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 & Food Standards Agency and the other Government Departments including the Regulatory Authorities. A new Committee has been recently appointed via open advertisement procedures established by the Commissioner for Public Appointments. The new appointments were made on 1 April 2000 to run for 3 years. I would like to welcome the new members (Professor D Harrison, Ms D Howel, Professor D Phillips, Dr R Roberts and Professor D Shuker) to the Committee. The details of the Membership are published on the Internet and the Agenda, Minutes and Statements are published on a regular basis.

During the year 2000 the COC has published 3 statements; alcohol and breast cancer, carcinogenicity of 3-MCPD, cancer incidence near municipal solid waste incinerators in Great Britain. The advice on alcohol and breast cancer was an update of data published between 1995 – 1999. The Committee made a recommendation for further research, namely a systematic review of epidemiology, which is being funded by the Department of Health. The Committee also provided advice on research to be sponsored by the Department of Health on the early identification of non-genotoxic carcinogens. A preliminary assessment of a pre-publication paper on the trends in the incidence of intrahepatic cholangiocarcinoma was undertaken. The Committee looks forward to assessing the final published version of this particular research. The Committee also provided advice on test strategies including the problems associated with poor survival in certain strains of rat.

During 2000, the Food Standards Agency was established and the COC now has a joint Secretariat with DH/FSA. The DH Toxicology Unit at the Imperial College of Science, Technology and Medicine now prepare some of the papers for the COC.

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3-Monochloropropane-1,2-diol (3-MCPD)

3.1 3-Monochloropropane-1,2-diol (3-MCPD) can be present as a contaminant in epichlorhydrin/amine copolymers used as flocculants or coagulant aids in water treatment. These polyamine flocculants have been available for many years as approved products for use in water treatment and thus 3-MCPD may be present as a contaminant in drinking water arising from this use. 3-MCPD is a member of a group of contaminants known as chloropropanols. The Committee was aware that 3-MCPD had been detected as a contaminant of several foods and food ingredients, including acid hydrolysed vegetable protein (acid-HVP) The COC was asked to evaluate and advise on the carcinogenicity of 3-MCPD by the Committee on Chemicals and Materials of Construction for use in Public Water Supply and Swimming Pools (CCM), a statutory committee which provides advice to the Secretary of State for the Environment, Transport and the Regions on the approval of chemical substances in contact with public water supplies.

3.2 The COC had reviewed the available carcinogenicity data on 3-MCPD in 1999 and had concluded that it "was not possible to draw a definite conclusion regarding the significance of the observed carcinogenic effects of 3-MCPD in the rat." However, the COM conclusions were noted. These were that 3-MCPD was an *in vitro* mutagen and that further *in vivo* data was needed to provide reassurances that this activity could not be expressed *in vivo*. The COC concluded that it would be prudent to assume that the compound was an *in vivo* mutagen. In view of these COM conclusions the COC agreed that it would be prudent to reduce exposures to as low as technologically practicable.

3.3 Another review of the carcinogenicity data was undertaken by the COC at its November 2000 meeting following further advice from the COM which had reviewed new *in-vivo* mutagenicity studies conducted using 3-MCPD. These provided evidence that reactive (mutagenic) metabolites of 3-MCPD are not produced *in vivo* in the tissues examined in these studies. In the light of the new data the COM was able to conclude that 3-MCPD is an *in-vitro* mutagen but has no significant genotoxic potential *in-vivo*. The COC was asked to consider the implications of these revised conclusions on the mutagenicity data for carcinogen risk assessment.

3.4 The Committee considered the proposal that all of the increases in tumours noted in rats were mediated by non-genotoxic mechanisms involving either cytotoxicity (in respect of the findings in the kidney) or hormonal disturbances. The possible influence of the stereoisomerism of 3-MCPD was also discussed. Members agreed that it was now probable that 3-MCPD induced tumours by non-genotoxic mechanisms.

3.5 The Statement on 3-MCPD can be found at the end of this report.

Accelerator Mass Spectrometry - An aid to carcinogen risk assessment

3.6 Accelerator Mass Spectrometry (AMS) is the most sensitive technique available for measuring the formation of adducts with DNA. AMS technology allows the accurate measurement of very low levels of radiolabelled chemicals (particularly ^{14}C) in biological samples at around 10^{-21} to 10^{-18} mole. The Committee was asked to consider the value of AMS for the assessment of chemically induced carcinogenicity.

3.7 The Committee noted that high levels of sensitivity and reproducibility in the analysis of biological samples were reported with AMS. The sensitivity of the technique was related to the background level of radioactivity in the sample and, if individual adducts are being investigated, the quality and effectiveness of the HPLC separation used in the sample preparations.

3.8 The Committee concluded that AMS is a highly sensitive and reproducible technique. Its main uses in the area of chemical carcinogenicity are in hazard characterisation, measurement of tissue levels of administered radiolabelled compounds and mechanistic investigations. However, the biological significance of the very low levels of binding that may be observed is difficult to assess. Furthermore, the very high cost of the technology currently limits the use of AMS.

The association between alcohol and breast cancer

3.9 Breast cancer is the most common cancer in women. In England, approximately 30,000 cases are registered each year and there are roughly 11,000 deaths from breast cancer. It is clearly important to identify preventative measures to reduce the incidence of breast cancer.

3.10 The COC last reviewed the extensive literature on the association between alcohol and breast cancer in 1995, at the request of the Interdepartmental Working Group on Sensible Drinking (IDWG), as part of the review of medical and scientific evidence on alcohol and health and interpretation of the long term effects of drinking alcoholic beverages. The Committee advised the IDWG that drinking alcoholic beverages causes a dose-related increase in the risk of squamous carcinomas of the upper aerodigestive tract as a whole, and of cancers of the oral cavity, pharynx, larynx, and oesophagus which is independent of the effect of smoking tobacco.

3.11 With respect to breast cancer, the Committee concluded "... while there is no decisive evidence that breast cancer is causally related to drinking alcoholic beverages, the potential significance, for public health, of even a weak association between alcohol and breast cancer is such that we recommend, in particular, that this matter be kept under review." The IDWG endorsed the COC's conclusions and the recommendation that the relationship between alcohol and breast cancer should be kept under review.

3.12 The Committee undertook a detailed review of the literature published since 1995 at three meetings in 1999 and finalised a statement at its March 2000 meeting. It was evident that a large number of epidemiology studies had been published since the first review. The Committee's finalised statement is appended to this report. The detailed secretariat papers considered during the review have been published on the COC Website (www.doh.gov.uk/coc.htm)

3.13 Following publication of the COC statement, the Department of Health is funding a systematic review of the epidemiological literature at Imperial College of Science, Technology and Medicine. The study is due to be completed by the end of 2001. The Committee discussed further the potential mechanism by which alcohol might induce breast cancer at its November 2000 meeting where members considered a draft scoping study by Dr Tim Keys (ICRF, Oxford) on the investigation of the effects of alcohol on oestrogen metabolism. The Committee will consider this aspect in more detail when the report of the systematic review becomes available.

3.14 The Statement on Alcohol and Breast Cancer can be found at the end of this report.

Cancer incidence near municipal solid waste incinerators on Great Britain

3.15 According to the Department of the Environment, Transport and the Regions (DETR), currently around 26 million tonnes of municipal waste is produced in the UK each year; around 10% of this is disposed via incineration. In the UK all municipal waste incinerators (MWIs) are regulated by the Environment Agency or local authorities. Since 1 December 1996, all MWIs have been required to meet the standards in the Municipal Waste Incineration Directives 89/369/EEC and 89/429/EEC and this resulted in the closure of the majority of the existing incinerators and the upgrading of the remainder. A dioxin emission limit of 1 nanogram per cubic metre ($ng.m^{-3}$) was imposed at the same time although, in practice, most existing plants already achieve dioxin emissions close to 0.1 $ng.m^{-3}$. The Committee was informed that there is expected to be a significant increase in UK incinerator capacity over the next

10-20 years to meet the requirements of the EC Landfill Directive which sets limits for the percentage of biodegradable waste which may be landfilled.

3.16 There have been very few epidemiological studies published which investigated cancer incidence or mortality amongst individuals living in proximity to incinerators in Great Britain. The COC was asked during 1993-4 to comment on a study undertaken by the Small Area Health Statistics Unit (SAHSU) which investigated the cancer incidence of over 14 million people living near to 72 MWIs. SAHSU is a research unit based at the Department of Epidemiology and Public Health, Imperial College School of Science, Technology and Medicine. The study was subsequently published [Elliott P, *et al* (1996) Cancer incidence near municipal solid waste incinerators in Great Britain. *British Journal of Cancer*, **73**, 702-710]. The study reported an increased incidence of liver cancer in people living near to MWIs. However, it was difficult to interpret this finding because it is known that there is often misdiagnosis of liver cancer, with secondary tumours originating in other organs being wrongly recorded as primary liver cancer. The COC recommended that there should be a histological review of the liver cancer cases identified in the first study, to determine whether there really was an increase in primary liver cancer in people living near MWIs. The report of this review was considered at the June 1999 meeting and a statement subsequently agreed in March 2000 to coincide with publication of the follow-up investigation [Elliott P *et al* (2000) Cancer Incidence near Municipal Solid Waste Incinerators in Great Britain 2 : Histopathological and Case Note Review of primary liver cancer cases. *British Journal of Cancer*, **82(5)**,1103-1106].

3.17 The Committee concluded that any potential risk of cancer due to living near to MWIs (for periods in excess of 10 years) was exceedingly low and probably not measurable by the most modern epidemiological techniques. The Committee agreed that, at the present time, there was no need for any further epidemiological investigations of cancer incidence near MWIs.

3.18 A copy of the full statement is given at the end of this section.

Code of Practice for Scientific Advisory Committees

3.19 In July 2000, the Office of Science and Technology published a consultation paper, inviting comments on a proposed code of practice for Scientific Advisory Committees. The paper outlined proposed guidelines for Scientific Advisory Committees and complemented a second document on "Review Of Risk Procedures Used By The Government's Advisory Committees Dealing with Food Safety", which was published in September 2000. The consultation's paper described the duties, rights and responsibilities of Committee Members and their independence from the Committee's secretariat, stressing the need for inclusivity, transparency and proportionality and raising the issue of the manner in which confidential information is handled. It stressed the need for clear explanation of levels and types of uncertainty, and how this information is incorporated into advice, and called for training of Committee Members in communication skills.

3.20 Members felt that the current arrangements for openness (publication of agenda, minutes, statements) were adequate. The Committee discussed the holding of open meetings. Some members felt that there would be no impact on Committee work whereas others felt that the role of specialist advisory Committees was to produce advice which could be subject to public scrutiny. It was agreed that any further proposals for greater openness needed careful planning in consultation with members and would place additional resource requirements on the secretariat.

Early identification of non-genotoxic carcinogens

3.21 The development of rapid methods for the identification of chemicals that induce cancer by non-genotoxic mechanisms would be beneficial for public health, because it would enable more compounds to be tested. It would also reduce the need for long term studies which use large numbers of animals. For these reasons the COC identified this as an important research area when considering research priorities in 1996. The COC reviewed a paper on this topic, prepared by the DH Toxicology Unit, at the November 1999 meeting. Members agreed that the most important non-genotoxic mechanisms could be placed into one of four groups, (i) persistent cytotoxicity accompanied by proliferative regeneration, (ii) chronic inflammation accompanied by the production of reactive oxygen species, (iii) hormomimetic activity and (iv) ligand binding with xenobiotic induction receptors. Members considered that increased cellular proliferation (mechanism (i)) was of particular significance.

Members also noted that no one test would be suitable for the detection of all non-genotoxic carcinogens.

3.22 The COC recommended that further research to develop such tests was desirable and a project was commissioned from Professor Kevin Chipman. Professor Chipman made a presentation to the COC on the outline of the proposed research project. The studies were to involve daily administration of selected chemicals to rats over a period of 28 days, using three dose levels selected from the available information from carcinogenicity bioassays. Molecular markers indicative of disturbance of cell cycle control, intercellular communication and inhibition of apoptosis would be studied at two time points (after 3 days and 28 days of dosing). The evaluation of mediators would involve the use of immuno-histochemical methods including analysis of phosphorylated gene products.

3.23 The Committee was asked to advise on priority chemicals for inclusion in the research project. Members agreed that priority should be given to carcinogens that pose the greatest hazard to humans and were also carcinogenic to the rat. For pragmatic reasons the work would only consider the oral route of exposure. Members stressed the need for appropriate negative controls. It was noted that inclusion of a further positive control (such as phenobarbitone or a peroxisome proliferator) and d-limonene as a negative control in the female rat would be valuable. Members agreed that TCDD, oestrodiol, hexachlorobenzene and tetrachloroethylene should be considered as high priority. It was suggested that chloroform, nitrobenzene, alachlor, methapyriline, pyrilamine (a non-carcinogenic structural analogue of methapyriline), dichlorobenzene and paracetamol could be considered to be of interest.

Evidence for an increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968-1996.

3.24 An increase in the age-standardised mortality rate (ASMR) for all causes of liver cancer has been documented in England and Wales over the period 1979-1994. A preliminary investigation suggested that the increase in mortality from liver cancer may in part be due to an increase in the incidence of intrahepatic cholangiocarcinoma. Intrahepatic cholangiocarcinoma is a relatively rare tumour in the UK, and the prognosis for patients with this tumour is poor. The COC was asked to review the evidence for an increase in the incidence of this tumour.

3.25 The Committee was provided with a prepublication copy of a draft report which presented a detailed analysis of mortality data provided by the Office of National Statistics (ONS). At the November 1999 meeting of the Committee members heard a presentation from Professor Howard Thomas and colleagues at the Department of Medicine, Imperial College of Science, Technology and Medicine.

3.26 The total number of deaths attributed to particular tumours [using the International Classification of Disease (ICD) 8th and 9th revisions] were analysed by year and sex. Professor Thomas noted that in 1978 there was a total of 95 deaths reported from intrahepatic cholangiocarcinoma in England and Wales, whereas there were 736 cancer deaths reported in 1996. Preliminary data from 1998 indicated a total of 835 deaths from intrahepatic cholangiocarcinoma. The increase in the ASMR over the period 1968 to 1996 was from 0.1/100,000 to 1.22/100,000 in males and from 0.05/100,000 to 0.92/100,000 in females. The age-specific mortality rates (ASpMR) in both males and females aged 45+ for intrahepatic cholangiocarcinoma increased by approximately 15 fold over the study period.

3.27 It is possible that the recorded increase in intrahepatic cholangiocarcinoma was an artefact due to confounding factors. The Committee noted that a number of potential confounding factors had been considered by the authors, Professor Thomas and colleagues, such as changes in criteria for International Classification of Disease codes (ICD revisions 8 and 9), the introduction of endoscopic retrograde cholangiopancreatography in the mid to late 1970s as a new diagnostic technique for facilitating precision in the location of site for several cancers of the hepatobiliary system and the consequent possibility that tumours which had previously been classified as tumours of the pancreas, gallbladder and extrahepatic biliary tree were now being classified as cholangiocarcinoma. The Committee agreed that changes in diagnostic standards over time could account for the reported increase in age-standardised mortality rate for intrahepatic cholangiocarcinoma over the period 1968 to 1996. It was therefore important to undertake additional investigations before a definite conclusion could be reached about the apparent increase in the incidence of intrahepatic cholangiocarcinoma.

3.28 The Committee agreed that it was important to keep this topic under review, and to assess further the work of Professor Thomas and colleagues when published.

Longevity of carcinogenicity studies: consideration of a database prepared by Pesticides Safety Directorate (PSD)

3.29 The proper conduct of carcinogenicity studies in rats is an important part of the evaluation and prediction of potential human carcinogens. For a rat carcinogenicity bioassay to be considered acceptable, survival at 24 months should be 50% or greater in all groups (see OECD, EPA and EC guidelines). Significant reductions in the number of control rats surviving to the scheduled end of the study linked to obesity have been widely reported in the scientific literature. This is a matter of concern since inadequate carcinogenicity studies could result in failure to identify potential human carcinogens. In addition, inadequate studies could be rejected by regulatory agencies with the consequent need to repeat the study using more animals to obtain a valid result.

3.30 PSD reviewed survival in control animals from 26 rat carcinogenicity studies which had been submitted over the period 1993-1998. These carcinogenicity tests had been undertaken between 1983 and 1995. Of these studies, 18 had used Sprague-Dawley rats (from various sources), six used Wistar rats and two used Fischer 344 rats. Adequate survival was reported for 3/18 studies in Sprague-Dawley rats, all of the studies in Wistar rats, and one study undertaken in Fischer 344 rats. Most inadequate studies had been undertaken using Charles River Sprague-Dawley rats. There was no evidence to support a previous suggestion that virus antibody status had an effect on survival. Improved survival has been shown to occur in Sprague-Dawley rats which have been fed diets containing fewer calories or smaller portions. The US Food and Drugs Administration has been considering ways to improve survival by reducing the amount of food available to individual animals.

3.31 The Committee reached the following conclusions:

i) Information from the database of rat carcinogenicity studies reviewed by PSD supports the view that unacceptable survival at termination (<50%) in carcinogenicity tests is predominantly confined to Charles River Sprague-Dawley rats. Survival in long-term carcinogenicity bioassays should be compliant with current UK and EC guidelines for a negative result from such studies to be acceptable.

ii) The available information supports the view reached by the COC in its guidelines published in 1991 that dietary restriction in carcinogenicity studies should be applied with caution and is the responsibility of the toxicologist undertaking the study. This subject may be reviewed when more information is available.

3.32 The Committee agreed to consider this topic further when the US Food and Drugs Administration publishes its revised proposals for dietary restriction. A short statement was published on the COC website in April 2000.

Ongoing work

3.33 Full details of ongoing work can be found in the minutes of meetings published on the COC website. This has been substantially upgraded and now contains a "What's new" section. A brief review of the discussions about the influence of genetic susceptibility on chemical induced carcinogenesis is given below.

Genetic susceptibility

3.34 The Committee was aware of increasing recognition of the modulating role of genetics in human disease and that there was evidence in some published epidemiological studies that genetic variation had a role in the metabolism of chemical carcinogens in determining risk of cancer. The Committee was also aware that potential genetic susceptibility to environmental chemicals had been the subject of media attention. Members held an initial discussion at the July 2000 meeting and agreed to a further detailed review. Members asked for papers on three topics to be prepared for discussion. These are:

i) Criteria for the design of gene-environment epidemiology studies

ii) A review of potential target genes for susceptibility to carcinogenesis

iii) A review of how gene-environment studies should be used in risk assessment process

3.35 These papers will be presented to the Committee for discussion in 2001.

Risk procedures used by the Government's Advisory Committees dealing with food safety

3.36 COC was informed that, at the Prime Minister's request, Sir Robert May (then Chief Scientific Advisor to the Government) together with the Chief Medical Officer, Professor Liam Donaldson, and the Chairman of the Food Standards Agency, Sir John Krebs, had carried out a review of risk procedures in scientific committees that deal with food safety. The review group also included representatives of the devolved administrations and Dr Jim McQuaid, former Health and Safety Executive (HSE) Chief Scientist and

Chairman of the Interdepartmental Liaison Group on Risk Assessment (ILGRA). The completed review outlined how the committees approached risk analysis and provided recommendations for best practice.

3.37 Members agreed that the role of COC predominately concerned hazard identification and risk assessment but not risk management. The Committee agreed that it should focus its work on scientific considerations and it was not the role of the Committee to consider policy options.

Statements of the COC

Statement on Evidence for Association Between Consumption of Alcoholic Beverages and Breast Cancer : Update of Information Published Between 1995 –1999

Statement on Carcinogenicity of 3-Monochloropropane-1,2-diol (3-MCPD)

Statement on Cancer Incidence Near Municipal Solid Waste Incinerators in Great Britain

STATEMENT ON EVIDENCE FOR ASSOCIATION BETWEEN CONSUMPTION OF ALCOHOLIC BEVERAGES AND BREAST CANCER: UPDATE OF INFORMATION PUBLISHED BETWEEN 1995-1999

Introduction

1. Breast cancer is the most common cancer in women and the most common cause of cancer mortality in women. Each year there are approximately 30,000 cases registered in England and approximately 11,000 deaths from breast cancer.[1] The aetiology of breast cancer is very complex (see paragraph 5 below). The most clearly established risk factors which are reproductive (eg age at first full term pregnancy, parity, age at menarche) offer limited scope for prevention. The reason for the interest in further consideration of the association between alcohol and breast cancer is that even a small risk, if causally associated with alcohol, could have serious public health implications in terms of the number of breast cancer cases attributable to drinking alcoholic beverages. An extensive literature on the association between alcohol and breast cancer was reviewed by the World Health Organisation's International Agency for Research on Cancer in 1988[2] and by this Committee in 1995[3] but both groups were unable to establish a causal association between drinking alcoholic beverages and breast cancer. The factors which prevented definite conclusions from being drawn are considered in detail in a section of this statement. As a large number of research publications have become available since 1995, including some recent studies investigating the potential mechanism by which alcohol could induce breast cancer, it is now timely for the Committee to update its assessment.

Background to COC consideration

Statement for the Interdepartmental Working Group on Alcohol (1995)

2. The Committee first considered the epidemiological evidence for an association between alcohol and breast cancer in 1995 at the request of the Interdepartmental Working Group (IDWG) on Sensible Drinking[4] as part of the review of medical and scientific evidence and its interpretation of the long term effects of drinking alcoholic beverages. The Committee provided a

statement to the IDWG on the evidence for alcohol and cancer at all sites and concluded that drinking alcoholic beverages causes a dose-related increase in the risk of squamous carcinomas of the upper aerodigestive tract as a whole, and for cancers of the oral cavity, pharynx, larynx, and oesophagus which was independent of the effect of smoking tobacco. There was a substantial amount of information available to members who were able to draw conclusions on dosimetry, duration and frequency of drinking alcoholic beverages and the effect of abstinence and of smoking.[3]

3. A substantial amount of research was available to the Committee on drinking alcoholic beverages and breast cancer in 1995. Members reviewed the 1988 IARC monograph, which provides an evaluation of four large prospective and 13 case-control studies. The Committee also reviewed seven additional prospective studies,[5-11] 17 new case control studies[12-28] and two meta-analyses.[29,30] In addition a number of reviews of the available information were also considered.[31-33] The Committee agreed that the adequacy of control for confounding by known and/or alleged risk factors for breast cancer varied in the different accounts. A dose-related association was reported in most cohort studies and in some hospital-based case-control studies. The results of population-based case-control studies did not generally support an association. A statistically significant dose-related increase in relative risk (RR) was reported in the two meta-analyses [RR at 3 drinks/day 1.38 (95% CI 1.23-1.55)]. The Committee noted that the small increases in relative risk documented in epidemiological studies ranging between approximately 1.2-3 were associated with highly variable estimates of consumption (ca 1-60g ethanol/day). It was agreed that clear evidence of causality had not been demonstrated.[3,4]

4. The Committee concluded "...that while there is no decisive evidence that breast cancer is causally related to drinking alcoholic beverages, the potential significance, for public health, of even a weak association between alcohol and breast cancer is such that we recommend, in particular, that this matter be kept under review."[3] The Interdepartmental Working Group endorsed the COC's conclusions and the recommendation that the relationship between alcohol and breast cancer should be kept under review.[4]

Evaluation of epidemiological data on alcohol and breast cancer

5. The factors which may affect the adequacy and interpretation of any epidemiological studies, such as bias, confounding and errors of measurement have been discussed in detail in the Committee's guidelines for the evaluation of chemicals for carcinogenicity.[34] The assessment of the available epidemiological literature on drinking alcoholic beverages and breast cancer

is particularly difficult as the size of the relative risk estimates reported in the literature (ca 1-3) are within the range where it is difficult to exclude bias and/or confounding as explanations for the results. It is therefore important to highlight the relevant factors of particular concern in interpreting studies of drinking alcoholic beverages.

Estimating alcohol consumption data

6. The difficulty in obtaining an accurate drinking history is an important cause of the observed variation in estimates of the consumption of alcohol and of relative risks for breast cancer at particular levels of drinking alcoholic beverages. Factors which affect the collection and interpretation of alcohol consumption data include inaccurate recall of drinking alcoholic beverages, leading to under reporting, changes in drinking patterns over time, cultural and regional variations in drinking habits, and differences in quantifying alcohol intakes between studies. The inadequate and inconsistent stratification of exposure groups further complicates the assessment of epidemiological data.

Confounding

7. Adequate measurement or control for confounding breast cancer risk factors is also difficult to achieve. Known risk factors for breast cancer include age, ethnic group, family history of the disease, age at birth of first child, at menarche and at menopause, history of biopsy for benign breast disease, socio-economic status, obesity and, in premenopausal breast cancer, history of lactation.[1] Other proposed risk factors have been cited, such as parity (in addition to age at birth of first child), use of oral contraceptives and hormone replacement therapy.

Introduction to current review

8. The Department of Health commissioned three discussion papers from its Toxicology Unit based at Imperial College of Science, Technology and Medicine to assist the Committee in its review. The first paper considered an update of the epidemiological literature from 1995 to March 1999[35] and the second paper was a review of the evidence (up to June 1999) on possible mechanism(s) by which drinking alcoholic beverages could induce breast cancer.[36] The third paper was requested by the Committee following an initial consideration of the evidence on possible mechanisms, and presented a tabulation of data on plasma and urinary sex hormones following consumption of alcohol.[37] The full evaluation of confounding and the

demonstration of a plausible mechanism between drinking alcoholic beverages and breast cancer would be significant steps towards establishing a causal relationship. A summary of the literature reviewed in these papers is given below.

9. All of the information was evaluated in accordance with the Committee's guidelines[34] and also with regard to the criteria proposed by Sir Austin Bradford-Hill.[38] These latter criteria, which are listed below, are generally regarded as being valuable in the consideration as to whether or not an association between an outcome (in this case breast cancer) and a putative risk factor (drinking alcoholic beverages) is causal.[39]

Bradford-Hill criteria

Strength
Consistency
Specificity
Temporality
Biological gradient
Plausibility
Coherence
Experiment
Analogy

Objectives of current review

10. The primary objectives of the current COC review were:

i) To update the assessment of breast cancer in relation to alcohol consumption; to assess this risk in relation to the level and type of alcohol consumption; to examine any differences in risk between premenopausal and postmenopausal women and/or between women using or not using exogenous hormones [oral contraceptives (OCs) and hormone replacement therapy (HRT)].

ii) To review the evidence relating to the mechanistic basis for an association between alcohol consumption and breast cancer.

iii) To assess whether any association between alcohol consumption and the risk of breast cancer can be considered as causal.

iv) If a conclusion regarding causality cannot be reached, to identify the nature of any additional research required to reach a definite conclusion.

Review of new information

Update on epidemiological evidence[35]

11. Three new prospective studies were identified in the DH Toxicology Unit discussion paper.[40-42] These investigations found a small but statistically significant association between drinking alcoholic beverages and increased risk of breast cancer and thus confirmed the findings of prospective studies reviewed by the COC in 1995. A further 22 case-control studies were reported.[43-64] A statistically significant association between drinking alcoholic beverages and increased risk of breast cancer was reported in 17 of these studies with relative risks in drinkers estimated to be between 1.2 and 2.5. A dose-related trend for the association between drinking alcoholic beverages and breast cancer was reported in the two cohort studies where this aspect was considered[40,42] and in the majority of the case-control studies reviewed.[45,47,50,53,57,64] A significant trend between increasing alcohol consumption and relative risk of breast cancer was documented in a pooled analysis of six prospective studies.[65] The extent of correction for potential confounding risk factors varied between the different studies and a number of different methods for estimating alcohol consumption were used. An analysis of risks in pre menopausal and post menopausal women separately was undertaken in nine case-control studies[43,45,46,48-50,59,62,64] and in one pooled analysis of six prospective studies[65] but no conclusions could be drawn regarding these data in view of the variation in quality and results between the individual investigations. Other important variables, such as beverage type and duration and frequency of drinking alcoholic beverages were considered in a number of the epidemiology studies but no clear conclusions could be drawn from the narrative review provided.

Consideration of epidemiological data

12. The Committee noted that the DH Toxicology Unit had considered dose-response and duration of drinking alcoholic beverages and had come to similar conclusions to that reached by the COC in its 1995 review; namely that there was evidence for an association between drinking alcoholic beverages and breast cancer. Overall, there were no definitive data on an effect of beverage type on relative risk and thus the authors had concluded that most information pointed to an effect of alcohol itself rather than any congeners or other ingredients. The Committee agreed that a more comprehensive review of all the epidemiological data was required, particularly with respect to the quality assessment of the individual investigations, and suggested that the epidemiological papers should be

assessed for quality using a scoring method and that a formal systematic review, and where appropriate, meta-analyses of all the epidemiological data should be undertaken. Two further epidemiological studies published after the DH Toxicology Unit report considered the evidence for a risk of breast cancer in premenopausal women.[66,67] The Committee agreed that the results of these studies needed further consideration as part of the systematic review.

Possible mechanisms for association between drinking alcoholic beverages and Breast Cancer[36,37]

13. The discussion paper drafted by the Department of Health Toxicology Unit identified sparse evidence for a number of potential mechanisms by which alcohol could induce breast cancer including enhanced metabolism of carcinogens,[68-70] increased cellular permeability to potential carcinogens,[71] impaired immune responsiveness,[72] and abnormal differentiation of mammary tissue.[73] A further published paper presented a hypothesis that alcohol could induce tissue and DNA damage via the formation of reactive oxygen species in breast tissue.[74] However, most of the available studies on mechanism examined the effects of drinking alcoholic beverages on oestrogen metabolism in humans. There was evidence from both cross-sectional and intervention studies that alcohol consumption affected oestrogen metabolism in premenopausal[75,76] and postmenopausal[77-83] women. The mechanism by which alcohol affected oestrogen metabolism was not readily apparent from these studies particularly in view of the evidence for confounding and interaction by other possible breast cancer risk factors such as obesity,[77] the use of oral contraceptives[84] and hormone replacement therapy.[82] One small study published after the DH Toxicology Unit review[86] provided evidence suggesting that among premenopausal women there may be a group which is more susceptible to the effect of alcohol consumption on breast cancer, because of genetic differences in alcohol metabolism. The results obtained in this latter study need to be confirmed before any definite conclusions can be reached.

Consideration of potential mechanisms

14. The Committee agreed that there was now substantially more information on the potential effects of alcohol on oestrogen metabolism than was available in 1995. However the interpretation was complex and it was requested that the data be reviewed by an independent expert endocrinologist who would advise on what effects alcohol might have on the metabolism of oestrogens in premenopausal and postmenopausal women. A further discussion paper[37] prepared by the Department of Health Toxicology Unit was considered

together with a submission from Professor H S Jacobs (Emeritus Professor of Reproductive Endocrinology, University College Medical School, London) who provided an oral assessment of the data to the Committee. The Committee agreed with Professor Jacobs that there was sufficient evidence from the available studies in humans to conclude that drinking alcoholic beverages can elevate blood concentrations of oestrogens (particularly oestradiol) and that the data concerning oestrogen-receptor status in breast cancer suggested a plausible link between alcohol consumption and an increased risk of breast cancer.[85] Overall the available data suggested a plausible mechanistic link between consumption of alcohol and breast cancer mediated via an effect of alcohol on hormones. The interpretation of these data was particularly complicated and difficult; for example, the influence of confounding effects of other possible breast cancer risk factors such as obesity, use of oral contraceptives and hormone replacement therapy and their potential interaction with drinking alcoholic beverages needed to be considered carefully.

15. Some recent research has noted that the effects of alcohol on serum oestradiol concentrations occur in premenopausal women using oral contraceptives.[87] The Committee agreed that further epidemiological work should consider a number of sub-groups, ie premenopausal women who either used or did not use oral contraceptives and postmenopausal women who had or had not taken HRT. The Committee agreed that there were insufficient data available to describe a threshold of action for alcohol-induced elevation in oestrogens.

16. The Committee agreed that it was important to consider carefully all the available evidence relating to potential mechanisms and therefore asked the COM to update its conclusions, reached in 1995, on any new and relevant mutagenicity studies.

Consideration of causality

17. The Committee felt it helpful to consider all the available evidence under the Bradford-Hill criteria which were outlined above in paragraph 9, in order to assess whether a definite conclusion on causality between drinking alcoholic beverages and breast cancer can be reached and, if not, to use the criteria to identify key areas where further work is required. An assessment of the available evidence has been tabulated as shown below.

Criterion	Evidence regarding alcohol and breast cancer	Comments
Strength	Limited. Magnitude of association is small	The RR in alcohol drinkers is modest and, even for heavy drinkers, rarely exceeds 3. However the RR for most other identified breast cancer risk factors also rarely exceed this value.
Consistency	Limited. Under review.	The available published meta-analysis by Longnecker MP[30] reported significant heterogeneity. A reason for marked variation in results across studies was not found. The pooled analysis of prospective studies published by Smith-Warner SA et al[65] found evidence of heterogeneity in results for premenopausal women but not postmenopausal women. There is a need for a further systematic review, using all studies available to date, to evaluate heterogeneity more fully. (A DH funded study is in progress).
Specificity	Not relevant.	Cancer risk attributed to alcohol is not specific for breast cancer (e.g. prolonged alcohol consumption can induce cancers of the head and neck and oesophagus and liver).[3] The mechanism for alcohol induced causation of these cancers is unknown but is unlikely to be related to that for breast cancer.
Temporality	Yes	Association demonstrated in prospective studies where alcohol consumption can be studied before the occurrence of disease.
Biological gradient	Limited. Some evidence available	There is some evidence for a dose-response effect but the RR rarely exceeds 3 even in heavy drinkers. Assessment of potential confounding and bias required to reach a conclusion on this criterion.
Plausibility	Yes	Evidence for effect of alcohol consumption and elevations in blood levels of oestrogen metabolites (in particular oestradiol) documented.[36,37] Raised oestradiol is a risk factor for breast cancer.[39] The evidence therefore suggests a plausible mechanism in both premenopausal and postmenopausal women.
Coherence	Limited	Evidence for an increased risk of breast cancer in alcoholics[88] and for a relatively low rate of breast cancer incidence among populations abstaining from alcohol (e.g. Mormons).[89] Difficult to assess this criterion on these data.
Experiment	Limited. Some evidence available.	No evidence that alcohol is carcinogenic in experimental animals.[3] Some evidence that alcohol affects breast tissue differentiation in animals.[90]
Analogy	Yes	Other causes of significantly increased oestradiol levels in exposed populations are suggested risk factors for breast cancer (e.g. use of oral contraceptives and HRT).[39]

18. Taking all the available data into account there is evidence to satisfy three of the criteria (temporality, plausibility, and analogy) and some limited evidence to satisfy a further four of the criteria (consistency, biological gradient, coherence, and experiment). The Committee agreed that there was no evidence that alcohol is carcinogenic from experimental studies in animals. The Committee considered that the criterion of specificity was not relevant to the assessment of breast cancer risk. The Committee agreed that there was considerable evidence to support an association between drinking alcoholic beverages and increased risk of breast cancer but the magnitude of the association was small (ie the relative risk is modest and, even for heavy drinkers, rarely exceeds 3) and it was difficult to ascertain the nature of the dose-response relationship from the available information. The small magnitude of the association between drinking alcoholic beverages and risk of breast cancer and the complex aetiology (ie it is not specific to a single risk factor) of breast cancer are the main reasons for the difficulty in reaching a definite conclusion based on the Bradford-Hill criteria. The association could be due to biases in the studies or to confounding by other breast cancer risk factors.

19. The Committee conclude that, in view of the difficulty in assessing the data on drinking alcoholic beverages and breast cancer, there is need for a rigorous systematic review of the epidemiological literature using appropriate methods (ie meta-analysis) to identify and evaluate potential biases, confounding and heterogeneity so that an assessment of causality and risk associated with drinking alcoholic beverages can be facilitated. The Committee agreed that it would be important for any further analyses of the data to provide a population-attributable risk estimate for the UK. The Committee subsequently agreed an outline proposal for a meta-analysis study prepared by a research team from Imperial College of Science, Technology and Medicine. The study has been commissioned by the Department of Health and was initiated in December 1999. A draft report should be available for scrutiny by the Committee in approximately 18 months time. The Committee was also aware that additional relevant data on alcohol consumption and risk of breast cancer from the Oxford Collaborative Group on Hormonal factors in Breast Cancer would be forthcoming and should be reviewed when available.

Conclusions of current review

20. The Committee reached the following interim conclusions based on its updated review of the published literature since 1995.

i) There is an association between drinking alcoholic beverages and increased risk of breast cancer. It is difficult to resolve whether this is causal. The magnitude of the observed association is small (ie the relative risk is modest and, even for heavy drinkers, rarely exceeds 3) and within the range where it is difficult to exclude bias and/or confounding as explanations for the observed results in epidemiological studies. It is difficult to derive a quantitative relationship from the dose-response data available in the literature.

ii) Further epidemiological studies have been published since 1995. There is a need for further systematic review of the epidemiological literature to assess fully the influence of bias, confounding and effect modification. This will contribute to a conclusion on causality and population attributable risk associated with drinking alcoholic beverages.

iii) Studies of possible mechanisms provide evidence for a plausible basis for the causation of breast cancer by consumption of alcohol. Alcohol increases blood levels of oestrogens and in particular oestradiol in both premenopausal and postmenopausal women. These data suggest a similar mechanism to other known breast cancer risk factors.

iv) The COM should be asked to update its opinion of 1995 on the mutagenicity data on alcohol.

April 2000
COC/00/S4

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CARCINOGENICITY OF 3-MONOCHLOROPROPANE-1,2-DIOL (3-MCPD)

Introduction

1. 3-Monochloropropane-1,2-diol (3-MCPD) can be present as a contaminant in epichlorhydrin/amine copolymers used as flocculants or coagulant aids in water treatment. These polyamine flocculants have been available for many years as approved products for use in water treatment and thus 3-MCPD may be present in drinking water from their use. 3-MCPD is a member of a group of contaminants known as chloropropanols. This group includes some known genotoxic carcinogens in animals such as 1,3-dichloropropan-2-ol. The COC was asked to evaluate and advise on the available carcinogenicity data on 3-MCPD by the Committee on Chemicals and Materials of Construction for use in Public Water Supply and Swimming Pools (CCM), a statutory committee which provides advice to the Secretary of State for the Environment on the approval of chemical substances in contact with public water supplies.

2. The Committee was aware that 3-MCPD had been detected as a contaminant of several foods and food ingredients, including acid hydrolysed vegetable protein (acid-HVP) and that the EU Scientific Committee for Food had published an opinion in 1994 where it was agreed that 3-MCPD should be regarded as a genotoxic carcinogen.[1] The Committee also had access to published mutagenicity data on 3-MCPD, a safety evaluation prepared by CanTox. Inc (Ontario, Canada) for the International Hydrolysed Protein Council,[2] and a review document published by the Institute of Toxicology, National Food Agency of Denmark.[3] The COC asked for advice from the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) in respect of the mutagenicity of 3-MCPD. In reviewing these documents in 1999, members commented that the available metabolism data on 3-MCPD were relatively old and focused on metabolic pathways following intraperitoneal administration. There was no oral mass balance investigation available. The Committee considered the proposal by CanTox Inc regarding the formation of bacterial-specific mutagens and agreed that there was no evidence to support this speculation. However, additional *in-vivo* mutagenicity data became available to the COM in 2000, namely a bone marrow micronucleus test and a rat liver UDS assay. Both studies were conducted to appropriate protocols and 3-MCPD was negative in both studies.

Conclusions

3. The Committee has now reached the following conclusions on all the available mutagenicity and carcinogenicity data.

i) 3-MCPD has a chemical structure which suggests that it may be metabolised to genotoxic intermediates (particularly glycidol).

ii) The COM has advised that 3-MCPD is an *in-vitro* mutagen but has no significant genotoxic potential *in-vivo*. (The COM statement on mutagenicity of 3-monochloropropane-1,2-diol has also been revised). The COM also noted that the predominant urinary metabolite in rats following dietary or intraperitoneal doses of 3-MCPD was beta-chlorolactic acid[4],(ie resulting from a pathway not producing glycidol or other genotoxic intermediates). A study has also shown that 3-MCPD may be also metabolised by a minor pathway and undergo conjugation with glutathione ultimately to form a mercapturic acid in urine of rats [N-acetyl-S-(2,3-dihydroxypropyl) cysteine].[5]

iii) 3-MCPD has been tested in four long-term animal carcinogenicity experiments, two in mice and two in rats.[6-8] However, three of these studies [6,7] were conducted between 1970 and 1981 to inadequate protocols. The conclusions reached by the COC therefore refer to the one study conducted to contemporary standards.[8] The Committee had access to the full study report [8] and to published reviews of this study.[2,3] The tumour data have been evaluated by a number of statistical methods. The analyses reported below refer to the Fishers pair-wise comparisons with controls.

iv) In the study undertaken by Sunhara et al (1993)[8] 3-MCPD was administered via drinking water to groups of 50 male and 50 female F344 rats (aged 6 weeks at study initiation) for a period of 104 weeks. Concentrations of 0, 20, 100, and 200 ppm were used. These equated to dose levels of 0, 1.1, 5.2, or 28 mg/kg bw/day in males and 0, 1.4, 7.0, or 35 mg/kg bw/day in females. 3-MCPD was also detected in the drinking water used in this study at 2.7 ppm and thus control animals were given doses of approximately 0.1 mg/kg bw/day. The high dose group exceeded the Maximum Tolerated Dose as evidenced by a decrease in body weights relative to controls of 33% and 35% in males and females respectively. There was no evidence of any treatment-related increase in mortality in this study. Survival to termination was acceptable (ie >50%) in all dose groups with the exception of the male high dose group where 21/50 animals survived to termination.

v) In males, a statistically significant increase in the incidence of Leydig-cell adenoma was documented at the intermediate and high dose levels. Three animals at the high dose level had Leydig-cell carcinomas. A statistically significant increase in the incidence of mammary gland fibroadenoma was noted in the high dose male group. A statistically significant increase in mammary gland hyperplasia was recorded in the male mid and high dose groups. A small but not statistically significant increase in the incidence of preputial gland adenoma was recorded in the mid and high dose male groups. One animal in the intermediate dose group and two in the high dose group had preputial gland carcinomas. It is difficult to evaluate these findings since only a limited number of preputial glands were examined histologically (5-16/group) in this study. A small (not statistically significant) increase in renal tubular adenomas was documented in the intermediate and high dose male groups. A statistically significant increase in the incidence of nephropathy and renal tubular hyperplasia was also recorded at the intermediate and high dose levels in this study.

vi) In females, a statistically significant increase in the incidence of renal tubular adenoma was recorded at the high dose level. A statistically significant increase in nephropathy and renal tubular hyperplasia was also recorded at the intermediate and high dose levels in this study. A slight but statistically non-significant increase in mammary gland hyperplasia was reported at the high dose level.

vii) The Committee noted that tumours were reported in both sexes in the kidney and in males only at hormonally responsive sites (ie the testes, mammary gland and preputial gland) at dose levels which exceeded the maximum tolerated dose. Evidence from previously conducted investigations with 3-MCPD was considered in evaluating possible explanations for these findings.

viii) In the kidney, the Committee noted that tumours in both sexes were benign (renal tubular adenoma) and that these were accompanied by a chronic progressive nephropathy. In considering possible mechanisms, the Committee were aware of earlier findings that metabolism to beta-chlorolactic acid is a major pathway in the rat [4] and that this metabolite is further broken down to yield oxalate and CO_2. Oxalate is known to induce severe renal cytoxicity.[3,9] Other evidence, including a study which reported crystals of oxalate in the urine of rats treated with 3-MCPD (single dose of 100mg/kg ip),[4] supported a role for sustained cytotoxicity as a possible mechanism for the induction of kidney tumours. The renal adenoma recorded in one female animal at the lowest dose was not considered to be biologically significant, and the

Committee agreed that a dose of 1.1mg/kg bw/day was a no observed effect level for the induction of kidney tumours. The Committee, however, noted some evidence of a toxic effect upon the kidney at this dose level (ie increased tubular hyperplasia and statistically significant increase in absolute kidney weight).

ix) With regard to the sex-specific tumours in male rats (in the testes, mammary gland and preputial gland), the Committee noted that the testicular tumours needed to be viewed against the high spontaneous incidence of Leydig-cell tumours common in ageing F344 rats, which may be up to 100% in control groups.[10,11] The high proportion of Leydig cell adenoma (between 86% and 100% in treated animal groups, compared to 76% in controls) was particularly noted in this study. However, Leydig-cell carcinoma developed only at the highest dose in 3/50 treated animals. As 3-MCPD has been shown to induce a prolonged increase in circulating hormone levels [a single intraperitoneal dose of 80mg/kg bw causing increased serum levels of follicle stimulating hormone (FSH), luteinising hormone (LH) and prolactin],[12] it is possible that increases in the spontaneous rate of Leydig-cell tumours may have been promoted by hormonal imbalance caused by 3-MCPD. Subsequently, the increase in tumours at other hormonally responsive sites (ie in the male mammary gland and the preputial gland) may be secondary to further hormonal disturbances known to be induced by proliferating Leydig cells.[2] Overall, the Committee noted that there was no evidence of a significant increase in tumourigenic response at any of these sites at a dose of 1.1 mg/kg bw/day.

x) The Committee considered the suggestion that all of the increases in tumours noted in this study in rats were mediated by non-genotoxic mechanisms involving either cytotoxicity (kidney) or hormonal disturbances.[2,3,8] The possible influence of the stereoisomerism of 3-MCPD was also discussed. Members agreed that the proposed non-genotoxic mechanisms advanced were plausible, now that specific evidence was available that reactive metabolites were not produced *in-vivo* in tissues where genotoxicity was assessed.

xi) The Committee concluded that the no observed effect level (NOEL) for tumourigenic effects of 3-MCPD in rats was approximately 1.1mg/kg bw/day.

xii) The Committee agreed that an approach utilising the NOEL with appropriate uncertainty factors would be acceptable for carcinogenic risk assessment for 3-MCPD. An overall uncertainty factor of 1000

was considered appropriate in view of the uncertainties identified in the data, particularly in respect of the quality and incompleteness of the metabolic data on 3-MCPD.

xiii) The Committee concluded that 3-MCPD was unlikely to present a carcinogenic risk to man, provided the exposure was 1000 times lower than the NOEL of 1.1mg/kg bw/d for tumourigenicity.

December 2000
COC/00/S5

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CANCER INCIDENCE NEAR MUNICIPAL SOLID WASTE INCINERATORS IN GREAT BRITAIN

Introduction

1. There have been very few epidemiological studies published which investigated cancer incidence or mortality amongst individuals living in proximity to incinerators in Great Britain.[1,2] The COC was asked during 1993-4 to comment on a study undertaken by the Small Area Health Statistics Unit (SAHSU) which investigated the cancer incidence of over 14 million people living near to 72 solid waste incinerators. This investigation had been initiated following the publication of several reviews of the potential health risks associated with incineration which highlighted the lack of appropriate epidemiological investigations of cancer risk.[1, 3,4] and was published in the scientific literature in 1996.[5] However, before drawing any conclusions on the SAHSU study, the Committee requested further information in respect of the data on liver cancer; namely a histopathological and case-note review of primary liver cancer cases. The Committee considered the report of this latter investigation during 1998 and at its March 1999 meeting. This statement presents some background information on municipal solid waste incineration in the UK, a review of the SAHSU investigations of cancer incidence near to municipal solid waste incinerators and conclusions reached by the Committee regarding the risk of cancer associated with living near to municipal incinerators.

Municipal solid waste incineration in the UK

2. According to the Department of the Environment, Transport and the Regions (DETR), currently around 26 million tonnes of municipal waste is produced in the UK each year; around 10% of which is disposed via incineration. In the UK all municipal waste incinerators (MWIs) are regulated by the Environment Agency or local authorities. Since 1 December 1996, all MWIs have been required to meet the standards in the Municipal Waste Incineration Directives 89/369/EEC and 89/429/EEC and this resulted in the closure of the majority of the existing incinerators and the upgrading of the remainder. A dioxin emission limit of 1 nanogram per cubic metre (ng m^{-3}) was imposed at the same time although, in practice, most existing plants already achieve dioxin emissions close to 0.1 ng m^{-3}. There are currently 11 MWIs in operation in the UK, with another due to start operating in 2000. The Committee was informed that there is expected to be a significant increase in UK incinerator capacity over the next 10-20 years to meet the requirements of the proposed EC Landfill Directive which sets limits for the percentage of biodegradable waste which may be

landfilled (it has been estimated that a further 16 MWIs may be required by 2006).[6] However, the draft Waste Incineration Directive currently being discussed within the EU seeks to reduce further emissions of key pollutants from incineration processes, including particulates, dioxins, and heavy metals.

SAHSU studies of municipal solid waste incinerators.

A. 1996 Investigation of health statistics

3. The cancer incidence of over 14 million people living near to 72 municipal solid waste incinerators in Great Britain was examined from 1974-1986 (England), 1974-1984 (Wales), and 1975-1987 (Scotland).[1] The study was conducted in two stages: the first involved a stratified sample of 20 incinerators and the second considered the remaining 52 incinerators. Overall there was a statistically significant decline in risk with distance from incinerators for all cancers combined and for stomach, colorectal, liver and lung cancers. The excess risk in people living within 1 km of a MWI for these cancers after allowing for a 10 year lag period, was estimated from the second stage investigation to vary from 5% (colorectal) to 37% (liver; 0.95 excess cases 10^{-5} $year^{-1}$). SAHSU estimated a total of 23 excess cases of liver cancer in the 0-1 km zone from the second stage of the analysis. There was evidence of residual confounding which the authors suggested was a likely explanation for the findings for all cancers, stomach and lung, and also to explain at least part of the excess of liver cancer. For this reason and because of the substantial level of misdiagnosis (mainly secondary tumours) believed to occur among registrations and death certificates for liver cancer, the COC asked for a further investigation. This was to comprise a histological review of the liver cancer cases identified in the first study, in order to determine whether or not an increase in primary liver cancer had occurred.

B. Histological and case-note review of primary liver cancer cases

4. This diagnostic histopathological and case-note review considered 235 cases (155 males, 80 females) registered with primary liver cancer and included all 87 cases within 1km of a MWI, and random samples of 74 cases from 1-7.5 km and 74 from the rest of Great Britain. Diagnostic material was available for 94 cases (of which 26 also had clinical notes available) and medical records only were available for 25 additional cases. Histopathological slides were reviewed independently by three pathologists and any discrepancies resolved at case conferences. The medical records were reviewed independently by one senior clinician.

5. Primary liver cancer was confirmed in 66/119 cases (55%, 95% CI 46-64%) while 21 cases (18%; 95% CI 11-24%) were considered to be definite secondary cancers. The remaining cases could not be distinguished between primary and secondary cancers (26 cases) or no malignant tissue was found in the specimens available (6 cases). There was no evidence to suggest that the proportion of cases confirmed as having primary liver cancer, nor of those with evidence of cirrhosis and associated risk factors, differed with distance from incinerators. The Committee agreed that the confirmation of 55% of registered primary liver cancer cases following diagnostic review, is in accordance with a previous study in Great Britain.[7] The Committee agreed that the finding of a high concordance between cancer registration and death certificate data for the confirmed primary liver cancer cases (80%) was unexpected but important new information which suggested that the use of death certificates was acceptable in epidemiological investigations of liver cancer.

6. Two cases of angiosarcoma were diagnosed on histopathological review within 7.5 km of a MWI (cf 0.26 expected based on a national register ($p<0.05$)), but there was no evidence more generally of clustering near incinerators of cases ascribed to angiosarcoma in a national register. Neither of these two cases had been diagnosed previously, both being registered as hepatocellular carcinoma, and neither was an industrial case. The Committee noted that there was no background information on the extent to which angiosarcoma was misdiagnosed routinely as hepatocellular carcinoma or carcinoma (not otherwise specified) in the general population. The Committee agreed that SAHSU had adopted an acceptable approach to the evaluation of the significance of the two cases of angiosarcoma given the limitations in the national register data used.

7. The histopathology diagnostic review allows a range of estimates to be made of possible (absolute) excess of “true” primary liver cancer near incinerators, based on relative risk estimates from the previous study. Assuming that primary liver cancer was the correct diagnosis in 55% of all registered cases then the excess number of cases among the population living within 1 km of an incinerator is reduced from 23 to 12.6, i.e. an excess of 0.53 excess cases 10^{-5} $year^{-1}$. With only definite secondary cancer cases excluded (18%) then the excess within 1km is reduced to 18.8 cases, ie 0.78 excess cases 10^{-5} $year^{-1}$. [8]

COC evaluation of SAHSU studies

8. The Committee was informed that there have been considerable reductions in the levels of emissions of pollutants from incinerators in recent years. The Royal Commission on Environmental Pollution recognised that epidemiological studies are much less likely to reveal any health effects in relation to current standards of controls on emission of pollutants from MWIs.[1] Thus estimates of the relative risk derived from the SAHSU investigations would, if causally associated with exposure to emissions, be related to accumulated exposures prior to the introduction of the controls implemented through the 1989 Municipal Waste Incineration Directives.

9. The Committee agreed that there were a number of factors that should be considered in deriving conclusions on the SAHSU studies of MWIs: i) accuracy of health statistics, ii) accuracy of cancer diagnosis, iii) potential confounding factors for individual cancers, and iv) a number of environmental variables particular to incineration such as type of waste burnt, geographical and meteorological conditions, and controls placed on the emission of pollutants.

10. With regard to the 1996 study of cancer incidence, the Committee agreed that the excess of all cancers, stomach, lung and colorectal cancers were due to socio-economic confounding as has been reported by the SAHSU group following adjustment of the data by use of a deprivation index. Post-hoc analyses which compared cancer incidence prior to establishment of an incinerator with cancer incidence following a 10 year lag period since first exposure was consistent with this conclusion.

11. With regard to the diagnostic histopathology study of liver cancer, the Committee agreed that whilst the excess of primary liver cancer near incinerators was not readily explained by known confounding or other factors, residual confounding by socio-economic factors could not be excluded in view of the strong association of deprivation with liver cancer incidence.

Conclusions

12. The Committee agreed the following overall conclusions with respect to the SAHSU investigations of cancer incidence near MWIs:

    i) The SAHSU studies found a small excess of primary liver cancer near municipal solid waste incinerators (estimated to be between 0.53-0.78 excess cases 10^{-5} $year^{-1}$). It is not possible to conclude that this small increase in primary liver cancer is due to emissions of pollutants from incinerators, as residual socio-economic confounding cannot be excluded. The Committee agreed that an excess of all cancers, stomach, lung and colorectal cancers was due to socio-economic confounding and was not associated with emissions from incinerators.

    ii) The finding of two cases of angiosarcoma during the histopathology review in individuals who were resident within 7.5 km of a municipal solid waste incinerator was unexpected. The Committee considered that the evaluation of this finding was difficult given the limitations in the registration of angiosarcoma and lack of information regarding accuracy of diagnosis in the general population. The Committee, however, agreed that there was no evidence more generally of clustering near incinerators of cases ascribed to angiosarcoma in a national register.

    iii) The Committee was reassured that any potential risk of cancer due to residency (for periods in excess of 10 years) near to municipal solid waste incinerators was exceedingly low and probably not measurable by the most modern epidemiological techniques. The Committee agreed that, at the present time, there was no need for any further epidemiological investigations of cancer incidence near municipal solid waste incinerators.

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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
Prof P G Blain (Chairman)	NONE	NONE	Unilever plc	Research Studentship
Prof C Cooper	Halifax Norwich Union	Share Holder Share Holder	NONE	NONE
Prof D Forman	Halifax Woolwich	Share Holder Share Holder	NONE	NONE
Prof D Harrison	Medical Solutions AstraZeneca GenoVar Diagnostics	Share Holder Consultant Consultant	Fairfield Imaging	Research Support
Ms D Howel	NONE	NONE	NONE	NONE
Dr S J Kennedy	Unilever	Share Holder	NONE	NONE
Ms M Langley	NONE	NONE	NONE	NONE
Prof J M Parry	Compass Catering JIB Insurance National Power SmithKline Beecham Quintiles	Share Holder Share Holder Share Holder Consultant Consultant	Astra BAT Boehringer Glaxo/Wellcome Pfizer Welsh Water	Grant Grant Grant Grant Grant Grant
Prof D Phillips	Abbey National plc BG Group Bradford & Bingley Centrica CGNU Lattice Group National Grid	Share Holder Share Holder Share Holder Share Holder Share Holder Share Holder Share Holder	NONE	NONE
Prof A G Renwick OBE	International Sweeteners Association	Consultant	Hoffmann-La Roche SmithKline Beecham Unilever FEMA Pfizer	Research Support Research Support Research Support Grant Grant

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Dr R Roberts	AstraZeneca Eli-Lilly P & O Zeneca	Share Holder Share Holder Share Holder Salary	Baxter Healthcare European Council for Plastics and Intermediates (ECPI) Halogenated Solvents Industry Alliance (HSIA) Novartis	Departmental Support Departmental Support Departmental Support Departmental Support
Prof D Shuker	NONE	NONE	Glaxo-Wellcome Unilever	Postgraduate Studentship Project Support
Prof G T Williams	Abbey National plc AMP Ltd Bradford & Bingley CGNU Aphton Corporation	Share Holder Share Holder Share Holder Share Holder Consultant	NONE	NONE