited horizon scanning for a short period at each future meeting.

3.33 As part of the discussion of this item, members commented on the proposal regarding the occurrence of "hormesis" (ie the occurrence of a "U" shaped dose-response curve at low dose level). A report of the discussion is given under Test Strategies and Evaluation (see section below).

3.34 Regarding other topics, members agreed a review of oesophageal cancer and the induction of DNA repair following exposure to low doses of carcinogens would be valuable. Members also considered evaluation of potential risks of chemical induced cancer in children had received considerable interest in the scientific literature and it would be appropriate for COC to form a view on the subject.

Further discussions on Openness of Committee Business

3.35 The COC currently publishes an agenda and many of its discussion papers before each meeting, whilst minutes of meetings and Committee statements are published when finalised. The Committee considered a draft protocol that set out procedures for conducting meetings in open forum. It is intended that after discussion by all three Committees had been completed, a finalised document would be agreed and published as part of a revised code of practice for openness.

3.36 The COC agreed in principle to conducting meetings in open forum. Members noted that it was important to manage applications for attendance according to the procedures set out in the draft protocol. Of particular importance was the need to seek information from attendees on their declarations of interest prior to the discussion of items. It was noted that observers at open COT meetings had usually attended for a specific item and it was agreed that, if this were so, then it was appropriate to undertake the proposed question and answer session with the relevant item. The Committee also raised a number of concerns regarding the need to avoid attributing comments to individual members and dealing with in-confidence data submitted to the Committee. The secretariat was asked to consider these further and report back to COC.

Test Strategies and Evaluation

Biobank project

3.37 The Committee heard a presentation on the aims, objectives and preparatory work undertaken to establish the Biobank project in U.K. Further information can be obtained from (http://www.ukbiobank.ac.uk/).

3.38 It was noted that the publication of the draft code for the human genome and new techniques for rapid sequencing Single Nucleotide Polymorphisms of DNA had opened the way for research to investigate the combined effects of genetics and lifestyle or environmental factors on common multifactorial diseases of adult life. Thus the strong scientific base in the UK, the population size and diversity and the almost universal coverage of the NHS indicated that large scale prospective research on disease occurrence and genetics was feasible in the UK. A key factor in the design of the study

would be including enough individuals so that sufficient clinical outcomes could accrue within a reasonable period of time. For this reason, the Biobank would be established with a minimum of 500,000 individuals aged between 45-69y with a follow-up period of 10 years. People registered with general practices would be asked to join the study. Participants would be asked to complete a self-administered questionnaire and interview with a research nurse, give a blood sample, and sign a consent form for participation and follow-up. Participating individuals would be flagged through the ONS and incident data on morbidity would be obtained through practice records and hospitalisation data. A key policy for participation was "opt-in", and that individuals would be able to leave the project at any time.

3.39 The Committee made a number of comments regarding the recruitment of individuals, ascertainment of disease status, and quality control of sample handling and analysis. A key concern of members was the limited information on chemical exposure that would be available for cohort members. This would limit the potential for studies to investigate the association between genotypes and susceptibility to chemical induced disease.

EPA risk assessment guideline: supplemental data for assessing susceptibility from early life exposure to carcinogens

3.40 The US Environmental Protection Agency had issued a draft consultation document on the assessment of susceptibility to carcinogens from early life exposures. The USEPA had argued that conventional bioassays underestimated risks (from the dose response slopes) arising from early life exposures for genotoxic carcinogens, but not for non-genotoxic carcinogens. These data led the USEPA to propose adjustment factors of 10 (for below 2 years of age) and 3 (for ages 3-15 years). The Committee's view was requested on this and the implications, if any, for the UK approach to risk assessment for chemical carcinogens and the methodology used.

3.41 Members felt that it was very difficult to draw any definite conclusions from the comprehensive EPA comparisons between results with conventional carcinogen bioassays and the studies involving neonatal/ perinatal exposure. This was because of the great variability in the study designs used for the neonatal/perinatal studies. Rarely were any pharmacokinetic data available to allow a comparison to be made between the systemic doses achieved by oral exposure in the conventional assays and the parental routes frequently used in the studies involving exposure of neonates. Furthermore there were only limited consideration of the mechanism involved and the target tissues (tamoxifen was given as an example of when the approach adopted was inappropriate due to differing tissue specificity).

3.42 It was agreed that there was some biological plausibility to the argument of increased sensitivity in the early life stages (due to factors such as differing metabolism and cell turnover), and the analysis did provide some limited data to support this. However, this was not always the case. It was pointed out that the document was concerned with the risk of cancer in later life, and whether early life stage exposure made this more likely. It did not address childhood cancer, only the lifetime risk of cancer following early life exposure.

3.43 As the COC does not recommend the use of slope of the dose response from animal bioassays to calculate human cancer risks (and the estimation of the tolerable exposure levels) it was agreed that the adjustment factors being proposed by the US EPA were not relevant to the UK. In the UK a risk management approach of reducing exposures to as low as reasonably practical for all age groups is adopted for genotoxic carcinogens.

3.44 The Committee considered that in some instances the data suggested that animal models that include perinatal exposure may be more sensitive; these difference were quantitative, and there was no evidence that the use of conventional cancer bioassays in animals would fail to detect chemical carcinogens.

3.45 The Committee agreed that these data supplied by the USEPA had very limited implications for the way carcinogenicity assessment was carried out in the UK.

Hormesis (The occurrence of "U" shaped dose dose-response curves)

3.46 Members were asked to comment on the recent publication from Calabrese EJ and Baldwin LA (Nature, vol 421, 691-692, 2003.) which provided an argument for the occurrence of hormesis (ie the occurrence of a "U" shaped dose-response curve at low dose level).

3.47 The Committee noted that although it was stated that there were up to 5000 examples of the hormetic effect in the published literature, it was not possible to assess this claim on the evidence available. It was noted that in the few studies on genotoxic carcinogens using group sizes sufficient to detect effects at 1% levels or below, the evidence was generally consistent with the absence of a threshold. Also, DNA adduct formation with genotoxic carcinogens was linear down to the lowest measurable dose levels. The dose-response data for non-genotoxic carcinogens was consistent with the occurrence of a threshold.

3.48 Members considered that there was no evidence available to justify the use of a hormetic approach to risk assessment for chemical carcinogens. It was agreed that the evidence for DNA repair following exposure to very low doses of genotoxic carcinogens warranted further review.

3.49 Overall members felt that the arguments presented by Calabrese and Baldwin should be considered further in the future. It was agreed that there might theoretically be a point of departure in the dose-response for a genotoxic carcinogen but it was not possible to identify any potential threshold with methods available. Members considered it prudent to reaffirm that for practical purposes genotoxic carcinogens should be presumed to have no threshold.

Ongoing reviews

Alcohol and Breast Cancer

3.50 The Committee has continued its consideration of the association between drinking alcohol and breast cancer. The research commissioned for the Committee from the Department of Epidemiology and Public Health, Imperial College, London has been finalised. The publication of the COC views on this work awaits publication of the research report in a peer-reviewed journal.

Organochlorine insecticides and risk of breast cancer

3.51 The Committee initiated a review at its September 2003 meeting. There is a large number of new epidemiological and other investigations to consider. The Committee will consider a draft statement at its April 2004 meeting.

Olfactory Neuroblastoma: Possible association in dentists and dental nurses

3.52 The Committee heard a presentation from a researcher on some preliminary data. Further consideration is expected at the April 2004 meeting.

Prostate Cancer

The Committee considered an overview report prepared by the DH Toxicology Unit at Imperial College, London. Further consideration of some aspects is expected at the April 2004 meeting.

Revised COC guidance on risk assessment of carcinogens

3.54 A draft document has been produced for consultation. Further consideration is expected at the June 2004 meeting. http://www.doh.gov.uk/coc/guideline03.pdf

Statements from COC published during 2003

Carcinogenicity of Dibenzo(a,l)pyrene

Environemental Tobacco Smoke (ETS) and lung cancer: Consideration of paper by Enstrom JE and Kabat GC (2003). British Medical Journal volume 326, 1057-1066.

Evaluation of carcinogenic impurities in the pesticide 1-methylcyclopropene,

Risks Associated With Exposures to Low Levels of Carcinogenic Air Pollutants.

Carcinogenicity of dibenzo (a,l) pyrene

Introduction

1. In 1995, at the request of MAFF and the Department of Environment, the COC agreed a hazard-ranking scheme for the carcinogenicity of 25 polyaromatic hydrocarbons (PAHs)[1]. It was based on classification into one of 5 categories. The COC in 1995 had accepted the principle that the carcinogenicity of PAHs was additive. Advice on dibenzo(a,l)pyrene (DB(a,l)P) had not been requested in 1995. Since then, air pollution monitoring in the UK had detected the presence of dibenzo(a,l)pyrene in a number of samples[2]. An assessment of the relative carcinogenic potency of DB(a,l)P compared to benzo(a)pyrene (claimed to be about 100 times) had been published in an Environmental Health Criteria Document (International Programme on Chemical Safety)[3].

2. The COC was asked to consider the mutagenicity and carcinogenicity data on dibenzo(a,l)pyrene and to consider to what category of the COC hazard ranking scheme of PAHs dibenzo(a,l)pyrene could be assigned. Additionally the committee was asked whether the relative carcinogenic potency of DB(a,l)P compared with benzo(a)pyrene could be determined from the available data and in particular whether it was possible to make any statement on the relative potency by the inhalation route of exposure. The Committee considered the available published mutagenicity and carcinogenicity data on DB(a,l)p at its November 2002 meeting.

Introduction to Dibenzo(a,l)pyrene; DB(a,l)P

3. Dibenzo(a,l)pyrene (DB(al)P) CAS Number191-30-0, Chemical Abstracts Name; Dibenzo(def,p)chrysene). There is very little information available on the chemical characteristics of this compound. Its Molecular weight is 302.38 D and its melting point is 162-164°C. Dibenzo(a,l)pyrene occurs in some products of incomplete combustion; it also occurs in fossil fuels[4]. It has been identified in mainstream cigarette smoke and products of coal gasification[4]. There are few data on levels in the environment. Some measurements have been reported for urban and industrialised areas of Holland and from air quality monitoring in Canada[5,6]. It is noted that in some early analyses dibenzo(a,e)fluroanthene has been mistaken for DB(a,l)P [4].

Evaluation of DB(a,l)P

4. The following paragraphs give an overview of the mutagenicity and carcinogenicity data on DB(a,l)P. This is followed by a discussion of the studies where the carcinogenicity of, and DNA adducts formed by DB(a,l)P have been compared to equivalent studies with other PAHs. This statement does not present a review of the large number of investigations which have considered the pathways of metabolic activation of DB(a,l)P, although some references to studies with pro-carcinogenic metabolites are made.

Mutagenicity

DB(a,l)P

5. DB(a,l)P was mutagenic *in-vitro* in *Salmonella typhimurium* TA 100 and TA 98 in the presence of exogenous metabolic activation (using Aroclor 1254 pre-treated rat liver S-9)[7]. Positive results have also been reported in an *in-vitro* cell transformation assay using CH310T1/2 cells, although the significance of these findings for mutagenicity are unclear[8].

6. No *in-vivo* mutagenicity studies were identified in a literature search but DB(a,l)P has been shown to act as an initiator in mouse skin promotion assays[6,10]. It is also noted that an increase in mutations of codon 12 and 61 of Ki-ras was documented in pulmonary adenomas from mice treated with single intraperitoneal doses of 0.3-6 mg/kg bw of DB(al)P[11]. The distribution of mutations at codon 12 (GGT-TGT, GGT-GTT and GGT-CGT) and of codon 61 (CAA-CTA, CAA-CGA and CAA-CAT) was different from those reported by the same investigators in pulmonary adenomas from control animals. (There are no concurrent *in-vitro* mutagenicity spectra data for DB(a,l)P.) Finally DB(a,l)P has also been shown to induce DNA adducts in rat mammary tissue following intramammary instillation using ^{32}P-postlabelling with adduct enrichment via nuclease P1[12].

7. Thus the available mutagenicity data in studies where DB(a,l)P has been used in conventional tests is very limited. (This concurs with the conclusion reached in the IPCS Environmental Health Criteria document 202 on PAHS[3].)

Metabolites of DB(a,l)P

8. The pathways leading to metabolic activation of DB(a,l)P are complex and not reviewed in detail in this statement. It has been suggested that stereospecific metabolism may be important with the fjord region syn-and anti-11,12-dihydrodiol 13,-14-epoxides (DB(a,l)PDE) being of most importance in the activation of BD(a,l)P to DNA reactive metabolites[13].

9. Investigations of pathways leading to activation using 3-methylcholanthrene pre-treated liver microsomes from Sprague-Dawley rats and CD-1 mice in Chinese hamster V79 cells showed a preferential steroeselective oxidation of (-) -11R,12R dihydrodiol of DB(a,l)P at the 13,14 position to form the diol-epoxide[14]. The authors noted that this finding was consistent with the results of mutagenicity studies in V79 cells using the individual steroeisomers.

Summary: Mutagenicity

10. DB(a,l)P and some of its diol-epoxide metabolites are mutagenic *in-vitro*. Other PAHs which have been shown to be metabolised to diol-epoxides have also been shown to be mutagenic *in-vivo*. DB(a,l)P is an initiator in mouse-skin promotion assays, binds DNA in mammary tissue when instilled directly into mammary tissue. There is also limited evidence that DB(a,l)P induces a specific mutational signature in Ki-ras in lung tumours in mice following intraperitoneal administration. Overall the data are consistent with DB(a,l)P being an *in-vivo* mutagen.

Carcinogenicity of DB(a,l)P

Dose levels in the following studies have been cited in the units used by the investigators which have included dosed expressed in terms of number of moles or weight of test material dosed. Thus dosages of DB(a,l)P have been reported in terms of nmoles/kg bw in several of the studies reported. 1 nmole of DB(a,l)P is approximately equal to 0.3 μg DB(a,l)P by weight. Additionally 1μmole of DB(a,l)P is approximately equal to 300 μg DB(a,l)P by weight (or 0.3 μg DB(a,l)P by weight.

Mouse

Dermal administration

11. DB(a,l)P was applied to shaved skin of groups of 22-27 female Swiss mice twice weekly (either 4 or 8 nmol in 100ul of acetone) for 40 weeks. DB(a/l)P was carcinogenic in this study inducing squamous cell carcinomas in 90% of mice at 8 nmol and 70% at 4 nmol[9]. Tumours were also recorded at other sites; these included adenoma of the lung, malignant lymphoma of the spleen and malignant lymphoma with multiple organ involvement. A dose level of 8 nmol was the maximum dose that could be applied without erythema occurring. These data are consistent with DB (a,l)P being a potent carcinogen in the mouse.

12. A single dose of 100 nmol DB(a,l)P was applied to the shaved skin of a group of 24, eight week old SENCAR mice. Mice were killed after 27 weeks. It was reported that 7 mice treated with DB(a,l)P each developed a skin tumour (4 papillomas and 3 squamous cell carcinomas)[10].

Intraperitoneal administration

13. Groups of 70 male A/J male mice (5-6 weeks old) were given a single intraperitoneal administration of DB(a,l)P in tricaprylin at 0.3, 1.5, 3.0, or 6.0 mg/kg bw. Approximately half of the animals were used at various time points up to 28 days for DNA adduct studies. Remaining animals (30-35/group) were subject to necropsy at 8 months post dose and the number of surface lung adenomas counted using a dissecting microscope. A dose level of 0.3 mg/kg bw resulted in 43% Tumour Bearing Animals (TBA), whereas 1.5 μg/kg bw resulted in 97% TBA and doses of 3 μg/kg be and above 100% TBA. The mean number of adenomas per mouse at 6 mg/kg was 16.1 ± 7.26[11]. Maximal levels of DNA adducts occurred between 5-10 days after injection followed by a gradual decrease. The Time Integrated DNA Adduct Levels (TIDAL) were linearly related to dose.

Rat

Intramammary instillation

14. Groups of 20 Sprague-Dawley rats (8 weeks old) were given intramammary doses of 0.25 or 1μmol/gland in 50μl of trioctanoin. Administration was to the nipple region of glands 2, 3, 4, 5 on the right and left sides. The development of tumours was monitored for the following 24 weeks. Animals with tumours >2cm were killed. Full necropsies were undertaken in all animals and mammary glands and any other abnormal tissues examined microscopically. All animals given DB(a,l)P developed mammary tumours (predominantly mammary epithelial adenocarcinmas with a smaller number of mesenchymal fibrosarcomas and squamous cell carcinomas of the skin). The number of tumours/TBA animal was 10.8/animal at 1μmol and 6.6/animal at 0.25 μmol[10]. (Lung tumours were not specifically assessed in this study).

Initiation-Promotion models

15. Groups of 24 female SENCAR mice (eight weeks of age) received a single dermal dose to shaved dorsal skin of 33.3, 100 or 300 nmols DB(a,l)P in 100µl acetone. One week later promotion treatments using 12-O-tetradecanoylphorbol-13-acetate (TPA, 3.24 nmol/100µl acetone, twice weekly) were begun. All mice treated with DB(a,l)P developed erythemas after the first application of TPA. Severity was proportional to DB(a,l)P dose. Promotion treatments were therefore stopped until the fourth week of the study. Promotion treatment was re-started and continued for 11 weeks. Animals killed after 16 experimental weeks[10].

16. In a second experiment, the same investigators undertook a further initiation-promotion study using dose levels of 4, 20, 100 nmols DB(a,l)P. In concurrent studies, initiation-promotion investigations were undertaken using DB(a,l)P 11,12 dihydrodiol and DB(a,l)P 8,9-dihydrodiol. Erythema was noted in the 100 nmol DB(a,l)P group after 10 days. Promotion was delayed till the third experimental week. Promotion treatments (as above) were undertaken for a further 24 weeks[10].

17. In the first experiment it was noted that tumours were already present in some animals at 100 and 300 nmol DB(a,l)P before promotion treatment was resumed in the 4th experimental week. An increase in the percent TBAs was reported compared to acetone control (No tumours seen in controls) of 96%, 92% and 100% at 33.3, 100 and 300 nmol respectively. The number of tumours/animal was increased in a dose-related fashion, 3.29, 5.29, 6.26 respectively. An increase in percent tumour bearing animals and numbers of tumours/animal was recorded in the second experiment at all dose levels of DB(a,l)P but the dose-response was noted to show an inversion. The authors considered this was most likely due to a more severe toxicity of DB(a,l)P in the second experiment. However it is noted that 92% of surviving animals at 4 nmol had tumours (6.96/animal). It was also documented that substantial carcinogenic response was recorded in initiation-promotion studies with DB(a,l)P11,12- dihydrodiol but not with DB(a,l)P 8,9-dihydrodiol using the same treatment regime as with DB(a,l)P[10].

18. In a subsequent study, the same research group investigated initiation-promotion of DB(a,l)P and DB(a,l) 11,12-dihydrodiol in female SENCAR mice using dermal application of 0.25 or 1nmol in 100µl acetone. Promotion, twice weekly for 27 weeks, was undertaken using a lower dose of TPA (2.16 nmol in 100µl acetone) in order to reduce sensitivity to erythema induced by these chemicals. DB(a,l)P induced 2.6 tumours/mouse and 0.79 tumours/mouse at 1 nmol and 0.25 nmol respectively. DB(a,l)P 11,12-dihydrodiol induced 0.17 tumours/mouse at 1 nmol but was reported to be virtually inactive at the lower dose level. Tumours were seen following treatment with 1 nmol DB(a,l)P in mice after 5 weeks of TPA promotion[9].

19. Initiation-promotion assays in mice using dermal application of enantiomerically pure 11,12-dihydrodiols of DB(a,l)P revealed that (-) -11R,12R trans-dihydrodiol of DB(a,l)P induced skin tumours in 93% of animals (4-5/animal) after a single induction dose of 10 nmole whereas the (+) -11S,12S trans-dihydrodiol of DB(a,l)P induced no tumours at 10 nmole and only 13% of animals had tumours following application of 20 nmoles[15]. The results of this study were consistent with the *in-vitro* mutagenicity studies in V-79 cells using these enantiomers[13].

Summary: Carcinogenicity

20. DB(a,l)P is carcinogenic in mice following dermal or intraperitoneal application. DB(a,l)P is also carcinogenic in rats following intramammary instillation. It acts as an initiator in mouse skin promotion assays. The 11,12-dihydrodiol also acted as an initiator in mouse skin promotion assays. These data are consistent with DB(a,l)P being a genotoxic carcinogen in experimental animals.

COC discussion: DB (a,l)P ranking under 1995 COC scheme

21. The COC agreed that the *in-vitro* mutagenicity tests and information on *in-vivo* DNA adduct formation was consistent with dibenzo(a,l)pyrene being an *in-vivo* mutagen. Members also agreed that dibenzo(a,l)pyrene was carcinogenic in mice and rats. Dermal application to mice produced tumours at a number of sites (including the skin, lung, and malignant lymphoma of the spleen and malignant lymphoma with multiple organ involvement) and intraperitoneal administration to rats produced lung tumours. Intramammary instillation in rats resulted in mammary tumours. Dibenzo(a,l)pyrene also acted as an initiator in mouse skin carcinogenicity promotion assays. The COC therefore considered that dibenzo(a,l)pyrene should be assigned to group A of its hazard ranking scheme for PAHs. This category includes chemicals for which 'there is a high level of concern about a carcinogenic hazard for humans because the compound is an *in-vivo* mutagen and/or a multi-site carcinogen in more than one species.'

COC Discussion: Relative potency of DB(a,l)P compared to Benzo(a)pyrene

22. Regarding potency, the committee agreed that dibenzo(a,l)pyrene was a very potent genotoxic carcinogen and that potency varied depending on factors such as species, route of administration, dose and site of tumour produced. From the available data where a comparison could be made, members considered that the dibenzo(a,l)pyrene carcinogenic potency was likely to be in the range of 10-100 times more potent than benzo(a)pyrene depending on the tests system used. The measurement of DNA adducts (TIDAL) following intraperitoneal dosing of DB(a,l)P showed that in comparison to other PAHs, DB(a,l)P bound much more extensively to DNA, due presumably to the higher reactivity of its diol-epoxide metabolite(s). This might explain its greater carcinogenic potential.

23. The Committee agreed that there were insufficient data available on dibenzo(a,l)pyrene to draw any conclusions on the relative potency compared to benzo(a)pyrene by the inhalation route of exposure. The committee agreed to reconsider the topic of the relative carcinogenic potency of PAHs by the inhalation route of exposure at a future meeting.

COC Conclusion

24. The Committee agreed the following overall conclusion regarding the carcinogenicity of DB(a,l)P:

    "Dibenzo(a,l)pyrene should be considered as a highly potent genotoxic carcinogen in experimental animals. There is a need for further consideration of the potential importance of exposure to dibenzo(a,l)pyrene and other highly potent carcinogenic polycylic aromatic hydrocarbons in air pollution."

COC/03/S5 – November 2003

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Statement on Environment Tobacco Smoke (ETS) and lung cancer: consideration of paper by Engstrom JE and Kabat GC (2003). British Medical Journal volume 326, 1057-1066.

Introduction

1. The COC undertook a detailed review of the evidence regarding the association between exposure to environmental tobacco smoke (ETS) and lung cancer during 1997. The review was requested by the Scientific Committee on Tobacco and Health (SCOTH). The full transcript of the COC statement can be found in the 1997 Annual Report[1] on the COC internet site (http://www.doh.gov.uk/coc/1997ar.pdf). The COC was asked to consider a new report of a cohort study2 at its June 26 2003 meeting.

Consideration of publication by Enstrom and Kabat British Medical Journal 17 May 2003, volume 326, 1057-1066[2,3].

2. The Committee considered the information presented in the paper, the editorial regarding this paper, commentaries published by the American Cancer Society, and the British Medical Association, and a number of papers published since the COC review in 1997.

3. The Committee agreed there was evidence that exposure to ETS of individuals in the Cancer Prevention-1 cohort could not be adequately assessed and thus no definite conclusions could be drawn with regard to the study by Enstrom and Kabat.

Additional evidence on ETS and lung cancer considered by the COC at 26 June 2003 meeting[4-9].

4. The Committee noted the results of an additional systematic review[4] published since the COC review in 1997 which were consistent with previous evaluations and suggested an increased risk in never smoking women exposed to ETS from spouses compared to never smoking women unexposed to ETS of 1.29 (95% CI 1.17-1.43).

5. The Committee noted additional evidence of exposure to carcinogenic tobacco-specific nitrosamines derived from ETS[5].

COC conclusion

6. i) The available additional data submitted to the 26 June 2003 COC meeting do not suggest that a full review of the literature since 1997 on this topic is required.

ii) The evidence from a recent systematic review (meta-analysis)[4], and information regarding excretion of tobacco-specific nitrosamines in urine in individuals exposed to ETS[5] support the conclusion reached in 1997.

iii) The evidence from a recent cohort study[2] should be reviewed with caution in view of inadequacies in assessment of exposure to ETS in this investigation.

iv) The COC concluded there was no reason to change the conclusion reached in 1997, namely:

"Taking all the supporting data into consideration we conclude that passive smoking in non-smokers exposed over a substantial part of their life is associated with a 10-30% increase in the risk of lung cancer which could account for several hundred lung cancer deaths per annum in the UK."

COC/03/S2 – July 2003

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Carcinogenic impurities in the pesticide 1-methylcyclopropene (1-MCP)

Introduction

1. 1-methylcyclopropene (1-MCP) is a new pesticide active ingredient (growth regulator) being assessed by the Pesticides Safety Directorate (PSD) under EU Directive 91/414/EEC. 1-MCP blocks the effects of ethylene release in apples thus preventing over ripening and softening. The Committee was asked for advice on the risks posed by the potential for exposure to two impurities present in the active ingredient namely impurities 1 and 2 which were presumed by the Advisory Committee on Pesticides to be genotoxic carcinogens on the basis of published mutagenicity studies and life-time bioassays in rats and mice using oral administration[1,2]. The COC was asked to advice on specific questions given in a referral note from DEFRA which are reproduced below. The COC was not asked to evaluate the active ingredient and data on this compound have not been reviewed. The COC has not been asked to evaluate the other two impurities present in 1-MCP.

2. The COC was provided with published information on the mutagenicity, carcinogenicity and metabolism of impurity 1 and impurity 2 and with details of the manufacture of 1-MCP, information on the formulation and product to be used in the U.K and estimates of potential exposures to impurities present in 1-MCP during use. The data holder is Rohm and Haas company. The data holder provided an estimation of the 5% Bench Mark Dose for the most sensitive carcinogenic response for these two impurities which was for forestomach tumours[3].

3. The Committee considered the questions posed by DEFRA at its 26 June 2003 meeting.

Referral to COC by DEFRA

4. The view of the Committee on Carcinogenicity is sought on whether:

   a. minimum risk levels for the impurities 1 and 2 can be derived

   b. exposures to the impurities 1 and 2 present any significant risks to consumers or operators

   c. maximum levels of the impurities 1 and 2 should be proscribed.

COC discussion

5. The Committee concurred that on the basis of the available evidence submitted it would be prudent to consider impurity 1 and impurity 2 as genotoxic carcinogens[1-7].

6. The Committee considered the available carcinogenicity data and the conditions of use anticipated for 1-MCP as a fumigant for apples, together with potential exposures to impurity 1 and impurity 2 that might arise, and agreed that a pragmatic minimum risk level could be established for these two

impurities. The Committee agreed that it should always be recognised that for impurity 1 and impurity 2 under likely conditions of use that a very small but unquantifiable risk existed and hence the policy of controlling exposures to "as low as reasonably possible" (ALARP) should apply. The 5%BMD for impurity 1 was reported to be 0.6 mg/kg bw/day and for impurity 2 was reported to be 12.8 mg/kg bw/day.

7. The Committee agreed an application of an Uncertainty Factor (UF) of 10,000 to the estimated 5% BMD resulted in estimated minimum risk levels of 0.06 mg/kg bw/day for impurity 1 and 1.28 mg/kg bw/day for impurity 2. The Committee noted that the US EPA and Health Canada had previously stated that a factor of 10,000 represents the highest that could be used in the setting of TDIs. In an analysis of the use of LTD10 (extra life-time cancer risk of 10%) derived from calculations based on TD50s from the Gold database, it was concluded that the reference dose derived from the Gold database and use of a 10,000 UF applied to the LTD10 gave equivalent results to cancer risk at 10-5 derived from LMS modelling and hence represented a fairly conservative approach to setting a minimum risk level[8]. The Committee agreed that this was a conservative approach to estimating minimum risk levels. They had a reasonable degree of confidence that any carcinogenic risk posed at this level would be negligible.

8. The maximum predicted exposures for operators and consumers was reported to be below the proposed minimum risk level by factors varying from 3 to 5311 (as shown below). The risk of carcinogenicity posed by exposure to impurity 1 and impurity 2 following use to fumigate apples is considered to be negligible.

Impurity	Operators	Consumers
1	3	249
2	58	5311

COC response to questions posed by DEFRA

Whether a minimum risk levels for the impurities 1 and 2 can be derived

9. The COC concluded that pragmatic minimum risk levels could be established for impurity 1 and impurity 2. For impurity 1 this was equivalent to a daily oral does of 0.06 mg/kg bw/day. For impurity 2 this was equivalent to 1.28 mg/kg bw/day.

Whether exposures to the impurities 1 and 2 present any significant risks to consumers or operators

10. The maximum predicted exposures for operators and consumers will be below the proposed minimum by factors varying from approximately 3 to 5311. The risk of carcinogenicity posed by exposure to impurity 1 and impurity 2 is considered to be negligible.

Whether maximum levels of the impurities 1 and 2 should be proscribed

11. The COC agreed that maximum levels for these impurities should not result in doses exceeding the minimum risk level and restated that there was always a need to apply "as low as reasonably practical" (ALARP) to genotoxic carcinogens.

COC/03/S3 – September 2003

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Risks associated with exposures to low levels of carcinogenic air pollutants

Introduction

1. The COC has adopted a prudent approach to the assessment of chemical carcinogens which assumes that genotoxic carcinogens have the potential to damage DNA at any level of exposure and that such damage may lead to tumour development. Thus for genotoxic carcinogens it is assumed that there is no discernible threshold and that any level of exposure carries a risk. The general advice of the COM when considering the risk assessment of chemicals which are mutagenic *in-vivo* has been that it is prudent to assume a linear, non threshold dose response. Thus it is assumed that any exposure to an *in-vivo* mutagen is associated with some damage to DNA and consequently an increased risk of mutation leading to an increased risk of adverse health effects albeit that this may be small. In such instances the Committee has recommended that exposures be reduced to a low as is reasonably practicable[1,2]. The Expert Panel on Air Quality Standards (EPAQS) provides advice to U.K. Government Departments and Agencies on air quality issues, in particular the levels of pollution at which no or minimal health effects are likely to occur. (http://www.defra.gov.uk/environment/airquality/aqs/index.htm). EPAQS has adopted a pragmatic approach to developing air quality standards for air pollutants which are genotoxic carcinogens[3]. This does not involve the use of mathematical models to estimate cancer risks because of the concerns of COC regarding such approaches[2,3].

2. The Department of Health asked the COC for advice at its November 2002 meeting on whether it was feasible to identify a specific approach to modelling dose-response to carcinogenic air pollutants. The suggested approach would be restricted to modelling of data derived from acceptable epidemiology studies in exposed human populations (predominantly occupationally exposed cohorts). The derived dose-response curves could be then be used following the application of the most conservative model (considered to be the one-hit model)[4] to estimate the maximum upper bound risk of cancer at environmental exposure levels. There was no intention to use data derived from long-term carcinogenicity bioassays in rodents for quantitative estimation of risks to humans. Agreement to the proposed approach would be of value to the Department in formulating advice on prioritising measures for reducing levels of air pollutants.

COC consideration of dose-response modelling for carcinogenic air pollutants

3. The Committee restated its views, published in its guidelines in 1991, that use of mathematical models to evaluate the dose-response for carcinogens, namely that extrapolation of the dose-response curve below the lowest experimental data points, taken from animal bioassay data, gave an impression of precision which cannot be justified from the approximations and assumptions used[2].

4. The Committee considered that it might be acceptable to consider an approach based solely on use of epidemiological data from investigations considered to have been adequately undertaken. The COC cautioned that quantitative risk estimates based on extrapolation to dose levels of one or more orders of magnitude below the observed dose-response in epidemiology studies would involve uncertainties in that the shape of the dose-response curve could not be predicted with any degree of accuracy.

5. However the Committee noted that the one-hit model[4,5] assumed that a single mutation arising from the interaction of one molecule of carcinogen with DNA lead to the development of cancer. This was likely to represent the most conservative approach to risk assessment. Thus the COC agreed that the upper bound (95% Confidence Interval) cancer risk estimate from this approach was likely to overestimate the actual risk associated with exposure to the carcinogen. The Committee agreed to this approach to carcinogenic air pollutants provided the risk estimates were used in the consideration of risk management options rather than being considered as definite values relating to cancer risk levels. The Committee considered it important to restate that any exposure to a genotoxic carcinogen carried a small, but unquantifiable, risk of cancer.

Conclusion

6. The COC agreed to a proposal from the Department of Health, that the upper bound (95% Confidence Interval) cancer risk estimate at environmental exposure levels to air pollutants, which are genotoxic carcinogens, based on data from adequately performed cancer epidemiology studies, using the one-hit model for dose-response extrapolation, could be used as an aid in deriving risk management strategies. The COC agreed it important to restate that exposure to any level of a genotoxic carcinogen carried a small, but unquantifiable, risk of cancer.

COC/03/S4 – September 2003

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2003 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 P G Blain CBE (Chairman)	NONE	NONE	Unilever plc	Research Studentship
Prof A Boobis OBE	Abbey Life	Shareholder		
	Abbey National	Shareholder		
	Barclays Bank	Shareholder		
	BG Group	Shareholder		
	BT Group	Shareholder		
	Centrica	Shareholder		
	HBOS	Shareholder	Servier	Research support
	Marks and Spencers	Shareholder		
	National Grid Transco	Shareholder		
	Scottish Power	Shareholder		
	OSI Pharmaceuticals	Consultancy		
Dr P Carthew	Provalis	Share Holder	NONE	NONE
	Unilever	Salary		
Prof P B Farmer	Abbey National	Share Holder	NONE	NONE
	Bradford & Bingley	Share Holder		
	Celltech	Share Holder		
	Friends Provident	Share Holder		
	Torotrak	Share Holder		
Prof D Forman	Barclays	Share Holder	NONE	NONE
	Friends Provident	Share Holder		
	HBOS	Share Holder		
	Woolwich	Share Holder		
Prof D Harrison	Barclays	Share Holder	NONE	NONE
	Friends Provident	Share Holder		
	HBOS	Share Holder		
	Woolwich	Share Holder		
Ms D Howel	NONE	NONE	NONE	NONE

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Dr S J Kennedy	Unilever	Share Holder	NONE	NONE
MS M Langley	Business Consolidating Services	Share Holder	NONE	NONE
	Ciebel	Director		
	CREE Research	Share Holder		
	Cyber Care	Share Holder		
	Eshelon	Share Holder		
	HBOS	Share Holder		
	MMO2	Employee		
	Quelcom	Share Holder		
	Wibex	Share Holder		
Prof D Phillips	Abbey National	Share Holder	NONE	NONE
	BG Group	Share Holder		
	Bradford & Bingley	Share Holder		
	Centrica	Share Holder		
	CGNU	Share Holder		
	Lattice Group	Share Holder		
	National Grid	Share Holder		
	Servier	Consultant		
D R Roberts	AstraZeneca	Share Holder	NONE	NONE
	Aventis	Slary		
	P & O	Share Holder		
Prof D Shuker	NONE	NONE	NONE	NONE
Dr N Wallis	AstraZeneca	Share Holder	NONE	NONE
	Syngenta	Slary		
		Share Holder		