COMMITTEE ON THE 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 2004, the Committee provided advice on a wide diversity oftopics including alcohol and breast cancer, 1,3-dichloropropan-2-ol,2,3-dichloropropan-1-ol (1,3-DCP, 2,3-DCP), organochlorine insecticides and the possible association with breast cancer, malachite green/leucomalachite green, and polycyclic aromatic hydrocarbons in air pollution. The Committee also provided generic advice on oesophageal and prostate cancer.

in relation to potential chemical exposures which might be associated with these particular cancers, and on the observation of olfactory neuroblastoma in a small number of dentists/dental nurses. The COC epidemiologists provided advice to the Advisory Committee on Pesticides on the Ontario College of Physicians Report. Finally the COC (along with COT and COM) provided an input to the reassessment of tobacco products.

The Committee has an ongoing responsibility to provide Government Departments and Regulatory Authorities with advice on developments in procedures for the evaluation and risk assessment of carcinogens. During this year, the Committee provided advice to the Health and Safety Executive on the development of its proposed priority programme on occupational exposures to carcinogens and the risk assessment of genotoxic carcinogens and the effect of DNA repair at low doses.

During 2004, the Committee also said farewell to Dr Robin Fielder who retired from the COC secretariat. I wish to record my thanks for his excellent contribution and commitment to the work of the COC and to the improvement of public health in general during his many years of service for the COC.

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Alcohol and breast cancer

3.1 Breast cancer is the most common cancer in women and the most common cause of cancer mortality in women. Each year there are approximately 41,000 cases (2000 data) registered and 13,000 deaths (2001 data) in the U.K. The most clearly established risk factors for breast cancer are reproductive (e.g. age at first full term pregnancy, parity, age at menarche and menopause). Other known risk factors for breast cancer include age, ethnic group, family history of the disease, history of benign breast disease, socioeconomic status, use of oral contraceptives and hormone replacement therapy and, in postmenopausal women, obesity. The reason for the interest in the association between alcohol and breast cancer is that even a small risk, if causally associated with alcohol, may have serious public health implications. In addition, drinking alcoholic beverages may be one of the few risk factors for breast cancer where intervention might offer some scope for prevention. 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 and by this Committee for the Inter Departmental Working Group on Alcohol in 1995 but neither group was able to advise that there is a causal association between drinking alcoholic beverages and breast cancer.

3.2 A further review was undertaken by the COC in 1999 (http://www.doh.gov.uk/alcbrst.htm). The Committee concluded there was sufficient evidence to associate drinking alcoholic beverages with an increased risk of breast cancer but agreed that a systematic review (meta-analysis) of all the epidemiology studies and further evaluation of potential mechanisms were required before definite conclusions could be reached. The Department of Health commissioned a systematic review of the epidemiology from the Department of Epidemiology and Public Health at Imperial College, London.

3.3 The COC considered a draft report from the Imperial College London research group at a meeting in November 2002, an update review of mechanisms from the DH Toxicology Unit at Imperial College, and a published evaluation of the literature prepared by the Oxford Collaborative Group on Hormonal Factors in breast cancer (British Journal of Cancer, 87, 1234-1245, 2002). The COC considered further draft reports from Imperial College and updated searches of the published literature up to June 2004 when a COC statement (and non-technical summary) were finalised. The overall conclusions (as taken from the non-technical summary) reached by the COC are given below.

3.4 The new research estimates that a woman drinking an average of two units of alcohol per day* has a lifetime risk of developing breast cancer 8% higher than a woman who drinks an average of one unit of alcohol per day. The risk of breast cancer further increases with each additional drink consumed per day. There was no evidence for variation in the association with any specific type of alcoholic drink. (Key J, Hodgson S, Omar R, Kold-Jensen T, Thompson S, Boobis A, Davies D, Elliott P (2003). Alcohol and Breast Cancer: A meta-analysis. In-confidence paper submitted to COC and for publication).

* A standard 'unit' of alcohol contains 8grams of ethanol, the amount usually found in half a pint of normal strength beer, or cider, a single measure of spirits, or one small glass of ordinary wine. In recent years the average amount of alcohol in some drinks has increased and maybe up to 10grams ethanol.

3.5 The research also concludes that approximately 6% (between 3.2% and 8.8%) of breast cancers reported in the U.K. each year could be prevented if drinking was reduced to a very low level (i.e. less than 1 unit/week). This approximates to between 1290 and 3560 cases of breast cancer out of a total of approximately 41,000 new cases registered each year.

3.6 The risk of breast cancer associated with drinking alcohol increased with the amount of alcohol consumed. Thus, if a woman increased her drinking from the U.K average level of 1 unit per day by an extra 1, 2, or 3 units a day then the incidence of additional cases of breast cancer expected at 60 years and 80 years can be calculated.

The following table summarises the results:

Cumulative Incidence per 1000 women

	Current consumption	+1 unit per day	+2 units per day	+3 units per day
Age 60	60	65	70	75
Age 80	125	134	145	157

3.7. It is not known precisely how drinking alcohol can lead to breast cancer. The most likely explanation is that drinking alcohol can produce biochemical effects in the liver (such as changes to oestrogen metabolism and effects on growth factors) which if drinking alcohol is prolonged (i.e. over decades) could lead to breast cancer.

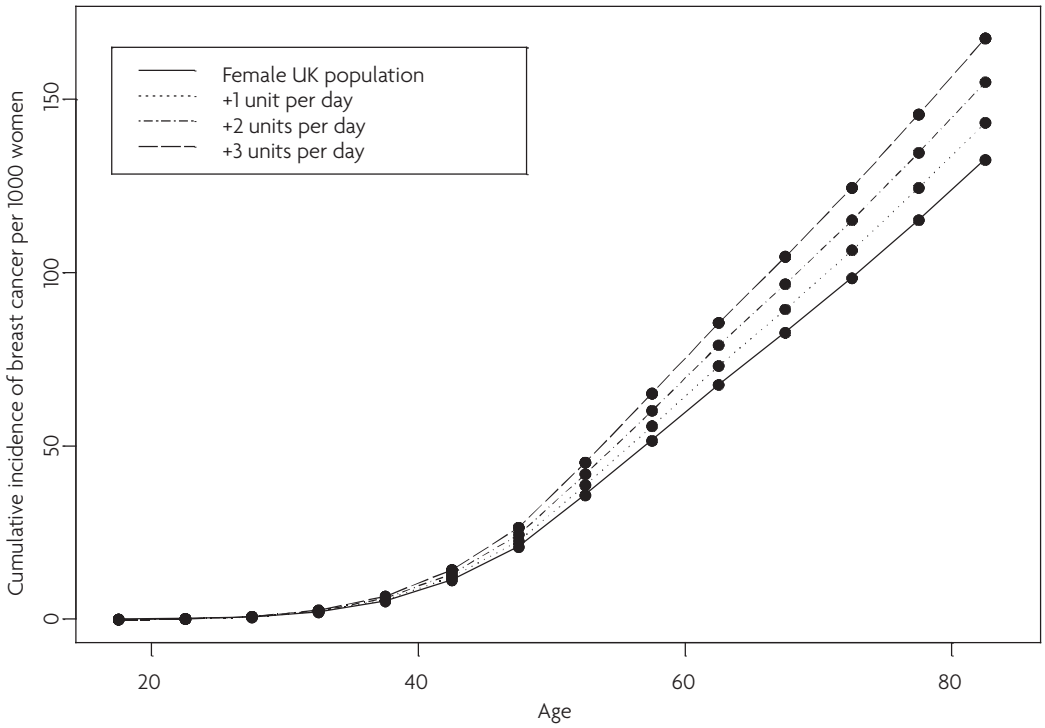
3.8 There is not enough information available to assess whether drinking alcohol can interact with the use of oral contraceptives or hormone replacement therapy by women to increase further the risk of breast cancer. More research on these aspects is required.

3.9 The Committee was concerned that recent evidence** demonstrated that the consumption of alcohol is increasing mainly in young women. If the increased consumption of alcohol is maintained over most of their lifetime, then the number of alcohol-related breast cancer cases may be even higher in these women than reported in paragraph 3.6 above. The Committee concluded that it was important to raise awareness of the potential risks of drinking alcoholic beverages, particularly amongst young women.

**There is a lot of information on the consumption of alcoholic beverages regularly obtained as part of the General Household Survey (GHS). (http://www.statistics.gov.uk/lib2001/index.html) and the Health Survey for England (HSfE) (http://www.doh.gov.uk/public/summary1.htm) Detailed information can be obtained from these sources. These studies examined alcohol in a variety of age groups. The youngest age group was 16-24 y.

Graph of cumulative incidence of breast cancer and effect of drinking additional units of alcohol.

The bold line indicates cumulative incidence at current average intakes alcohol (1 unit/day). The dotted lines show the effect of increasing intakes by additional 1,2, or 3 units per day.



3.10 A full statement is included at the end of this report.

1,3-Dichloropropan-2-ol, 2,3-Dichloropropan-1-ol

3.11 1,3-Dichloropropan-2-ol (1,3-DCP) and 2,3 dichloropropan-1-ol (2,3-DCP) are contaminants of some foodstuffs and of polyamine flocculants used in the treatment of drinking water. Both the COC and COM have previously published statements during 2000 on the closely related compound 3-chloro-1,2-propanediol (3-MCPD). 1,3-DCP and 2,3-DCP were considered by the COC and COM in 2001. In 2001, the COM recommended that appropriate in-vivo mutagenicity studies should be undertaken with 1,3-DCP and 2,3-DCP in accordance with the COM guidelines. In 2001, the COC came to the following conclusions:

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.

It is prudent to assume that 2,3-DCP may possess genotoxic activity in-vivo. Although no carcinogenicity data are available, it would however be prudent to reduce exposures to 2,3-DCP to as low a level as technologically feasible.

3.12 Both of these compounds have been recently considered by the COM which has updated its advice on the mutagenicity of 1,3-DCP and 2,3-DCP in the light of results from new *in-vivo* mutagenicity studies on these two compounds. An updated COM statement on 1,3-DCP was published in October 2003 and an updated statement on 2,3-DCP was published in June 2004.

3.13 The COC reviewed the available carcinogenicity data and the recent conclusions reached by COM. The following overall conclusions were reached:

1,3-DCP: The COC concurs with its previous advice that 1,3-DCP should be regarded as a genotoxic carcinogen. It is not possible to exclude a genotoxic mechanism for the induction of the tumours of rat tongue seen in a long-term drinking water study with 1,3-DCP. The Committee recommended that further investigations regarding the mechanism of 1,3-DCP carcinogenicity in the rat tongue should include information on contact-irritancy, cell proliferation and formation of adducts in tongue tissue using ^{32}P-postlabelling in animals treated with suitably high doses of 1,3-DCP.

2,3-DCP: The available evidence is consistent with the conclusion that 2,3-DCP does not posses genotoxic activity *in-vivo*. There are no appropriate carcinogenicity bioassays of 2,3-DCP available. No conclusions regarding carcinogenicity of 2,3-DCP can be reached.

3.14 A full statement is included at the end of this report.

Genotoxic carcinogens and DNA repair at low doses

3.15 The COC had asked the COM to provide advice regarding an approach to evaluating the significance of DNA repair induction at low doses of genotoxic carcinogens in the context of the hormesis hypothesis. The COM recommended a literature search targeted on low dose effects of a few direct acting chemical mutagens on DNA adduct formation, mutation rates, and the significance of DNA repair mechanisms. The COM had also recommended that the search should concentrate on low molecular weight compounds such as ethylene oxide and ethyl or methyl methanesulphonate, for which there was a rich database. Members had agreed that bacteria would most likely demonstrate more sensitivity to low does of mutagens than mammalian cells.

3.16 Overall, the COM had concluded that there was no convincing evidence for a 'J' shaped dose response relationship in any of the data considered. The COM agreed that the data considered in the paper did not warrant reconsideration of the COM's advice that it is prudent to assume that *in-vivo* mutagens do not have a threshold for mutagenicity, unless there is good evidence to the contrary.

3.17 The COC was asked whether any further consideration of DNA repair at low doses of mutagens should be undertaken and whether any further consideration of the concept of hormesis was warranted at the present time.

3.18 COC Members agreed with the COM conclusions and did not recommend further work at present, but considered that a watching brief should be kept on this topic. The COC felt that it was possible that DNA repair processes could be induced at low levels of exposure to mutagens, but that it would be very difficult to observe such effects experimentally in *in-vitro* mutagenicity assays. The committee concluded that for the purposes of carcinogen risk assessment it remained prudent to assume that there was no threshold for genotoxic carcinogens.

HSE Strategic Programme on Occupational Disease Reduction: Project on Chemical Carcinogens

3.19 Occupational carcinogens are a priority for HSE in a new strategic programme to reduce the incidence of occupational ill health. In June 2004, the COC was given a short introduction to the initial project plan for the work on carcinogens. The general objective of the project was to gather and analyse toxicological and occupational hygiene data on carcinogens, and then to formulate a strategy by mid 2006 that included recommendations for risk reduction. In November 2004, the COC was invited to comment on two early activities.

3.20 HSE had begun to collate available toxicological evidence on chemical carcinogens, their use and information on the adequacy of exposure controls in the workplace. The COC was asked to consider an initial list of 10 carcinogens that HSE was especially keen to learn more about. Members noted the difficulty of using currently available data on carcinogens and exposures to select priority lists. A number of suggestions were made which would be further considered by HSE during the review process.

3.21 HSE planned to hold two workshops of experts and undertake research to update the estimate of cancer mortality due to occupation published in 1981 by Doll and Peto (Doll R, and Peto R., J. National Cancer Inst, 66, 1191-1308, 1981). This much cited study estimated the proportion of cancer mortality in the USA due to occupational causes to be around 4%, uncertainty range 2-8%. The new work to be undertaken by HSE would provide an estimate of the burden of cancer that can be attributed to occupation in Great Britain.

3.22 Members felt that this was a worthwhile and ambitious project. It was noted that the Doll Peto analysis had analysed cancer attributed to occupation in the U.S.A. Members commented that industrial exposures to chemicals had changed rapidly over the past two decades and the estimate of cancer burden associated with chemicals in use could not be assessed on the available current cancer mortality data.

3.23 The Committee asked to be kept informed on developments arising from the workshop and review process.

Oesophageal cancer

3.24 The COC had asked for a review of oesophageal cancer during its discussion of the 2003 horizon scanning paper. The DH Toxicology Unit had drafted an overview paper. Oesophageal cancer is broadly classified into two histological types, squamous cell carcinoma (occurring mainly in the upper region of the oesophagus) and oesophageal adenocarcinoma (occurring mainly in the lower region of the oesophagus). Members agreed that the incidence of oesophageal adenocarcinoma (EAC) was increasing whilst the incidence of squamous cell carcinoma (SCC) had essentially stabilised.

3.25. Tobacco smoking and alcohol consumption are considered to be the predominant risk factors for SCC with about 90% of cases being attributable to these factors. There was no convincing evidence for an association between alcohol consumption and EAC. Members were aware of some studies which documented results supporting an association between tobacco smoking and EAC but agreed the evidence was less convincing than for tobacco smoke and SCC. Members agreed there was convincing evidence for an association between body mass index and gastro-oesophageal reflux disease (GERD) and EAC whilst the incidence of SCC did not appear to be affected by these two factors.

3.26 Members considered the evidence for particular chemical exposures and SCC and EAC. It was agreed that the limited evidence for an association between the rubber industry and an increased risk of oesophageal tumours was not convincing. In particular, it was noted that the available studies did not account for potential confounding by alcohol consumption or tobacco usage. Members commented that evidence for increased risk associated with occupational exposure to nitrosamines, PAHs, various dusts or other chemicals was limited. However many of these studies had not adjusted for confounding by alcohol consumption or tobacco usage and were therefore of limited value.

3.27 The Committee considered the available information on dietary nitrosamines in more detail. Nitrosamines were known to be oesophageal carcinogens in rodents and evidence suggesting similar metabolic pathways leading to activation was available for both rodents and humans. The metabolism and potential metabolic activation of nitrosamines in rats and monkeys were reported in the DH Toxicology Unit paper to be modified by ethanol. Nitrosamine exposure can occur through smoking and the diet and any effect on oesophageal cancer due to nitrosamines could potentially be influenced by alcohol.

3.28 There is some evidence from studies in China linking dietary nitrosamines and oesophageal cancer. However, no conclusions on the importance of nitrosamine exposure on oesophageal cancer in the UK could be drawn from these studies.

3.29 The Committee agreed with the overall conclusions in the DH paper, namely that lifestyle factors are likely to predominate in the aetiology of both types of oesophageal cancer. The available evidence did not clearly suggest any potential occupational or environmental exposure to chemicals that should be further considered at this point in time.

3.30 The Committee felt that a further review of the dose-response for alcohol and oesophageal cancer and a consideration of mechanism was warranted at this point in time.

Olfactory neuroblastoma and dentists/dental nurses.

3.31 Olfactory neuroblastoma (ONB. The alternative name is esthesioneuroepithelioma) is estimated to comprise approximately 3% of nasal neoplasms excluding benign polyps. The incidence in North America/Western Europe is estimated to be approximately 0.15/million/year. There is no evidence for a sex difference in incidence. It occurs in all ages (but is rare below 10 years and over 70 years). It has been reported to have bimodal incidence, with peaks in the 2nd -3rd decade and later in the 6th and 7th decades of life. It has also been estimated there have only been 950 cases cited in the scientific literature from 1924, when ONB was first cited in the literature, up to 1997. Thus the available evidence suggests that ONB is a very rare tumour.

3.32 ONB is described as a neuroectodermal neoplasm showing predominantly neural features. The most common symptoms in patients presenting with ONB are nasal obstruction (93%), epistaxis (55%) and rhinorrhea (30%). Other symptoms such as headache and anosmia occur at an incidence of below 10%. Diagnoses is based on clinical presentation, CT/MRI* screening and histology with the need for a battery of immunohistochemical stains to differentiate from other closely related head and neck cancers.

3.33 The Committee heard presentation from the Institute of Laryngology and Otolaryngology, London, on details of four individuals with ONB, two of whom had worked as dentists, and two who had been employed as dental nurses. Members heard that two pathologists had independently verified the diagnoses. Full details of these case reports had been submitted to a peer reviewed journal.

3.34 The Committee reviewed the available pathology literature and agreed that it was highly improbable that the researchers investigating wood workers would have misdiagnosed ONB as adenocarcinoma of the sinuses. The Committee considered available information on potential chemical exposures of dentists/dental nurses (eg to metallic mercury, oil of cloves (principle ingredient eugenol) and

* Computerised Topography/Magnetic Resonance Imaging

methymethacrylate). It was agreed that there was no evidence to associate exposure to these chemicals with ONB. The Committee considered that the first priority for further work would be to consider additional epidemiological investigations to confirm the finding reported by the Institute of Laryngology and Otolaryngology. This might include evaluation of case-reports of ONB from other countries or detailed evaluation of information held by centres of excellence (for head and neck tumours) and pathology departments from the UK, Europe and elsewhere.

3.35 A full statement is included at the end of this report.

Organochlorine insecticides and breast cancer

3.36 Organochlorine insecticides (OCIs) are a group of synthetic chemicals that were widely used in agriculture (and for the control of malaria) during the 1940s up until the 1960s. They were commonly used because they were very effective and were also relatively cheap. However, following evidence that they persist in the environment and in humans, concern about their use increased and they were subsequently withdrawn from use. Currently there are no approved pesticide formulations in the UK that contain OCIs.

3.37 People may be exposed to OCIs as environmental contaminants in their diet. In 1995, the Committee was asked to review studies where humans were exposed to OCIs to advise whether it was possible that environmental exposure to OCIs could be linked to the development of breast cancer in women.

3.38 Breast cancer is a very complex disease and the risk factors are well documented. They include the age at first birth, menarche and menopause, as well as obesity, parity and use of oral contraceptives and hormone replacement. A common feature associated with these various risk factors is the fact that they result in increased amounts of the female sex hormone oestrogen in the body. In women, oestrogen is normally secreted by the ovary and is responsible for producing typical female sexual characteristics. Some synthetic chemicals, including OCIs, may have a very weak ability to act like oestrogens in the body i.e. have 'oestrogen-like effects'.

3.39 Therefore in 1995 (and again in 1999) the Committee was asked to consider evidence that suggested exposure to certain OCIs i.e. DDT, dieldrin, β-HCH and lindane, might be associated to breast cancer.

3.40 To help determine whether OCIs could possibly be involved in breast cancer the following areas must be considered:

a) Does the chemical have oestrogen-like effects in animals?

b) How does the oestrogen-like effects of OCIs compare to other chemicals with these effects?

c) Does the presence of more than one OCI in a mixture change the way each component behaves?

d) Do OCIs actually persist in breast tissue?

3.41 The OCIs reviewed here had at most a very weak ability to act like oestrogen in the body, although the majority had no oestrogen-like effects. Even if added together these chemicals would still be very weak compared to the use of oral contraceptives, hormone replacement therapy (HRT) or flavenoids in food.

3.42 Furthermore, from the available studies the COC concluded that there is currently no evidence to support the view that OCIs can alter the behaviour of other OCIs at the levels humans are exposed to environmentally.

3.43 One way in which OCIs are thought to contribute to the development of breast cancer is by their capacity to accumulate in fatty (adipose) tissue. Under these circumstances the breast receives a continuous supply of oestrogen-like substances over a prolonged period. Various studies conducted across the UK, Europe and USA measured the concentrations of OCIs in human adipose tissue or breast milk. Upon reviewing data published by the UK Pesticides Residues Committee (PRC) collected over 37 years since the 1960s, the levels of OCIs in human tissue are decreasing.

3.44 Upon reviewing studies of humans exposed to OCIs, there is currently no convincing evidence that OCIs are associated with the development of breast cancer.

3.45 The Committee reached a number of specific conclusions regarding the individual chemicals under review, which are tabulated below for ease of reference.

Conclusions on the individual chemicals considered in the 2003/4 review

OCI	Does the chemical have oestrogen-like effects in animals?	Are the levels detected in human tissue significant?	What is the relationship between human exposure to particular OCI and breast cancer?	Are people who are exposed to environmental levels of a particular OCI at increased risk of developing breast cancer?
DDT	Yes, although its effects are very weak.	Levels of DDT are known to be declining.	There is no evidence for link.	No
Dieldrin	No.	Levels of dieldrin are known to be declining.	Overall there is Insufficient information to draw any conclusions.	No definite conclusions drawn. To be kept under review.
βHCH	Yes, although its effects are very weak.	Levels of HCH are known to be declining.	Overall there is no evidence for a link.	No.
Lindane	No.	No.	Overall there is insufficient information to draw any conclusions.	No.

Ontario College of Family Physicians: Report on pesticides

3.46 The Advisory Committee on Pesticides asked for advice from COC epidemiologists on the evaluation of this report. A letter cleared by the chairman explaining COC epidemiologists views was forwarded to the ACP secretariat.

Malachite green/Leucomalachite green

3.47 Malachite green (MG) is a cationic triphenylmethane dyestuff used in a number of industries including fish farming. Its use in fish for human consumption was banned in the EU in June 2002 but residues continue to be found in fish. The Food Standards Agency had asked for a review from the COT in 1999. The COM provided advice to the COT on the mutagenicity of malachite green and its lipophilic metabolite leucomalachite green (LMG) at that time. The COM had provided further advice in 2003 on preliminary data from *in-vivo* mutagenicity studies.

3.48 The COM had now provided up to date advice on the mutagenicity of MG and LMG. The COM had concluded that malachite green and leucomalachite green should be regarded as *in-vivo* mutagens (see section 2. of the COM annual report).

3.49 The COC considered the results of the NTP carcinogenicity studies on MG and LMG in June 2004. They noted that prior to the publication of the NTP bioassay data on MG and LMG there had been no data available to make any meaningful assessment of the carcinogenicity of these compounds.

Conclusions regarding carcinogenicity of malachite green

i) There was equivocal evidence of carcinogenicity in female F344 rats based on an increase in thyroid gland tumours (adenoma or carcinoma combined) hepatocellular adenomas and mammary gland carcinomas.

ii) There was no evidence of carcinogenic activity in female B6C3F$_1$ mice.

iii) Overall there was no convincing evidence for any carcinogenic effect with malachite green in these studies.

Carcinogenicity of leucomalachite green

i) There was evidence of carcinogenic activity in female B6C3F$_1$ mice based on an increase in hepatocellular adenoma or carcinoma combined.

ii) There was equivocal evidence of carcinogenic activity in male F344 rats based on an increase in interstitial cell adenoma of the testes and the occurrence of thyroid gland follicular cell adenoma or carcinoma (combined).

iii) There was equivocal evidence of carcinogenic activity in female F344 rats based on an increased incidence of hepatocellular adenoma or carcinoma (combined).

3.50 The COC considered the possible mechanisms by which LMG induced tumours in the liver of the female mice. It was noted that the overall tumour profile was not that which would be expected of a genotoxic carcinogen, with activity being limited to effects in the liver of the female mouse; furthermore this was mainly due to an increase in adenomas. However it was also noted that there was no evidence from the NTP studies to support any non-genotoxic mechanism. In view of this, and taking into account the views of the COM, the Committee agreed that it was not possible to discount a genotoxic mechanism for the induction of the liver tumours in female mice and it would therefore be prudent to regard LMG as a genotoxic carcinogen.

3.51 A full statement is included at the end of the COM section of this annual report.

Polycyclic aromatic hydrocarbons in air pollution

3.52 Polycyclic aromatic hydrocarbons (PAHs) are a large class of organic compounds that are present as pollutants in air, food and drinking water. PAHs are formed by incomplete combustion of organic matter. The main sources of PAHs are industrial processes (e.g. aluminium production, coal gasification, coke production and iron and steel founding), road traffic emissions and domestic fuel combustion (WHO, 1998). Other sources include natural fires and open agricultural burning, wood treatment and natural processes such as carbonisation. Cigarette smoke is also a major source of PAHs for individual

exposure. In food, PAHs may be formed during processing and domestic food preparation. Some complex mixtures containing PAHs, such as coal tar pitch and tobacco smoke, are considered by the International Agency for Research on Cancer (IARC) to be known carcinogens in humans (i.e. group 1) and a number of individual PAHs are considered to be probably (Group 2A) or possibly (Group 2B) carcinogenic to humans.

3.53 The Committee had been asked in 2003 to evaluate the relative carcinogenic potency of dibenzo(a,l)pyrene compared to benzo(a)pyrene The COC had agreed 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 polycyclic aromatic hydrocarbons in air pollution.

3.54 The COC agreed a 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. The DH Toxicology Unit drafted a paper which presented information on possible biomonitoring approaches for evaluating the potential contribution of high potency PAHs to air pollution related lung cancer. It had been suggested that data from biomonitoring studies might aid in the evaluation of which PAHs were more likely to pose the greatest risk of carcinogenicity from air pollution. The approach utilised the COC agreed position that DNA adducts may serve as a useful approach to ranking PAHs.

3.55 Several occupational and environmental PAH biomonitoring studies were reviewed, with particular focus on identifying appropriate exposure groups, study design, sample tissue, in particular the use of nasal tissues, and biomarkers used in each study. A proposal was developed which used a novel biomonitoring approach to evaluate exposure, uptake and the role of high potency PAHs in air pollution-related lung cancer. This is based upon an occupational study examining specific DNA adducts for DBA and DB[a,l]P in nasal cells to evaluate the extent to which these high potency PAHs might contribute to the increased risk of developing lung cancer from air pollution. A paper describing a proposed biomonitoring approach was submitted to a peer reviewed journal and has recently been accepted for publication.

Prostate cancer

3.56 Prostate cancer is the most common cancer in men in the UK, with over 24,700 new cases a year (2000 data). Prostate cancer is the second largest cause of death from cancer in the UK. There were 9,900 deaths reported in 2002 accounting for around 13% of cancer deaths in men. Around 70% of these deaths are in men aged over 70 years. The mortality rate for prostate cancer peaked in the early 1990s and has now fallen to 25 per 100,000 population at risk. The lifetime risk for being diagnosed with prostate cancer is 1 in 14. The cancer develops from cells within the prostate gland. The majority of prostate cancers are slow growing and many men are unaware that they have this cancer. However, a small number of prostate cancers grow more quickly and may spread to other parts of the body. Cancer Research UK reported a 57% increase in prostate cancer incidence in Great Britain between 1991 and 2000. The Committee was asked to review the available epidemiological and other research to identify if there were any potential chemical exposures which might be associated with prostate cancer.

3.57 The conclusions reached by COC are given below:

i) The increase in incidence of prostate cancer reported over the past 2-3 decades is largely accounted for by improved identification of cases due to increased numbers of individuals undergoing surgery for benign prostatic conditions and the use of Prostate Specific Antigen Screening.

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

iii) The information from the available epidemiological studies are consistent with the view that overall, there is no convincing evidence of an increased risk of prostate cancer in rubber workers as a whole.

iv) There is no convincing evidence to associate other occupations with prostate cancer.

v) There is no convincing evidence to associate occupational exposure to cadmium with cancer of the prostate. The possibility that cadmium might induce androgen imbalance and thus might potentially be associated with prostate cancer should be monitored and relevant new information considered in the future.

vi) The one available epidemiological study on dietary zinc supplementation and risk of prostate cancer dose found increased risk of prostate cancer at high levels of supplementation (>100 mg/day). Further epidemiology studies are unlikely to provide sufficient numbers of individuals regularly consuming high doses of supplements for a study to be undertaken in the UK. The Committee agreed that it could not identify a biologically plausible rationale as to why zinc should be associated with prostate cancer.

3.58 A full statement is included at the end of this report.

Reassessment of tobacco products

3.59 The Committees (COT/COC/COM) were asked to provide advice on the toxicological assessment of tobacco products with reference to the assessment of Potentially Reduced Exposure Products (PREPS) and in particular tobacco-based PREPS which are smoked. The Committees agreed that it was important to state that the ideal way forward to reduce risks and hazards of tobacco smoke was to encourage smokers to stop or people not to start in the first place and any attempt to reduce toxicity should not be allowed to detract from that. Members acknowledged that the primary remit of the Committees' discussions was to provide advice based on the information provided in the discussion papers.

3.60 The COC commented on the complexity of tobacco induced cancer and noted that the mechanism(s) and information on the chemical agents responsible for tobacco induced cancer in humans had not been fully elucidated. In addition members noted the importance of the interaction between chemical carcinogens and susceptibility factors regarding the pathogenesis of tobacco-induced cancer. The COC concluded there is no strategy which could be used to compare PREPS for carcinogenic potency and that the approaches used are not informative on the risk of tobacco induced carcinogenicity. The COC agreed that it was not possible to draw conclusions on the carcinogenic risk of tobacco-based PREPS on the available biomarker studies reviewed. The COC commented on the need to examine a wide range of biomarkers for carcinogenicity and their interaction with susceptibility factors.

3.61 A statement providing details of all the conclusions reached by COT/COC/COM is included in the COT section of this annual report.

Review of Committee Procedures

3.62 The Committee's publication scheme (prepared in accordance with Freedom of Information Act 2000) is available on the COM internet site (http://www.advisorybodies.doh.gov.uk/foi/publicationscheme.htm). The COM meetings are now held in open session. The procedures adopted by COC are equivalent to those used by COT. Details can be found on the COC internet site. (http://www.advisorybodies.doh.gov.uk/foi/open.htm)

Horizon scanning

3.63 The COC undertakes "horizon scanning" exercises at regular intervals to identify new and emerging issues which have the potential to impact on public health and which might require COC advice. The DH Toxicology Unit at Imperial college had drafted a discussion paper. Members discussed the following topics.

3.64 *Target organ mutagenesis and implications for carcinogen risk assessment*.

This topic was suggested by the recent consideration of malachite green and leucomalachite green. COM had agreed it would be useful to have a joint COC/COM symposium to provide guidance on how data from mutagenicity in target organs can be fed into the risk assessment process. Members agreed this was an important topic to follow-up in order to provide advice on the assessment of multi-site carcinogens.

3.65 *Use of transgenic animal models in carcinogen risk assessment.*

Members recalled the conclusions reached in 2002 by COC with regard to the proposals from ILSI regarding us of hemizygous p53 and Tg.AC and other mouse models to replace the conventional mouse long-term bioassay. Members agreed there was a value in developing specific transgenic animal models for mechanistic studies but overall considered this topic should be given low priority for further COC consideration.

3.66 *Risk assessment of non-genotoxic carcinogens.*

This subject was extensively reviewed during the preparation of the COC guidelines (see paragraphs 3.71-3.76 below of this Annual report). An update of the research which was funded by DH on investigation gap junction function for inclusion in possible screens for non-genotoxic carcinogenesis is provided. Members considered that further consideration of some worked examples of evaluation using the IPCS mode of action and the ILSI Human Relevancy Framework would be valuable for the Committee. It was noted that further developmental work which aimed to amalgamate these two approaches was being considered in international fora.

3.67 *Single exposure carcinogens.*

A short overview was provided regarding definitions of single and short duration exposures and the identification of single exposure carcinogens. Members agreed that this suggestion should be given high priority. Members also asked whether there was any evidence that non-genotoxic carcinogens could induce tumours over a short duration of exposure.

3.68 *Potential mechanisms of metal induced carcinogenesis*.

A very short overview of the literature had been provided. Members agreed that the research initiatives would be valuable with regard to elucidating the mechanisms of metal-induced carcinogenesis but considered overall that further work on this subject was not merited at this point in time.

3.69 *Epidemiology.*

Members agreed to take forward the review of alcohol consumption and oesophageal cancer but asked the secretariat to undertake some initial work to define the key outcomes of the review.

3.70 *Nanotechnology.*

COM considered it would be worthwhile undertaking a review of this subject. A similar short overview section had been provided with regard to carcinogenicity. Members agreed that this was a potentially important and also interesting area of work. It was agreed that COC would be interested to see papers on this topic in the future.

Test Strategies and Evaluation

COC guidance on a strategy for risk assessment of carcinogens

3.71 The COC first published guidelines for the evaluation of chemicals for carcinogenicity in 1982. These dealt in the main with the design, conduct and interpretation of long-term animal bioassays and provided guidance to the relevant government departments and agencies on best practice for testing at that time. The need for guidelines to be periodically updated, to reflect advances in development and validation of methods, was recognised and revised guidelines were published in 1991, which addressed the evaluation of chemicals as potential carcinogens. The revised strategy published during 2004 concentrated on one section of the aforementioned 1991 guidelines, namely the risk assessment of chemical carcinogens, with reference to new approaches such as 'minimum risk levels'. However, the detailed approaches to the evaluation of epidemiological studies used in the risk assessment of carcinogens are to be considered later in a separate document.

3.72 The Committee on Carcinogenicity evaluates carcinogenicity data on chemicals on a case-by-case basis, taking into account the weight of all the available evidence. The range of data considered may differ with circumstances, for instance, it will not always be possible to obtain epidemiological data and each assessment will be considered on its own merits. It is not possible to provide a universally applicable list of data that will be needed for a carcinogenic assessment. However, it is hoped that this document will provide some guidance on a suitable strategy that could be adopted.

3.73 The Committee recommends a four stage evaluation strategy for the risk assessment process of carcinogenic hazard. Initial identification of a carcinogenic hazard at stage 1 should be based upon a review of the toxicity data, the results of toxicity testing, and any knowledge of effects on human health. The Committee considers it essential to determine whether carcinogens act via a genotoxic or non-genotoxic mechanism, therefore the Committee fully endorse the strategy published by the Committee on Mutagenicity (http://www.doh.gov.uk/com/guidance.pdf). Hazard characterisation (stage 2) should determine the dose-response relationship from epidemiological or animal data. During this stage it is important that factors such as interspecies variation in susceptibility, and information on mode of action are considered. Exposure assessment (stage 3) should estimate probable human exposure, routes of entry and levels of potential exposure taking into account the limitations of exposure models. The final stage (stage 4) should characterise the carcinogenic risk by summarising the previous stages and developing appropriate approaches to genotoxic and non-genotoxic carcinogens.

3.74 If a putative carcinogen is found to be non-genotoxic, the Committee recommends the adoption of a threshold approach. Thus a method based on the identification of a NOAEL and the use of uncertainty factors is appropriate, as is used in other areas of chemical risk assessment.

3.75 If a putative carcinogen is found to be potentially genotoxic, the Committee recommends a non-threshold approach for risk assessment. The assumption of no threshold, together with the practical difficulties of using low doses of human relevance in animal carcinogenicity studies, has led to the development of mathematical models that attempt to provide a 'best estimate' of the likely extrapolation of the dose-response curve below the lowest experimental data points. These models may give an impression of precision, which cannot be justified from the approximations and assumptions upon which they are based. Therefore, the Committee on Carcinogenicity recommend that the ALARP (as low as reasonable practicable) approach should be adopted. This can be supplemented in specific situations e.g. low exposures to contaminants or impurities by the setting of a minimum risk level. This approach should be based on expert judgement of available data. The use of potency estimates can be used to rank priorities for genotoxic carcinogens within a particular class of compounds (e.g. polycyclic aromatic hydrocarbons). The Committee agrees that it should always remain important to keep any exposure to genotoxic carcinogens as low as reasonably practicable (ALARP).

3.76 The Committee emphasises the importance of further research in order to refine the process of risk assessment. This includes the development of toxicological methods to refine extrapolation between animals and humans. In addition, biomarkers of effect need to be further investigated to aid in the extrapolation of low doses and exposure. Continued research on carcinogenic mechanisms with the ultimate aim of developing appropriate models for low dose extrapolation is also required.

3.76 A detailed guidance document can be obtained from the COC internet **site.** http://www.advisorybodies.doh.gov.uk/coc/guideline04.pdf

COT/COC/COM review of Toxicogenomics

3.77 The COT/COC/COM held a joint symposium on the use of genomics and proteomics in toxicology in October 2001. The Committees agreed to further consider toxicogenomics as part of the horizon scanning exercise initiated at the February 2004 COT meeting. It was noted that there was a considerable increase in the number of publications using toxicogenomic approaches. A number of discussion papers were subsequently prepared for the Committees which reviewed the available published literature. The data from 50 studies were considered during the review which also included available information from the HESI (Health and Environmental Sciences Institute of the International Life Sciences Institute (http://www.ilsi.org/)) collaborative scientific program on toxicogenomics. The current review considered information on use of metabonomics in toxicology for the first time. The COT requested a further paper and presentation on the use of statistics/bioinformatics in toxicogenomics. A presentation was given by Dr David Lovell (University of Surrey) to the COT at its meeting on the 7 September 2004.

[The Committees used the following definitions for the methods used in Toxicogenomics. Transcriptomics refers to gene expression as measured through cDNA or oligonucleotide or cRNA microarray based approaches, proteomics refers to determination of protein levels through gel or solid phase approaches and metabonomics refers to measurement of metabolites in tissues, plasma or urine.]

3.78 The COC reached the following conclusions after discussions held at its June 2004 meeting. The COC reached a number of general conclusions on toxicogenomic studies in experimental animals regarding dose-response evaluation, investigations of reversibility, statistical handling of data and bioinformatic developments which are consistent with those reached by COT. COC members also commented on the need for "pathway mapping" for the identification of toxicologically relevant gene changes. The COC agreed with the COM conclusion that a gene expression pattern had been reported in studies in rodents using genotoxic hepatocarcinogens.

a) A number of studies in rodents using model carcinogens had reported on toxicogenomic approaches to investigate the process leading to neoplasia from initiation to tumour formation and growth. However no conclusions could be drawn from these limited studies. It was noted from the preliminary evidence considered by the committee that it was difficult to distinguish between chemical induced changes in gene expression from those occurring as a result of the neoplastic process.

b) It was not possible in studies in animals using model non-genotoxic carcinogens to identify common gene expression changes which might be of value in developing an approach to early detection of non-genotoxic carcinogen. The available study identified more distinct than common changes in studies in mice using two model non-genotoxic hepatocarcinogens.

c) Potentially valuable information on mechanisms of carcinogenesis could be derived from experiments designed to investigate particular specific mechanisms. Some preliminary information on non-genotoxic liver carcinogenesis in mice was available.

d) Comparison of gene expression changes in stomach tumours in rodents induced by a model genotoxic carcinogen had shown similarities with gene expression profiles from human stomach cancers. These preliminary data could be used for hypothesis generation regarding the aetiology of stomach cancer. However caution was required in interpreting the studies considered by the committee as the range of toxicological effects in animals given relatively high doses of model carcinogens did not reflect the likely effects in humans exposed to much lower doses in the environment.

3.79 A statement providing details of all conclusions reached by COT/COC/COM is included in the COT section of this annual report.

Ongoing reviews

Childhood cancer

3.80 A preliminary discussion overview paper had been drafted as the result of a horizon scanning exercise for 2003 to evaluate the published literature on the possible increased incidence of childhood cancer in the UK and to address whether evidence from epidemiological studies suggests a possible chemical aetiology. Based on the available epidemiological data, four childhood tumours were identified as being relevant for further consideration i.e. CNS tumours; acute lymphocytic leukaemia (ALL); germ cell tumours (GCT) and neuroblastomas (NBT). The review would also consider the possible role of transplacental carcinogens, paternal exposure and the significance of animal models in the risk assessment of childhood cancer. The Committee has also recommended that a review of the epidemiology literature on environmental exposure and childhood leukaemia with residence near to petrol stations and garages and roads should be undertaken.

Joint Symposium with COM on use of target organ mutagenicity in carcinogen risk assessment

3.81 The COC and COM have agreed to hold a joint symposium on this subject on the 9 June 2005 at the Department of Health, Skipton House, Elephant and Castle. It is hoped that a peer reviewed publication would result from this meeting.

Biobank

3.82 COC has corresponded with the Biobank research team regarding approaches to exposure evaluation. It is anticipated that there would additional exchanges of views and collaboration in the future.

Statements

Alcohol and Breast Cancer

Breast cancer risk and exposure to organochlorine insecticides: consideration of the epidemiology data on dieldrin, DDT and certain hexachlorocyclohexane isomers

Carcinogenicity of 1,3-dichloropropan-2-ol (1,3-DCP) and 2,3-dichloropropan-1-ol (2,3-DCP)

Olfactory Neuroblastoma: Evidence For An Elevated Incidence Among Dentists And Dental Nurses?

Prostate cancer

The Joint statements with COT/COM on Toxicogenomics and reassessment of tobacco products are included in the COT section of this annual report.

The joint statement with COM on malachite green and leucomalachite green is included in the COM section of this annual report.

Consumption of alcoholic beverages and risk of breast cancer in women: consideration of significance to public health

Introduction

Breast Cancer in U.K

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 41,000 cases (2000 data) registered and 13,000 deaths (2001 data) in the U.K[1,2]. The most clearly established risk factors for breast cancer are reproductive[3] (e.g. age at first full term pregnancy, parity, age at menarche and menopause). Other known risk factors for breast cancer include age, ethnic group, family history of the disease, history of benign breast disease, socioeconomic status, use of oral contraceptives and hormone replacement therapy and, in postmenopausal breast cancer, obesity. The reason for the interest in the association between alcohol and breast cancer is that even a small risk, if causally associated with alcohol, may have serious public health implications. In addition, drinking alcoholic beverages maybe one of the few risk factors for breast cancer where intervention might offer some scope for prevention. 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[4] and by this Committee for the InterDepartmental Working Group on Alcohol in 1995[5] but neither group was able to advise that there is a causal association between drinking alcoholic beverages and breast cancer.

2. A further review was undertaken by the COC in 1999 (http://www.doh.gov.uk/alcbrst.htm)[6]. The Committee concluded there was sufficient evidence to associate drinking alcoholic beverages with an increased risk of breast cancer but agreed that a systematic review of all the epidemiology studies and further evaluation of potential mechanisms were required before definite conclusions could be reached. The conclusions reached following the 1999 review are summarised in paragraphs 11-14 below. The Department of Health commissioned a systematic review of the epidemiology from the Department of Epidemiology and Public Health at Imperial College, London. The Committee agreed to undertake a further review of all the available information when the report of the systematic review became available. The Committee was also aware that additional relevant data on alcohol consumption and risk of breast cancer was expected from the Oxford Collaborative Group on Hormonal Factors in Breast Cancer and should also be reviewed when available. The draft report of the systematic review undertaken by Imperial College and a copy of the published report by the Oxford Collaborative Group on Hormonal Factors[7] both became available in November 2002 and thus a further review was initiated.

Consumption of alcoholic beverages in the U.K.

3. Estimates of the consumption of alcoholic beverages are generally reported in terms of units of alcohol or grams of ethanol consumed per day. One unit of alcohol is approximately equivalent to half a pint of normal strength beer, lager, or cider, a single measure of spirits, one small glass of ordinary strength (9% by volume) wine or one small glass of port, sherry or other fortified wine. This is approximately equivalent to 8 grams by weight or 1 centilitre (10 ml) by volume of pure alcohol (ethanol)[8]. One research publication has reported that the average amount of ethanol in a standard drink in the U.K ranges between 8-10 grams with an average of 9.5 grams[9]. This later figure has been used by the Imperial College research group in its systematic review.

4. The Department of Health for England advises that women should drink no more than 2-3 units of alcohol per day (i.e. 16 g – 24g ethanol/day). This daily benchmark applies whether individuals drink every day, once or twice a week, or occasionally. This guidance on sensible drinking was derived from an Interdepartmental Working Group (IDWG) report published in 1995. The IDWG considered all of the evidence relating to potential health benefits to women from drinking 1-2 units per day and the evidence for progressive health risk from consistently drinking 3 or more units per day[10]. Prior to 1995 the sensible drinking message had been expressed in terms of a weekly intake of alcohol units (i.e. less than 14 units/week was unlikely to damage a woman's health). The effect of the change in advice from a weekly limit to a daily benchmark has only recently been investigated in routine surveys which evaluate drinking patterns among women (see paragraph 6 below).

5. There is a lot of information on the consumption of alcoholic beverages regularly obtained as part of the General Household Survey (GHS). (http://www.statistics.gov.uk/ssd/surveys/general_household_survey.asp) and the Health Survey for England (HSfE) (http://www.official-documents.co.uk/document/deps/doh/survey02/summ03.htm) Detailed information can be obtained from these sources and therefore only a very brief review of the main conclusions on drinking patterns amongst women in the U.K. is presented below. (No comment on regional or socio-economic influences on drinking patterns has been included in this statement.) The GHS is a face-to-face interview survey conducted with a sample of 13,200 households across Great Britain and gathers a large amount of information on social, economic and health-related topics. The GHS has reported annually since 1971 (with breaks in 1997, 1999 and 2000 when the survey was re-developed) The HSfE is an annual survey which has provided information on consumption of alcoholic beverages since 1991. Both surveys have been adapted in recent years to take into account the change to expressing the sensible drinking message in terms of daily benchmark intake of alcohol units. The Committee also had access to an evaluation of the HfSE undertaken by Dr Paola Primatesta and colleagues from University College London[11].

6. The available information from these surveys provides similar findings. The average consumption of alcoholic beverages (expressed either as weekly or, where available as daily intakes) in women of all ages has increased over the last decade. Thus the weekly average intake from the HSfE was 6.2 units/week in 1993, 7.1 units/week in 1998 and 8.4 units/week in 2002. This trend was most noticeable in women aged 16-24 years where consumption rose from about 8 units/week in 1993/4 to almost 12 in 2001 and 13.3 units/week in 2002. The GHS reported a similar finding for women aged 16-24 across Great Britain with average weekly consumption reported to be 7.3 units in 1992 and 14.1 units in 2002. Primatesta and colleagues reported a strong correlation between mean or median intake and proportion of women exceeding the Sensible Drinking Limit (expressed as 14 units/week). A marked increase in women aged 16-24 years reporting consumption in excess of 14 units/week is noticeable from 1992 to 2002. The GHS reports this increase to be from 17% to 33%. The HSfE reported similar findings (from 20% in 1992 to 33% in 2002). Information on daily consumption of alcoholic beverages collected from 1998 in the GHS documented that the proportion of women aged 16-24 years who had drunk 6 or more units on at least one day in the previous week rose from 24% to 28% between 1998 and 2002. The equivalent proportion among women aged 25-44 years of age was 11% in 1998 rising to 14% in 2001, and 13% in 2002.

7. Thus, overall, the evidence supports the view that consumption of alcoholic beverages among women is increasing with the predominant increase in young women aged 16-24. The evidence suggests that increased consumption among women aged 45 years or more is spread evenly across the week whilst the increase in intakes in younger women, and particularly those aged 16-24 years predominantly occurs on one or two days per week. The GHS survey authors did note that there were too few data on daily consumption patterns to reach any conclusions about long term trends in daily consumption of alcoholic beverages.

Background to COC consideration

COC Statement for the Interdepartmental Working Group on Alcohol (1995)

8. 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[10] 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. 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[5].

9. 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[12-18], 17 new case control studies[19-35] and two systematic reviews[36,37]. In addition a number of reviews of the available information were also considered[38-40]. 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 systematic reviews (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[5].

10. 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"[5]. 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[10].

COC review of information published between 1995-1999
http://www.advisorybodies.doh.gov.uk/coc/index.htm*).*

11. The Committee considered review papers prepared by the DH Toxicology Unit at Imperial College on the published epidemiology studies and investigations into potential mechanisms by which drinking alcoholic beverages could increase the risk of breast cancer[41-43]. The epidemiological evidence included three prospective studies[44-46] and a further 22 case-control studies[47-68]. The results were in accordance with the conclusions reached in the 1995 review in that most studies reported a small association between drinking alcoholic beverages and increased risk of breast cancer with evidence for a dose-response in the majority of studies examined. A pooled analysis of six prospective studies also reported a significant trend between increasing alcohol consumption and increased risk of breast cancer[69]. The Committee agreed that no conclusions on the influence of menopausal status, type of beverage, frequency of drinking could be reached from the available information.

12. The DH Toxicology Unit paper[42] identified sparse evidence for a number of potential mechanisms by which alcohol could induce breast cancer including enhanced metabolism of carcinogens[70-72], increased cellular permeability to potential carcinogens[73], impaired immune responsiveness[74], and abnormal differentiation of mammary tissue[75]. 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[76]. 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[77,78] and postmenopausal[79-85] women. Some recent research provided evidence that drinking alcoholic beverages affected serum oestradiol concentrations in premenopausal women using oral contraceptives[86]. The Committee considered that the data on effects of drinking alcohol on hormones were complex and asked for a further tabulation of data on plasma and urinary sex hormones following consumption of alcohol. Overall the available data from the 1999 review suggested a plausible mechanistic link between consumption of alcohol and breast cancer involving effects 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.

13. The Committee assessed all of the available data using the Bradford-Hill criteria as a guide to consideration of causality. The Committee concluded there was considerable evidence to support an association between drinking alcoholic beverages and risk of breast cancer but the magnitude of the association was small (i.e. the relative risk is modest and, even for heavy drinkers, in most studies does not exceed 3 (i.e. 3 times that of non-drinkers). The Committee also considered that 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 (i.e. there are weak associations with a number of other risk factors) of breast cancer are the main reasons for the difficulty in reaching a definite conclusion. The association could be due to systematic biases in the studies or to confounding by other risk factors. The Committee concluded that a rigorous systematic review (including appropriate meta-analyses) was needed in an attempt to identify and evaluate potential biases, confounding and heterogeneity so that a fuller assessment of causality and the magnitude of the risk associated with drinking alcoholic beverages could be made. It would also be important for any further analyses to provide an estimate of the Population-Attributable Risk (PAR). A systematic review was subsequently commissioned with the Department of Epidemiology and Public Health, Imperial College London.

14. The Committee had also asked its sister committee, the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) to update its 1995 review on the evidence regarding the potential for alcoholic beverages to induce mutagenicity *in vivo*. The COM considered the available evidence up to November 2000. The COM reaffirmed its 1995 conclusion that consumption of alcoholic beverages does not present any significant concern with respect to mutagenic potential. The statement can be found on the COM internet site. (http://www.advisorybodies.doh.gov.uk/com/index.htm)

Introduction to current review

15. An initial draft report of the systematic review was considered at the November 2002 COC meeting. Further drafts were considered at meetings during 2003. The Department of Health also commissioned a further review of evidence on possible mechanisms by which drinking alcoholic beverages could induce breast cancer from the DH Toxicology Unit at Imperial College. The Committee also received a copy of the published paper from the Oxford Collaborative Group on Hormonal Factors in Breast Cancer just prior to its November 2002 meeting. The Committee agreed that it would be important to compare the approaches used and results reported in the commissioned systematic review study by the Imperial College group with results published by the Oxford Collaborative Group as this might help it to draw conclusions about causality. The Committee also reviewed additional epidemiological studies on the association between drinking alcohol and breast cancer retrieved up to June 2003. The primary objectives of the current COC review were;

    a) To evaluate the report of the systematic review undertaken by the Department of Epidemiology and Public Health, Imperial College and the investigations undertaken by the Oxford Collaborative Group study and to consider whether the association between drinking alcoholic beverages and increased risk of breast cancer can be explained by bias or confounding and the extent of heterogeneity in the reported association.

    b) To review the available evidence for a mechanistic basis for the observed association between drinking alcoholic beverages and breast cancer.

    c) To assess whether the association between drinking alcoholic beverages and risk of breast cancer can be considered causal.

    d) To evaluate quantitative estimates for population attributable risk (PAR).

Review of new information

Uncertainties in evaluation

16. Potential uncertainties that might affect the interpretation of results obtained in the two systematic reviews considered by the Committee (i.e from Imperial College and the Oxford Collaborative Group) could include misclassification of cases and controls, misclassification of exposure, misreporting of alcohol consumption, the evaluation of dose-response, and the evaluation of potential effects of confounding factors for breast cancer on estimated risks associated with drinking alcohol. The Committee considered that the different approaches used by the two groups complemented each other. Thus the evaluation of individual subject level data by the Oxford group would allow for a more consistent classification of exposure and adjustment for confounding factors. The evaluation of study quality by the Imperial group would aid in the assessment of the sensitivity of findings to study design.

Systematic review undertaken by Department of Public Health and Epidemiology[87-89] (Draft reports reviewed at November 2002 and meetings during 2003). Finalised report submitted to peer reviewed journal and considered by COC at June 2004 meeting[120].

17. The objectives of the systematic review and subsequent meta-analyses undertaken by Imperial College were to determine the magnitude of any association between drinking alcohol and primary breast cancer, to explore the dose-response relationship, to examine whether any association was related to specific beverages or to consumption of all alcoholic beverages, to explore possible heterogeneity, bias and confounding and to estimate the population attributable risk. All publications, in any language, between January 1st 1966 and 31st December 2003 were eligible for inclusion. The results from studies were examined after data on study design and methods had been abstracted and reviewed independently by two members of the team. Duplicate reports of the same study were carefully evaluated to include only a single and the most complete dataset. A simple scoring scheme was used: suboptimal design (1), good design but insufficient control for confounding (2), good design and adequate control of confounding (3). Meta-analyses were undertaken for least, at-least-age, and multivariate-adjusted odds ratios (where possible) separately for all reports, those scoring 2 or 3 and, finally those scoring 3. Dose response modelling used standardised exposures (converted to grams/day (g/day)), the mid-point estimates for consumption, and a linear model with a variable intercept and meta-analysis of dose-response using a random effects model. The authors assumed that an average drink in the U.K. contained approximately 9.5g ethanol and used this as a conversion factor in reporting their analysis of risk of breast cancer associated with drinking alcoholic beverages.

18. A total of 298 papers were identified. Data from 111 were considered appropriate for inclusion in the review. These related to 98 unique studies. The number of studies that provided data that could be included in the ever versus never analysis was 89 and was based on 75,728 cases. Using all these studies and least adjusted odds ratios, a statistically significant risk associated with drinking alcohol of 1.11 (95% CI 1.06-1.17) was reported. Combining least adjusted odds ratios estimates from studies scoring 2 or 3, the risk associated with drinking was 1.12 (95% CI 1.06-1.18). The odds ratio for studies with a score of 3 and multivariate adjustment was 1.22 (95% CI 1.09-1.37). The use of a linear dose-response model with a variable intercept allowed for the presence of drinkers/exdrinkers in the referent group and also avoided the assumption that if a linear dose-response relationship existed then it would be linear through the origin. It was reported that when the adjusted dose-response slopes from studies of good design only (multivariate adjustment for confounders with a score of 3) were combined, the odds ratio was found to be 1.10 (95% CI 1.05-1.15) associated with drinking an extra 1g of ethanol (in alcoholic beverages) per day amongst drinkers. The Imperial research group reported that a woman drinking on average two drinks per day (assuming each drink contains 9.5 g ethanol) has a lifetime risk of breast cancer estimated to be 10% (95% CI 5-15%) higher than a woman who drinks an average of one drink per day. The relative risk can also be expressed in terms of units of alcohol consumed (where, as noted in paragraph 3 above each unit contains 8 g of ethanol). This is important since intakes in the U.K. are usually expressed in terms of unit of alcohol consumed. Thus a woman consuming on average two units per day has a lifetime risk of breast cancer estimated to be 8% (95%CI 4%-12%) higher than a woman who drinks on average one unit per day. There was no evidence for stronger or weaker associations with any particular type of beverage.

19. The Imperial research group found considerable unexplained statistical heterogeneity between the studies they reviewed. Thus meta regression with random effects was used to investigate heterogeneity. The following study characteristics were included: data collected before or after disease onset, hospital or community controls, pre and post menopausal participants and country of study population. It was noted that there was a significant difference in relative risk between case-control studies using hospital or community controls, but the association between drinking alcohol and breast cancer was still statistically significant in studies using either of these control groups. Otherwise none of the variables included in the meta regression significantly reduced heterogeneity between studies. Funnel plots were used to investigate the possibility of publication bias, and they did not indicate that this had been a problem. Bias and confounding could not be dismissed as an explanation of the results, but the study methods minimised their impact as far as possible.

20. A Population Attributable Risk (PAR) for the U.K had been calculated using Cancer Statistics for 1999 and information on drinking patterns derived from the Health Survey for England from 1993 and 1998. Assuming causality and that 1 unit of alcohol contains 8 g ethanol, the PAR calculated from the best quality studies was 6.0% (95% CI 3.2%-8.8%) (i.e the fraction of breast cancer cases that could be prevented if drinking was reduced to a very light level (i.e below 1 unit per week). Using 2000 cancer registration data for the U.K, this would suggest approximately 2430 cases each year (95% CI 1290-3560) could be prevented.

COC Comments on draft and final reports of systematic review undertaken by Imperial College

21. The Committee considered that the work had been thoroughly undertaken and was the largest and most comprehensive systematic review available.

22. The scoring system allowed examination of study quality and, further analyses had been undertaken to examine for bias and confounding. The Committee noted that the majority of analyses reported statistically significant positive associations. The investigators had acknowledged that the definition of non-drinker, use of mid point estimates of alcohol consumption and aggregate (study) data instead of individual data had limited the evaluation. Members noted there were limited data available on assessment of the influence of menopausal status and agreed no conclusions could be drawn on this aspect. The Committee agreed that the evaluation of dose-response was difficult, particularly at higher levels of drinker where there were comparatively fewer data available. Members accepted the rationale for adopting a linear model with a variable intercept.

23. It was noted that the available mechanistic data supported the possibility of a threshold for carcinogenesis. The Committee considered that the estimate of Population Attributable Risk (PAR) was potentially one of the most important outcomes of the systematic review with regard to presentation of the public health significance of the analyses. Members noted that there was no significant alteration in PAR when non-drinkers were excluded. The Committee concluded that the PAR estimate based on best studies and most adjusted model using intake data for England and cancer registration data for the UK represented an acceptable analysis. They recommended that the PAR estimate could be used in the consideration of policy options.

Publication by Oxford Collaborative Group on Hormonal Factors in Breast Cancer[7]. (Report reviewed at November 2002 meeting)

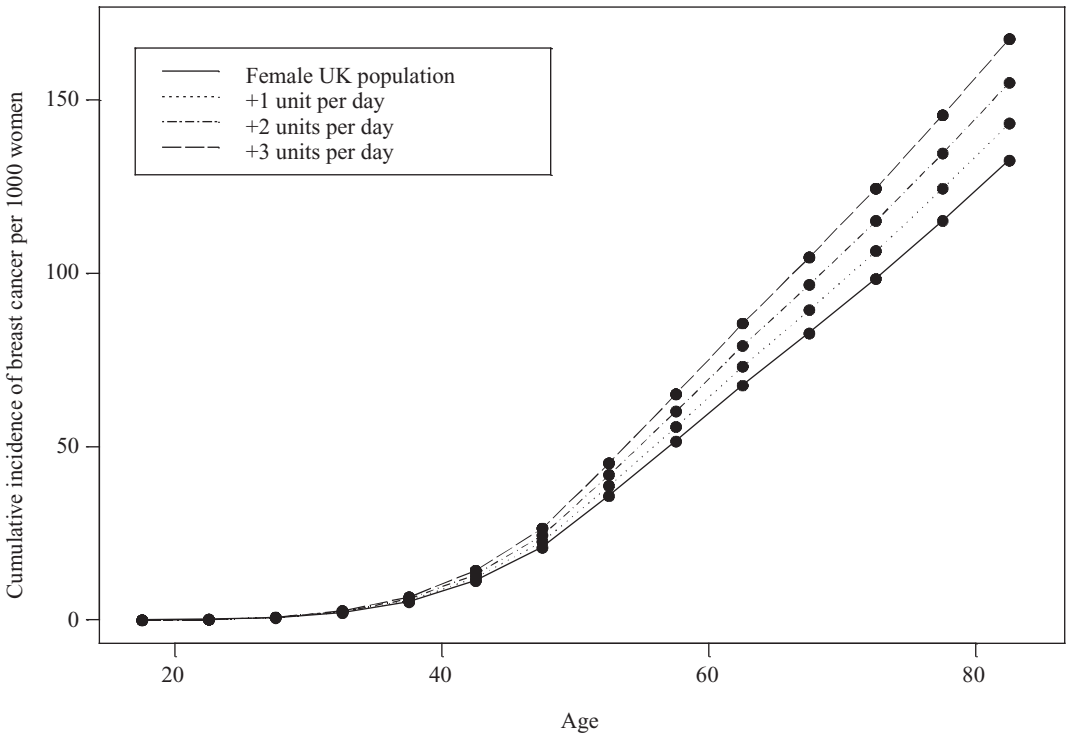
24. The Oxford Collaborative Group has collated individual subject data from epidemiology studies where the relationship between breast cancer and hormonal, reproductive and other factors (including alcohol consumption) had been investigated. Case-control studies were eligible if they included at least 100 women with incident invasive breast cancer and recorded appropriate information on the potential risk factors for breast cancer. Cohort studies were included using a nested case-control design, in which four controls were selected at random, matched on follow-up to age of diagnosis and, where appropriate broad geographical regions. There were 53 studies (two unpublished) that contributed data on alcohol and tobacco usage. There were a total of 58,515 cases where individual data were obtained and 95,067 controls. Relative risks of breast cancer were estimated after stratifying for age, study centre, parity, and where appropriate, women's age when their first child was born, and by tobacco use. A relative risk of breast cancer of 1.32 (95%CI 1.19-1.45) was reported for an intake of alcoholic beverages equivalent to 35-44 g ethanol per day (i.e. approximately 4-5 drinks/day) compared to non-drinkers. The relative risk of breast cancer increased by 7.1% (95% CI 5.5%-8.7%) for each additional 10 g/day intake of ethanol in alcoholic beverages. The authors estimated that approximately 4% of breast cancers in developed countries were attributable to drinking alcoholic beverages.

25. The Committee noted that the Oxford Collaborative Group had access to individual data from 58,515 women, including some from unpublished studies. They had been able to determine median intakes of alcohol. The dose response data reported suggested some evidence for a threshold below a median intake of 8 g/day. Overall it was felt that the Imperial College group had examined significantly more cases that the Oxford Collaborative group.

Discussion of Oxford Collaborative Group research and Imperial College review (March 2003 – June 2004 meetings)

26. The Committee noted the percentage of non-drinkers was 36% in the Oxford Collaborative study and 28.6% in the Imperial College report. The estimate of PAR reported by the Oxford Collaborative Group was 4 % compared to 6% by the Imperial research team. The Committee considered that this difference between the two studies was minor and probably resulted from different proportions of non-drinkers included in the respective calculations. Members considered that the approach used to determine cumulative incidence of breast cancer with age per 100 women at 2, 4 and 6 drinks per day was a useful way to present risks (see figure 5 of the Oxford Collaborative Group report[7]) and suggested the Imperial research group undertake a similar analysis based on their data. Taken together, the results of the two systematic reviews considered by the Committee (i.e. the Imperial research group report commissioned by the Committee and the published Oxford Collaborative Group paper) indicate that the association between drinking alcohol and risk of breast cancer is very unlikely to be due to chance.

27. Following the November 2003 meeting, the Imperial research group provided the figure given below which reports the cumulative incidence of breast cancer per 1000 women for each additional unit of alcohol drunk per day[120]. The solid curve shows the cumulative incidence for the female population in the U.K. (where the average consumption of alcohol is 1 unit per day). The dotted curves show the estimated cumulative incidence if women drank an extra 1,2, or 3 units per day, where a unit of alcohol contains 8 g ethanol. Studies included in the systematic review undertaken by Imperial College do permit an assessment of breast cancer in non-drinking women in the U.K.



28. The estimated cumulative incidence of breast cancer for women aged 60 and 80 assuming daily consumption of alcohol throughout the majority of a life has been tabulated below.

Cumulative Incidence per 1000 women

	Current consumption	+1 unit per day	+2 units per day	+3 units per day
Age 60	60	65	70	75
Age 80	125	134	145	157

Additional published epidemiology studies retrieved after November 2002

29. The Committee reviewed a number of additional epidemiological papers at the March 2003 meeting retrieved after the November 2002 meeting[90-96]. The Committee noted new evidence from the Nurses Health Study I cohort that self reported diagnosis of Benign Breast Disease (BBD) might potentially be a useful marker for breast cancer and noted the dose-response relationship between BBD and alcohol intake[93]. This association might be explored in further research. Members noted the recent studies of receptor status in the association between drinking alcohol and breast cancer and agreed no conclusions could be drawn from the conflicting data. Members commented on one small case-control study which suggested an elevated risk of breast cancer in African-American women who drank alcohol and noted the claim that there was increased mortality in African-American women following diagnosis of breast cancer which might be attributable to drinking alcohol or represent a particular susceptibility of African-American women[91]. The Committee asked for additional literature review work on this topic to be undertaken.

30. Some additional papers were submitted to the 26 June 2003 COC meeting[97-100]. The information available, which included a review of all relevant studies published up to April 2001 suggested that there is no association between drinking alcohol and increased mortality from breast cancer following diagnosis[101,102]. A further review of the claimed variation in risk of breast cancer between different ethnic groups revealed that any association is unlikely to be due to consumption of alcohol. It was noted that, for women, alcohol consumption by ethnic minority groups in the U.K is lower than the estimate for the whole population[103,104]. One small study found that heavy drinking of alcohol did not modify the risk of early onset breast cancer in young women[98]. Two studies reported on the potential role of genetic polymoprhisms of metabolising enzymes but the results suggested that any modifying effect on alcohol induced breast cancer was minimal[99,100].

Further paper from DH Toxicology Unit on mechanisms[105]

31. The DH Toxicology Unit noted in its paper that alcohol may not be carcinogenic to the breast *per se*, but may facilitate carcinogenesis through a variety of mechanisms. Several pathways have been proposed, including effects on the permeability of cell membranes in the breast, induced hepatic metabolism of carcinogens by ethanol-inducible enzymes, inhibition of DNA repair mechanisms, effects on hormone metabolism and interactions of alcohol with other host and environmental factors. The paper has been published on the COC internet site (http://www.doh.gov.uk/coc/index.htm)

32. The Committee was aided in its deliberations by expert advice from Professor H S Jacobs (Emeritus Professor of Reproductive Endocrinology, University College Medical School, London) who attended the November 2002 meeting of the COC. The DH Toxicology Unit report highlighted evidence to support the view that alcohol induced hyperinsulinaemia and increased Insulin-like Growth Factors (IGFs) which subsequently induced an increase in breast tissue density through increased cell division[105-108]. It was noted that there were additional studies to support an association between drinking alcohol and effects on oestrogen metabolism[109]. There were considerably less convincing data

for a number of suggestions such as alcohol induced suppression of melatonin excretion products and aromatisation of androgens to oestrogens. The Committee agreed that it would be appropriate to focus the review on the effects of alcohol on oestrogens, hyperinsulinaemia and effects on IGFs. The evidence supporting other proposed mechanisms was preliminary and no conclusions could be drawn.

33. Evidence to support the association of alcohol with increased oestrogen levels has been documented in a number of studies[110,111] not previously reviewed by COC. The Committee considered a cross sectional study by Verkassalo PK et al[112] and agreed that sufficient numbers of premenopausal (n= 636) and postmenopausal (n = 456) women had been included. The results were inconsistent with the data previously reviewed by the committee in 1999 and suggested an effect of cigarette smoking, but not drinking alcohol, on levels of oestrogens. These results were not consistent with the available epidemiological data on breast cancer. The COC reviewed a study by Dorgan JF et al[113] in postmenopausal women and agreed that a satisfactory crossover design had been used for this intervention study, although there were some reservations about potential compliance of study participants. It was noted that there was some evidence for a small increase in oestrone sulphate and dehydroepiandrosterone sulphate (DEHA sulphate) following the consumption of 15 g or 30 g ethanol/day over an eight week period. There was no effect on oestradiol levels (free or bound) in this study. Members agreed the data supported a small effect of drinking alcohol on adrenal output of hormones. This study suggested the effect of drinking alcohol on hormone levels was milder than that suggested by the cross sectional studies previously reviewed by the COC in 1999.

34. The Committee agreed that the weight of evidence available suggested that drinking alcohol produced a number of biochemical effects in the liver which resulted in changes to oestrogen metabolism and IGF levels which, over a prolonged period of time, i.e. decades, could induce breast cancer. Both of these suggested mechanisms would potentially have a threshold with regard to induction of breast cancer.

Consideration of Causality

35. The Committee had previously considered the available evidence in accordance with the Bradford-Hill criteria[114] during its review in 1999. The Committee agreed it would be appropriate to undertake a further review using these criteria as an aid in the assessment of the potential causation of breast cancer by drinking alcoholic beverages as there were new epidemiological and mechanistic data available. An assessment of the evidence has been tabulated below.

Criterion	Evidence regarding alcohol and breast cancer	Comments
Strength	Limited	The RR* in alcohol drinkers is modest and, even for heavy drinkers, in most studies rarely exceeds 3 (i.e. risk in drinkers is 3 times that of non-drinkers). However the RR for most other identified breast cancer risk factors also rarely exceed this value.
Consistency	Yes.	Literature largely points towards a small positive association but there is still unexplained heterogeneity. The systematic review by Longnecker MP[37] also reported significant heterogeneity. The pooled analysis of prospective studies published by Smith-Warner SA et al[69] found evidence of heterogeneity in results for pre menopausal women but not postmenopausal women Heterogeneity was only partly explained in the systematic review report from the Imperial College group[87-89]. However the approach used by the Oxford collaborative group which used individual data from the same cases, gave substantially similar results to the Imperial College group[7].
Specificity	Not relevant.	Cancer risk attributed to alcohol is not specific to breast cancer (e.g. prolonged alcohol consumption can induce cancers of the head and neck and oesophagus and liver).
Temporality	Yes	Association demonstrated in prospective studies where alcohol consumption can be studied before the occurrence of disease.
Biological gradient	Yes	There is evidence for a monotonic dose-response curve in the submitted systematic reviews from Imperial College and in the Oxford Collaborative group analysis.
Plausibility	Yes	Evidence for effect of alcohol consumption and elevations in blood levels of oestrogen metabolites documented[77-86,110-112]. Raised oestradiol is a risk factor for breast cancer.[5] The evidence therefore suggests a plausible mechanism Further studies have also suggested that an effect of drinking alcoholic beverages could affect liver biochemistry and hence could affect insulin levels and Insulin dependent Growth Factors (IGFs) and thus induce increased cell numbers in in breast tissue.
Coherence	Limited	Evidence for an increased risk of breast cancer in alcoholics[115] and for a relatively low rate of breast cancer incidence among populations abstaining from alcohol (e.g. Mormons)[116].
Experiment	Limited.	Evidence from one limited study where ICR mice were given ethanol via the drinking water (at 10% or 15%) for 25 months[117]. No evidence that alcohol is carcinogenic in a large number of carcinogenicity studies including some conducted to acceptable standards .5 Some evidence that alcohol affects breast tissue differentiation in animals[118] .
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)[5]. IGFs may be involved in development and progression of breast cancer[107,108].

*RR = Relative risk

36. There was evidence to satisfy most of the criteria. The Committee agreed that, overall, there was no consistent evidence that alcohol is carcinogenic from experimental studies in animals. The isolated finding of mammary tumours in ICR mice[117] given extremely high doses of ethanol in the drinking water in excess of the Maximum Tolerated Dose level had not been demonstrated in other studies in rats and mice which also used high doses of ethanol. The Committee was aware of some preliminary findings which suggested that *in-utero* exposure to ethanol in rats may be associated with increased mammary tumourigenesis, but agreed that no conclusions could be based on the preliminary results of this work[119]. The Committee considered that the criterion of specificity was not relevant to the assessment of breast cancer risk.

37. The Committee agreed that the available evidence indicated there is a modest association between drinking alcohol and increased risk of breast cancer which was consistently demonstrated. The small magnitude of the association between drinking alcoholic beverages and risk of breast cancer and the complex aetiology of breast cancer (i.e. there are weak associations with a number of other risk factors) are the main reasons for the difficulty in reaching a definite conclusion. However the most recent review of mechanisms provided evidence for a number of plausible mechanisms which focused on a potential effect of drinking alcohol on liver function. Overall, the Committee considered it was prudent to assume a causal association exists.

Significance to Public Health

38. The Committee agreed that if, for practical purposes, a causal association is assumed, then it was important to consider the magnitude of the association between drinking alcohol and breast cancer in terms of potential impact on public health. The Population Attributable Risk (PAR) is an estimate of the proportion of cancer cases which might be prevented if the levels of alcohol consumption were reduced to very light levels of drinking (below 1 unit/week). The calculation of PAR from epidemiological data requires information on the rate of breast cancer in the population, the estimate of relative risk, and data on intake of alcoholic beverages. There are some uncertainties in all of these and, hence in the estimate of PAR produced. The estimate of PAR from the Imperial College group which takes some of the uncertainties into account in the estimate of relative risk is 6.0% (95% CI 3.2%-8.8%). Based on the 2000 data for breast cancer registration in the U.K this would indicate that approximately 2430 cases/year (95% CI 1290-3560) may be attributable to drinking alcoholic beverages.

39. The estimate of PAR from the Oxford Collaborative Group was slightly lower. The Committee agreed that it would be prudent to base its evaluation on the calculations proposed by Imperial College since these were based on intake data for England and could be readily applied to the U.K. The Committee noted that the systematic review undertaken by the Imperial College group had reported inconclusive results for the effect of Hormone Replacement Therapy on risk of breast cancer associated with drinking alcohol. The Oxford Collaborative group had reported that stratification for use of oral contraceptives and HRT had not affected the estimation of risk of breast cancer associated with drinking of alcoholic beverages. The Committee felt that the potential for oral contraceptive and HRT use to influence the association between drinking alcohol and risk of breast cancer had not been researched in detail and recommended further epidemiological studies to assess any potential interactions.

40. The Committee agreed with the reported assessment of cumulative risk submitted by the Imperial College group and noted that lifetime drinking of an extra 3 units of alcohol per day above the national average for the female population of 1 unit/day would result in an additional 15 cases of breast cancer/1000 women at 60 years of age. An extra 32 cases of breast cancer/1000 women would occur at 80 years of age at this increased level of drinking. This needs to be compared to background rates of 60 cases of breast cancer/1000 women at 60 years of age and 125 cases of breast cancer/1000 women at 80 years of age where the average intake of alcohol is 1 unit per day. The Committee agreed there was a progressive increase in the risk of breast cancer associated with increasing amounts of alcoholic beverages drunk and duration of drinking. A review of the sensible drinking message would have to balance the increasing risk of breast cancer against the benefit attributed to drinking alcoholic beverages of reduced mortality due from coronary heart disease. Such an evaluation would be outside the terms of reference of the COC.

41. The Committee noted the evidence for increasing consumption of alcoholic beverages by women in the U.K, and particularly amongst younger women and was concerned that if the increased intake of alcoholic beverages reported amongst this group were maintained over most of their lifetime then it would result in an increase in the number of alcohol-related breast cancer cases. The surveys of alcohol consumption reported to the Committee specifically reported drinking in various age groups. The youngest age group studied included women aged 16-24 years. It was therefore important to raise awareness of the potential risks associated with drinking alcoholic beverages particularly amongst young women.

Conclusions of current review

42. The Committee reached the following conclusions based on an evaluation of all the data available up to the end of June 2003 and a finalised report of a systematic review undertaken by Imperial College submitted to the June 2004 COC meeting.

    a) Taken together, the results of the two systematic reviews considered by the Committee (i.e. the Imperial College research group report, commissioned by the Committee, and the published Oxford Collaborative Group paper) indicate that the association between drinking alcohol and risk of breast cancer is very unlikely to be due to chance **(paragraph 26)**.

    b) From the Imperial College review, the best estimate for the relative risk of breast cancer associated with each additional gram of ethanol consumed was 1.01 (95% CI 1.005-1.015). This means that a woman drinking an average of two units of alcohol (each unit containing 8 g ethanol) per day has a lifetime risk estimated to be 8% higher compared to a woman who drinks an average of one unit of alcohol per day, There was no evidence for variation in the association with any specific type of alcoholic drink **(paragraph 18).**

c) The Population Attributable Risk (i.e. percentage of breast cancers which could be prevented if drinking were reduced to a very low level of less than 1 unit/week) using U.K. cancer registry data and intake data from the Health Survey for England is 6% (95% CI 3.2%-8.8%). This equates to approximately 2430 cases of breast cancer per year (95% CI 1290-3560) **(paragraph 20).**

d) The assessment of cumulative risks suggests that lifetime drinking of an extra 3 units of alcohol per day would result in an additional 15 cases of breast cancer/1000 women at 60 years of age and an extra 32 cases of breast cancer/1000 women at 80 years of age compared to current rates of 60 cases of breast cancer/1000 women at 60 years and 125 cases of breast cancer/1000 women at 80 years where the average intake is 1 unit per day (**paragraphs 28 and 40**).

e) The Committee agreed that the weight of evidence available suggested that drinking alcohol produced a number of biochemical effects in the liver which resulted in changes to oestrogen metabolism and IGF levels, which over a prolonged period of time, i.e decades, could induce breast cancer. Both of these suggested mechanisms would potentially have a threshold with regard to induction of breast cancer. **(paragraph 34).**

f) The Committee concluded it prudent to assume that drinking alcoholic beverages may cause breast cancer in women. **(paragraph 37).**

g) The Committee agreed that more research into the potential for interaction between use of oral contraceptives and use of Hormone Replacement therapy and the induction of breast cancer by drinking alcoholic beverages was appropriate. **(paragraph 39).**

h) The Committee was concerned to note that if the increased consumption of alcoholic beverages by young women were maintained over most of their life-time then it would result in an increase in the number of alcohol-related breast cancer cases in the future. It is therefore important to raise awareness of the potential risk of breast cancer in women associated with drinking alcoholic beverages. **(paragraph 41).**

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Glossary of terms/phrases used in statement.

Aetiology: The study of causation.

Benign Breast Disease: A proliferation of breast tissue which is not malignant. However some forms are indicative of an elevated risk of breast cancer.

Breast Cancer: A malignant tumour of breast tissue, usually arising from ductal or lobular epithelial cells. The great majority of breast cancers occur in women. Breast cancer is rare in men.

Causal Association: Describes the relationship between two factors which are associated where it can be established that one of the factors causes the other, i.e smoking cigarettes and lung cancer.

Collaborative Group On Hormonal Factors in Breast Cancer: A large international collaborative group of researchers. The secretariat is based at the Cancer Research UK Epidemiology Unit, Gibson Building, Radcliffe infirmary, Oxford OX2 6HE. The group had access to raw data from 65 epidemiology studies in its evaluation of the association between drinking alcoholic beverages and increased risk of breast cancer.

Epidemiology studies: Epidemiology is the study of the distribution and determinants of diseases in human populations. All of the studies included in the COC review of the association between drinking alcoholic beverages and increased risk of breast cancer are called Analytical studies. Very briefly, the basic outline of the types of studies included in this review are;

A. Case-control studies where drinking patterns are gathered from individuals with breast cancer and compared to patterns in control individuals who don't have breast cancer.

B. Cohort studies where information on drinking patterns is gathered from individuals who are then followed for a period of time (often decades) until the occurrence of breast cancer or death.

General Household Survey (GHS): The GHS is conducted on a yearly basis by the Social Survey Department of the Office for National Statistics (ONS). It has chartered the changes in British households and society since 1971. Questions about drinking habits were included every other year from 1978-1998 and every year from 2000 onwards. Questions regarding maximum daily amount drunk last week and weekly drinking habits have been included every year have been included since 1998.

Heterogeneity: A variation in an estimate which exceeds the expected.

Hormone Replacement Therapy: (HRT) HRT consists of oestrogen given continuously to women during the menopause to manage symptoms associated with loss of ovarian function. Cyclical progestogen is given to women who have not had a hysterectomy. HRT may also help to prevent osteoporosis.

IGFs: Insulin-like Growth Factors.

International Agency for Research on Cancer (IARC): The International Agency for Research on Cancer (IARC) is part of the World Health organisation. IARC's mission is to co-ordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships.

Interdepartmental Working Group on Alcohol (IDWG): The IDWG was established in 1994 and consisted of a group of officials. Its remit was to review current medical and scientific evidence and its interpretation on the long term effects of drinking alcohol and, to consider whether the sensible drinking message should be reviewed in the light of this, also taking into account Government policies on the short term effects of drinking alcohol and any other factors considered relevant by this group. The IDWG produced a report entitled "Sensible Drinking" in December 1995.

Mechanisms (by which alcohol could induce breast cancer): A term describing the effects of alcohol drinking on biochemistry and physiology which could, if sustained over a period of time, ultimately lead to induction of breast cancer. Evidence regarding mechanisms can come from a variety of sources including studies in cell culture (in-vitro), studies in animals, and investigations in human epidemiology or volunteer studies. A proposed mechanism for induction of cancer cannot be verified through statistical evaluation of cancer data and requires scientific judgement to assess plausibility.

Menarche: The beginning of menstruation.

Menopause: The cessation of menstruation, occurring usually around the age of 50y. Pre-menopausal (before menopause). Post- menopausal (after menopause).

Meta-Analysis: A meta-analysis study is a specialised statistical analysis which combines the results of individual studies producing a quantitative summary across all studies of the effect of interest. This type of study can provide valuable information to help in estimating the strength and consistency of the association between drinking alcohol and breast cancer.

Meta-Regression: A statistical analysis which aims to investigate how the size of an effect varies with characteristics of the studies in a meta-analysis

Oral contraceptive: A compound, usually hormonal, taken usually by the oral route in order to block ovulation and prevent pregnancy. Most oral contraceptives available in the U.K contain both an oestrogen and a progestogen.

Parity: Condition of a women with respect to having borne viable offspring.

Random Effects: A statistical model which assumes that an underlying strength of association can vary between studies.

Recommended level of drinking: The recommended number of units of alcohol which can be consumed without long term adverse effects. This has been set as daily benchmarks which are appropriate for regular and irregular drinkers. For women this is 2-3 units/day. Drinking in excess of 3 units/day accrues progressive health risks.

Risk factors for breast cancer: The aetiology (see above definition) of breast cancer is complex. An association has been demonstrated for many different factors including heredity, reproductive, hormonal, and lifestyle factors. A role for environmental factors can be deduced from geographical variation in rates of breast cancer and changes in rates among migrants toward those of the host country. Thus drinking alcohol is one of several risk factors for breast cancer.

World Health Organisation: The World Health Organisation, the United Nations specialised agency for health, was established on 7 April 1948. WHO's objective, as set out in its Constitution, is the attainment by all peoples of the highest possible level of health. Health is defined in WHO's Constitution as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The WHO has established agencies to assist in its work. One of which is IARC (see above for definition).

Breast cancer risk and exposure to organochlorine insecticides: consideration of the epidemiology data on dieldrin, DDT and certain hexachlorocyclohexane isomers

Introduction

1. In 1995, the COC reviewed the available epidemiological studies on three chemicals (DDT and isomers/metabolites, and the hexachlorocyclohexane isomers γ-HCH (lindane) and β-HCH. The Committee agreed that the available evidence indicated no clear association. It was felt, however, that the matter should be kept under review. The Committee on Carcinogenicity was asked by the Department of Health in 1999 to review the relevant information on four organochlorine insecticides (OCIs) in respect of the potential for an association with breast cancer. The additional chemical included was dieldrin, for which new epidemiological data had become available at the time of that review. The main conclusions of the 1999 review are given below;

   DDT Some DDT isomers and metabolites should be regarded as having weak *in-vivo* oestrogenic activity. The stable metabolite p, p/ DDE, a marker for exposure to DDT, can be found in samples of fat from most individuals. There is however, good evidence from investigations undertaken in the UK that concentrations of p, p/ DDE in human fat samples have been declining for several decades. There are now 14 epidemiological studies which have considered p, p/ DDE using both case-control and prospective study designs. There is no convincing evidence for an association with an increased risk of breast cancer. Overall the available data do not suggest that environmental exposure to DDT (and isomers/ metabolites) is a cause for concern as a risk factor for human breast cancer.

   Dieldrin Dieldrin is not considered to have *in-vivo* oestrogenic activity. There is thus no rationale to consider that exposure to this chemical should be associated with an increased risk of breast cancer. There is good evidence from investigations undertaken in the UK that concentrations of dieldrin in human fat samples have been declining for several decades. There is no convincing evidence from the five available epidemiological studies for an elevated risk of breast cancer in association with exposure to dieldrin. Overall the available data do not suggest that environmental exposure to Dieldrin is a cause for concern as a risk factor for human breast cancer.

   β-*HCH* β-HCH should be regarded as having weak *in-vivo* oestrogenic activity. β-HCH can be found in samples of fat from most individuals. There is evidence from investigations undertaken in the UK for a decline in β-HCH concentrations in human fat samples after 1982/3. There is no convincing evidence from the five available epidemiological studies for an elevated risk of breast cancer in association with exposure to β-HCH. It is recommended that the published literature on this chemical should be kept under review.

Lindane Lindane (γ -HCH) is not considered to have any *in-vivo* oestrogenic activity. There is thus no rationale to consider that exposure to this chemical should be associated with an increased risk of breast cancer. The available evidence for environmental exposure to lindane suggests that body burdens of this chemical in the UK are very small, being undetectable in most individuals. None of the five available epidemiological investigations found evidence for an association with breast cancer. Overall the available data do not suggest that environmental exposure to lindane is a cause for concern as a risk factor for human breast cancer.

2. The Committee was aware of a number of research investigations that were either planned or had been instigated at the time of the 1999 review and agreed to review relevant publications in the scientific literature at some point in the future. A large number of publications have become available and it is now timely to review the evidence.

Introduction to current review

3. The Committee considered a review paper presented to its 22 September 2003 meeting. Further review papers and tabulated summaries of epidemiology studies were considered at the 6 November 2003 and 1 April 2004 meeting. All papers can be accessed through the COC internet site (either via links from agendas or in the section entitled papers).

4. During the review process, members agreed that it was important to consider all of the epidemiology studies together rather than focus on studies published after the last review in 1999. However no additional relevant information has been retrieved on lindane (γ- hexachlorocyclohexane, (γ-HCH) since the 1999 review. The COC concluded in 1999 that there was no rationale that γ-HCH could be associated with breast cancer. A summarised tabulation of the studies available at the time of the review has been published as an Annex to this statement. A summary of the main results from epidemiology studies has been presented in a number of graphs which are also available as an Annex to this statement. The tables and graphs present information for DDT (and its isomers and metabolites), β-hexachlorocyclohexane (β-HCH) and dieldrin.

5. The Committee was aware that none of the OCIs included in this review are approved for use in pesticide formulations in the U.K.

6. The Committee agreed in 1999 that a number of observations and assumptions had led some observers to suggest the hypothesis that OCIs and other organochlorine compounds may be associated with an increased risk of breast cancer. The format of the statement agreed in 1999 presented a review of the biological plausibility that OCIs may be associated with an increased risk of breast cancer and then a review of the available epidemiology for each OCI under consideration. The conclusion reached for each of the OCIs under consideration in 1999 took account of the potential for an oestrogenic response *in-vivo*, the evidence for persistence in humans and the available epidemiological investigations. The Committee agreed that the format of the current statement should adopt the same procedure used for the 1999 review. Thus a brief overview of the proposed hypothesis that OCIs maybe associated with an increased risk of breast cancer is given below;

Overview of hypothesis that OCIs may cause breast cancer

7. i) Many of the known or proposed risk factors for breast cancer are related to endogenous or exogenous hormones (in particular oestrogen). These factors include age at first birth, at menarche, and at menopause, and obesity, parity and use of oral contraceptives and hormone replacement.

   ii) there is some evidence available to suggest that some of the OCIs under consideration may have weak oestrogenic activity[2-7].

   iii) these OCIs have been shown to induce tumours (predominantly of the liver) in experimental animals[8].

   iv) these OCIs persist in the environment and exposure of the population has occurred mainly via the diet[4,9].

Consideration of biological plausibility.

8. The Committee reviewed the evidence that dietary exposure to environmental levels of these OCIs might induce an oestrogenic response *in vivo* through the consideration of three questions, namely;

   i) these OCIs have oestrogenic activity *in vivo* and if so what is their potency relative to other sources of oestrogens?

   ii) Is there any evidence for synergistic effects?

   iii) Do these compounds persist in breast tissue?

Do these OCIs have oestrogenic activity in vivo and if so what is their potency relative to other sources of oestrogens?

9. A tabulation of the Committee's assessment of the evidence for oestrogenic activity of the OC insecticides under consideration is given overleaf. The new data published since the 1999 COC review provided additional information on the *in-vitro* oestrogenic effects of β-HCH[37,38] and DDT isomers/metabolites[32] and evidence to show that dieldrin had no effect on human placental aromatase activity *in vitro*[35]. An *in-vivo* study with dieldrin showed that very high lethal doses administered to rats did alter oestrogen metabolism[36]. However the Committee concluded that the data from this latter study were irrelevant with regard to assessment of the very low levels exposure experienced by the general population.

Table 1: Assessment of oestrogenic activity of OC insecticides

OCI	Evidence of oestrogenicity *in-vitro* through effects on i) Oestrogen receptors	ii) Oestrogen metabolism	iii) or by other mechanisms	*In-vivo* data	Conclusion
β-HCH	Evidence of very weak oestrogenic activity,[5,10] (ca 40,000 x weaker than oestradiol)	No data available.	Yes[5,10,37,38] Data suggest a number of mechanisms possible but relevance to *in-vivo* situation is uncertain.	Uterotrophic effects documented in rats and mice.[11,12]	Regard as a weak *in-vivo* oestrogen. Mechanism unknown
Lindane	No evidence of oestrogenic activity[7,13]	Effects noted in MCF-7 cells[14, 15,] but other investigators have been unable to identify xenoestrogens using this test system.[17]	No data available	Difficult to interpret but equivocal evidence for oestrogenic and anti-oestrogenic effects in rats.[17-20]. No evidence of uterotrophic effect in reproduction studies in rats and mice[21]	Considered not to have *in-vivo* oestrogenic activity
DDT isomers/ metabolites (in particular p,p DDE)	Evidence of weak oestrogenic activity[4,22,32] (ca 1000 x weaker than oestradiol)	Effects noted in MCF-7 cells[14, 15,] but other investigators have been unable to identify xenoestrogens using this test system.[16]	Yes[10, 22-24] relevance to *in-vivo* situation is uncertain	Oestrogenic effects in rodents reported with certain DDT isomers (e.g. o,p' DDT and o,p DDD) but not with p,p' DDE[4]	Regard some DDT metabolites and isomers as weak *in-vivo* oestrogens. Several mechanisms possible involved
Dieldrin	Evidence of very weak oestrogenic activity in the majority of studies ca 10,000-50,000 less potent than oestradiol[8,26-32]	No effect on human placental aromatase activity.[35]	Yes [39]relevance to *in-vivo* situation is uncertain	No evidence of uterotrophic effects in a number of studies in either rats or mice[27,30,32]. High oral doses given to rats (equivalent to LD50) induced cytochrome P450 enzymes and altered oestrogen metabolism[36]	Does not to have *in-vivo* oestrogenic activity. Effects on oestrogen metabolism at lethal oral doses is irrelevant to consideration of environmental exposure

10. The Committee reaffirmed the conclusions reached in 1999 that the evidence supported the conclusion that β-HCH and DDT (in particular some metabolites and isomers) could have weak oestrogenic activity *in vivo* which most probably occurs by several different mechanisms. Members agreed that dieldrin appeared to have weak oestrogenic activity *in vitro*, but no evidence of an effect had been documented *in vivo* in a number of studies in rats and mice. There was no convincing evidence that lindane had oestrogenic activity *in vivo.* The Committee reaffirmed its conclusion that there was no plausible reason for including lindane as a xenoestrogen for examination in epidemiological studies of breast cancer.

11. The Committee concurred with its conclusion reached in 1999 that in comparison to other potential sources of exposure to oestrogenic substances (e.g birth control regimes, post-menopausal hormone therapy, flavenoids in foods[40]) that OCIs represent an extremely small proportion of the potential oestrogenic burden.

Is there any evidence for synergistic effects?

12. The Committee undertook a detailed review of the potential for synergism between OCIs during the 1999 review. The evidence for synergism between xenoestrogens, and in particular in respect of OCIs, arose from the results obtained in *in-vitro* experiments undertaken by one research group in the USA and published in 1996 which concerned mixtures of dieldrin with endosulfan or methoxychlor[41,42]. The authors subsequently retracted their data in 1997 after they were unable to replicate the original experiments[43]. Many other research groups were unable to repeat the finding of synergism using a number of *in-vitro* [20,21,24,31] and *in-vivo* tests[4,24,31]. The results of the available experiments suggested, at most, an additive effect. The Committee also considered a claim by one group of authors[44] regarding evidence of synergism between certain xenoestrogens and concluded that any significant synergistic interactions in mammals should have been identified by the available published experiments.

13. A further six papers, retrieved since 1999, report the findings of a number of *in-vitro* studies using mixtures of OCIs or mixtures of OCIs with other xenoestrogens[45-50]. These studies used yeast or mammalian cell lines and a variety of different reporter systems for measuring activation of oestrogen receptors and were relatively complex in design particularly as dose-response effects for a range of combinations of chemicals under test were investigated. A separate investigation investigated the potential interactions of xenoestrogens but did not include any of the OCIs under consideration in this statement[51]. Most of these studies found no evidence for interaction between OCIs or between OCIs and other xeonoestrogens[45,46,48,49]. The Committee noted several studies from one research group based at the School for Pharmacy, London had reported significant interactions between xenoestrogens *in-vitro* using either a recombinant yeast system[51] or human breast cancer cells (MCF-7 cells)[50] which were evident when individual xenoestrogens were included in a mixture at concentrations below the No-observed concentration level when tested individually. The Committee considered that the results obtained in these latter experiments were consistent with an additive effect. A further study which used activation of luciferase linked to oesrtogen-receptor activation in T47D breast cancer cells reported evidence for an additive effect between dieldrin and endosulfan[47].

14. One recently published *in-vivo* study using the immature rat uterotrophic assay has been published which investigated mixtures of seven well established xenoestrogens at dose levels where individual chemicals were ineffective found a uterotrophic response when the mixture was tested. Further investigations by the authors confirmed that the observed response was below that predicted by simple addition of the observed or predicted activities[52].

15. The Committee was aware that a Working Group of its sister Committee, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) had undertaken a detailed consideration of the risk assessment of mixtures of pesticides and similar substances and a report was published on 15 October 2002[53]. (http://www.food.gov.uk/science/ouradvisors/toxicity/reports/cocktailreport) The Working Group on Risk Assessment of Pesticides and Similar Substances (WiGRAMP) considered the available evidence regarding all toxic endpoints including endocrine disruption effects such as oestrogenic effects. The overall conclusion of all the available evidence is given below;

    "Several studies claim to have identified synergistic interactions of some mixtures. However, for the most part, these studies have been inadequately designed and based on incomplete understanding of the concepts involved, but a few well designed studies have demonstrated both synergistic and antagonistic interactions, as well as additive effects in mixtures, usually at high concentrations or high experimental exposure levels, which are probably unrepresentative of exposure doses."

16. The information available to the Committee regarding OCIs is consistent with the conclusion reached in 1999 that there is no evidence to support the view that low levels of mixtures of xenoestrogens induce a biologically significant oestrogenic effect in mammals by acting synergistically. The possibility of a simple additive effect cannot be excluded but at the likely exposure levels for the OCIs concerned this will represent a negligible risk of any oestrogenic effect *in vivo*.

Do these compounds persist in breast tissue?

17. The observation that residues of certain OCIs persist in adipose tissue leading to bio-accumulation which might result in continuous exposure of breast tissue to weak oestrogenic substances has been cited as an essential part of the hypothesis that such compounds may cause breast cancer[36]. In 1999, the COC reviewed the available evidence from surveys of concentrations of OCIs in human adipose tissue or milk from a number of different sources including U.S.A. and countries in Europe. The most complete and appropriate data on adipose tissue concentrations of OCIs in the U.K. had been published by the Pesticides Residues Committee (formerly the Working Party on Pesticides Residues, WPPR) (http://www.pesticides.gov.uk/committees/PRC/prc.htm) The data collected from the early 1960s up to 1997 by the PRC which is retabulated below for ease of reference, indicated that body burdens of OCIs have been decreasing.

18. The results published by the Pesticides Residues Committee show that p, p/ DDE, and β-HCH can be detected in samples of fat or milk from most individuals studied whilst dieldrin was detected in fewer individuals. Lindane was infrequently found in human fat (3%) and milk (1.8%) samples, mainly at low levels (i.e. only one human fat sample contained > 0.01 mg/kg). The available literature shows that lindane is more rapidly metabolised and eliminated in mammals[44] than other OCIs such as dieldrin[45] and thus one possible explanation for the low frequency of detectable lindane residues in humans could be due to its metabolism[38,39].

Table 2: Concentrations of OC insecticides in human fat

OC	Mean concentration (mg/kg) in human fat. (Percentage of first reported residue level)				
	1963/4	1969-71	1976/7	1982/3	1995-7
Dieldrin	0.26 (100)	0.16 (61.5)	0.11 (42)	0.08 (30.7)	0.02 (7.6)
p,p'DDE	2.0 (100)	1.8 (90)	2.1 (100)	1.3 (65)	0.71 (35.5)
β-HCH	No Data	0.28 (100)	0.27 (96.4)	0.31 (110)	0.12 (42.8)

19. No new information has been retrieved since the 1999 review . However since it is evident that tissue levels of OCIs were declining, and none of these chemicals is approved for use in pesticide formulations in the U.K. and they have also been subjected to widespread restrictions on use in other countries, it would be appropriate to conclude that concentrations in human adipose tissue and milk have continued to decline.

Conclusions about Biological Plausibility

20. The Committee concluded that the OCIs considered, were, at most, very weak *in vivo* oestrogens and agreed that there was no evidence of any synergistic effects between these chemicals. The impact of exposure to oestrogenic chemicals would be the product of oestrogenic potency and bioavailability. The possibility of an additive effect of OCIs could not be discounted. However as OCIs are of low potency and occur at low concentrations, it is most unlikely that the effect of current exposures individually or collectively will significantly add to total oestrogenic burden in women and will not present any significant risk with regard to breast cancer.

Epidemiology

21. In 1995 when the Committee first reviewed the subject of organochlorine insecticides and the potential association with breast cancer, the available epidemiological data on breast cancer and exposure to OC insecticides were limited, comprising 6 case-control studies which investigated a total of 301 women with breast cancer using a variety of exposure analyses (in serum, plasma and breast adipose tissue)[62-67]. In 1999 a further eight additional epidemiological studies had been published[68-75], which considerably increased the number of women studied (for p,p', DDE this was estimated to be around 1500). By January 2004 (the deadline for this statement), over 80 estimates of odds

ratios/relative risks had been documented from a wide range of epidemiological investigations using different study designs involving both prospective and retrospective approaches, and analyses of OCIs in blood, serum or adipose tissue in women. A number of these investigations have also included an evaluation of hormone receptor status of breast cancer as part of the assessment[77-108]. However most of these studies have examined DDT or its metabolite p,p'DDE whilst relatively few have reported data for dieldrin and β-HCH and none for lindane (β-HCH). One meta-analysis of 22 investigations of the potential association between p,p'DDE and risk of breast cancer has been published[76]. It is not possible to provide a narrative summary of all these studies in this statement. A tabulated summary and graphical representation of the main results from the studies are appended to this statement as separate Annexes. The overall conclusions reached by the Committee on each OCI are given below.

DDT(and isomers/metabolites p,p'DDE)

i) 1999, the Committee concluded that overall, there was no convincing evidence from epidemiology studies for an elevated relative risk of breast cancer in association with DDT (as measured by pp' DDE). With regard to DDT, the available studies are overwhelmingly negative apart from one prospective cohort study[86] and one retrospective case-control study[80]. With regard to p,p'DDE a number of positive studies have also been published[65,73,95,96,103]. The Committee considered the meta-analysis study of published studies investigating the association between p,p'DDE and risk of breast cancer had been adequately undertaken and the summary risk estimate of 0.97 (95% CI 0.87-1.09) suggested there was no evidence for an association[110]. Overall the Committee considered there was no compelling evidence that DDT or its metabolite pp'DDE were associated with an increased risk of breast cancer.

Dieldrin

ii) In 1999 the Committee noted that there was relatively little epidemiological data on dieldrin. Overall, the Committee concluded there was no convincing evidence from epidemiological studies for an elevated relative risk of breast cancer associated with dieldrin. There have been relatively few studies published since 1999 on the potential association between dieldrin and risk of breast cancer. Hoyer and colleagues have reported positive findings in a number of analyses[72,87,88]. However the COC has previously stated there are methodological problems with these studies which prevent definite conclusions from being drawn[109]. Thus overall the Committee consider there are no convincing data available regarding an association between dieldrin and risk of breast cancer.

(It was not appropriate to calculate an overall estimate of the strength of association from the available data)

β-*HCH*

iii) In 1999 the Committee concluded that there was very little epidemiological information available on β-HCH and its possible association with breast cancer. The studies available at that time had all provided negative findings. None of the studies retrieved for the current review reported statistically significant positive findings[77,82,86,92,100,103]. Thus overall there is no evidence to associate β-HCH with an increased risk of breast cancer.

Lindane (γ-HCH)

iv) In 1999, the Committee noted there was very little epidemiological information on the potential association between lindane and risk of breast cancer. The available studies did not suggest an association. The Committee concluded that it was unlikely that further epidemiological investigations of breast cancer based on assessment of levels of lindane in adipose tissue, blood, or breast tissue would provide additional relevant information. There have been no additional epidemiological investigations retrieved. There is therefore no evidence to associate lindane with an increased risk of breast cancer.

Overall conclusion

22. The Committee noted the hypothesis that OCIs might increase the risk of breast cancer by virtue of their claimed oestrogenic effects **(para 2)**. The Committee reaffirmed conclusions reached in 1999 namely;

a) that the oestrogenic effects (if any) of these xenoestrogens were likely to be small in magnitude, especially compared with those of oral contraceptives or HRT, which entail much higher exposures to oestrogens **(para 7-11)**

b) there is no convincing evidence of oestrogenic synergy in mammals between different OCIs or OCIs with other xenoestrogens. The possibility of a simple additive effect cannot be excluded but at the likely exposure levels for the OCIs concerned this will represent a negligible risk of any oestrogenic effect in-vivo. **(para 15)**.

c) concentrations in human fat of the OCIs considered in this statement are decreasing in humans which provides some additional reassurance with regard to any potential risk of breast cancer **(para 18).**

23. The following overall conclusions were reached.

DDT (and isomers and metabolites p,p'DDE)

There is evidence that DDT and some of its isomers/metabolites such as p,p'DDE have weak xenoestogenic activity *in vivo.* Concentrations of p,p'DDE in human fat have been declining for

decades. There is extensive epidemiological data on the potential for an association between DDT its isomers and metabolites such as p,p'DDE and increased risk of breast cancer. There is no convincing evidence for an association with an increased risk of breast cancer. Overall the available data do not suggest that environmental exposure to DDT (and isomers/metabolites) is a cause for concern as a risk factor for human breast cancer.

Dieldrin

Dieldrin does not have any oestrogenic activity *in vivo*. There is evidence to show that concentrations in human fat are decreasing. There is no convincing epidemiological evidence for an association between dieldrin and increased risk of breast cancer. However the available epidemiological evidence on dieldrin and risk of breast cancer is limited and it is suggested that the relevant literature on dieldrin is kept under review.

β-*HCH*

β-HCH should be regarded as having weak *in-vivo* oestrogenic activity. There is evidence from investigations undertaken in the UK for a decline in β-HCH concentrations in human fat samples after 1982/3. The available epidemiological studies do not suggest any evidence for an association between β-HCH and increased risk of breast cancer. Overall the available data do not suggest that environmental exposure to β-HCH is a cause for concern as a risk factor for human breast cancer.

Lindane

Lindane (γ-HCH) does not have any *in-vivo* oestrogenic activity. It is not approved for use as a pesticide in the U.K. Exposure is likely to be negligible. The Committee have previously concluded that there is no biological rationale for including lindane in any epidemiology studies on risk of breast cancer. The Committee concluded there is no reason to undertake any further reviews of the association of this chemical with increased risk of breast cancer.

COC/04/S3 August 2004.

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Carcinogenicity of 1,3-dichloropropan-2-ol (1,3-DCP) and 2,3-dichloropropan-1-ol (2,3-DCP)

Introduction

1. 1,3-Dichloropropan-2-ol (1,3-DCP) and 2,3 dichloropropan-1-ol (2,3- DCP) are contaminants of some foodstuffs and of polyamine flocculants used in the treatment of drinking water. Both the COC and COM have previously published statements on the closely related compound 3-chloro-1,2-propanediol (3-MCPD)[1,2] 1,3-DCP and 2,3-DCP were considered by the COC and COM in 2001[3,4]. In 2001, the COM recommended that appropriate in-vivo mutagenicity studies should be undertaken with 1,3-DCP and 2,3DCP in accordance with the COM guidelines[(3,5)]. In 2001, the COC came to the following conclusions;

   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.

   It is prudent to assume that 2,3 DCP may posses genotoxic activity in-vivo. Although no carcinogenicity data are available, it would however be prudent to reduce exposures to 2,3 DCP to as low a level as technologically feasible.

2. Both of these compounds have been recently considered by the COM who has updated its advice on the mutagenicity of 1,3-DCP and 2,3-DCP in the light of results from new *in-vivo* mutagenicity studies on these two compounds. An updated COM statement on 1,3-DCP was published in October 2003 and an updated statement on 2,3-DCP was published in June 2004[6,7].

3. The available carcinogenicity and other relevant toxicological information on these two compounds including the recent conclusions reached by the COM are considered below. 1,3-DCP and 2,3-DCP have been considered separately in the following sections.

1,3 DCP

4. Available toxicology, mutagenicity and carcinogenicity data for 1,3 DCP has been summarised by the Joint FAO/WHO Committee on Food Additives (JECFA)[8] although much of the key data remain unpublished. From a 13-week oral toxicity study, a NOAEL of 1mg/kg/day had been identified. Limited information on the metabolism of 1,3 DCP indicates that it may be metabolised to form epichlorohydrin, which may, via glycidol, be conjugated to form mercapturic acid derivatives.[9]. *In-vitro* investigations with hepatocyte cultures indicate also a pathway involving CYP2E1 to dichloroacetone (a directly acting cytotoxic compound) leading to glutathione depletion[10-14].

Mutagenicity

Updated Advice from COM 2003

5. The metabolism of 1,3-DCP was likely to produce a reactive epoxide intermediate that could damage DNA. Members were aware that 1,3-DCP had been found to be mutagenic to *Salmonella typhimurium* strains TA1535 and or TA 100[15-22]. Studies with mammalian cells have produced increased frequencies of sister chromatid exchanges and chromosome aberrations[23,24]. A positive result has been obtained in a mouse lymphoma assay[25,26]. 1,3-DCP was negative in the wing spot test in *Drosophila melanogaster* (a somatic mutation and recombination test)[27].

6. The Committee considered two new *in-vivo* genotoxicity studies at its May 2003 meeting[28,29]. These comprised a rat bone-marrow micronucleus test[28] and a rat liver unscheduled DNA synthesis (UDS) assay[29], both of which are widely used to assess genotoxicity *in vivo.*

7. The Committee concluded that both the rat bone-marrow micronucleus test and the rat liver UDS test had been carried out to an acceptable standard and were negative. Thus the additional information recommended by the COM as being necessary to provide adequate reassurance that the mutagenic activity seen *in vitro* was not expressed *in vivo* had now been provided. The COM noted the uncertainties with regard to routes of metabolic activation of 1,3-DCP and agreed that the two new mutagenicity studies supported the view that reactive metabolites, if formed, did not produce genotoxicity *in vivo* in the tissues assessed. The COM concluded that 1,3-DCP can be regarded as having no significant genotoxic potential *in vivo*.

Carcinogenicity

Advice from COC 2001.

8. A 104-week toxicology and carcinogenicity study with 1,3 DCP in Wistar rats was previously considered by COC in 1991[30]. At the time COC concluded that 1,3 DCP was genotoxic and carcinogenic, although a formal committee statement was not issued. Additional information on the study was presented to the COC in 2001. The COC concluded that the spectrum of tumours observed in the 104-week rat study (which are reproduced below for ease of access), particularly in the liver and tongue was evidence of a clear carcinogenic effect of 1,3 DCP. It was possible that the tumours in the male kidney could be associated with the high rate of chronic progressive nephropathy observed in the study and additionally, the thyroid follicular cell tumours could be associated with hyperplasia, a toxic finding commonly seen in male rats, although no specific mechanism data were available.

9. A brief summary of the evidence for carcinogenicity of 1,3-DCP in the rat carcinogenicity study provided to COC in 2001 is given below.

   - In the *liver*, combined incidences of hepatocellular adenoma and carcinoma, showed a statistically significant dose-related increase ($p<0.001$) in both males and females. (eg males -controls 1/50, high dose 8/50; females – controls 1/50, high dose 41/50).

   - In the *tongue*, combined incidences of squamous cell papilloma and carcinoma showed a statistically significant dose-related increase ($p<0.001$) in both males and females. (eg males – controls 0/50, high dose 12/50; females – controls 0/49, high dose 11/49).

   - In the *thyroid* combined incidences of follicular cell adenoma and carcinoma showed a statistically significant dose-related increase ($p<0.001$) in both males and females (eg males – controls 0/50, high dose 4/50; females – controls 1/49, high dose 5/49).

   - In the *kidney*, combined incidences of renal tubular adenoma and carcinoma, showed a statistically significant dose-related increase ($p<0.001$) in males only (eg controls 0/50, high dose 9/50).

Updated Advice from COC 2004

10. The COC reaffirmed its previous opinion that 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. The Committee agreed that the evidence of hepatotoxicity, together with negative results from the *in-vivo* rat liver UDS assay, provided evidence of non-genotoxic mode of action in the liver.

Further consideration of tumours of the tongue (November 2003 and April 2004 meetings)

11. The Committee then considered possible modes of action of 1,3-DCP in inducing tumours of the tongue. The Committee considered that the finding of 2% papillary carcinoma in the mid-dose female group might not be treatment related but the incidence of tongue papilloma (14.3%) and carcinoma (8.2%) in high dose females was clearly treatment related. In male rats the incidence of tongue tumours in the high dose group was 12% (for both papilloma and carcinoma). There were no tongue tumours in males at the low and mid dose groups. The high dose level clearly exceeded the Maximum Tolerated Dose level in that there was an increase in treatment related mortality and hepatotoxicity. 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 discussed the suggestion that bacteria metabolised 1,3-DCP to the genotoxic carcinogen epichlorohydrin but agreed there was no specific evidence to support this proposal.

12. The COC discussed future research to investigate whether the tumours of the tongue occurred via a genotoxic mechanism and agreed that information on contact-irritancy, cell proliferation and formation of DNA adducts in tongue tissue using ^{32}P-postlabelling in animals treated with suitably high doses of 1,3-DCP was needed.

13. The COC concluded that until such data were available, it was not possible to exclude the possibility of a genotoxic mechanism for the tumours of rat tongue seen in a long-term drinking water study with 1,3-DCP.

2,3-DCP

14. There are very little data on the absorption, distribution, and excretion of 2,3-DCP. Theoretically, 2,3-DCP could be metabolised to produce epichlorohydrin (and subsequently glycidol) and therefore there were structural alerts for genotoxicity and carcinogenicity. One research group had provided some *in vitro* data to suggest that induction of CYP2E1 resulted in 2,3-DCP mediated hepatotoxicity and glutathione depletion[31]. The findings of Koga et al[31] suggest dechlorination/ hydroxylation of 2,3-DCP may occur but the evidence for epoxide formation was not conclusive. There are insufficient data to draw conclusions on the metabolic activation of 2,3-DCP but overall the evidence suggested metabolic activation of 2,3-DCP differs from 1,3-DCP. The COM considered these data and agreed that that the metabolism of 2,3-DCP had not been fully elucidated. Metabolic activation *in vivo* to active metabolites had been postulated but had not been proven.

Mutagenicity

15. The COM concluded in 2001 that 2,3-DCP was mutagenic *in vitro* in *Salmonella typhimurium* strains TA 100 and TA 1535 in a study with and without metabolic activation[18] and mutagenic in another Ames test[19]. Positive results were also obtained for sister chromatid exchange with Chinese Hamster V79 cells both with and without metabolic activation[23].

Updated advice from COM 2004

16. The COM considered two new *in-vivo* genotoxicity studies at its February 2004 meeting. These comprised a rat bone-marrow micronucleus test[32] and a rat liver unscheduled DNA synthesis (UDS) assay[33], both of which are widely used to assess genotoxicity *in vivo*.

17. The Committee concluded that both the rat bone-marrow micronucleus test and the rat liver UDS test had been carried out to an acceptable standard and were negative. Thus the additional information recommended by the COM as being necessary to provide adequate reassurance that the mutagenic activity seen *in vitro* was not expressed *in vivo* had now been provided. The Committee noted the

uncertainties with regard to routes of metabolic activation of 2,3-DCP and agreed that the two new mutagenicity studies supported the view that reactive metabolites, if formed, did not produce genotoxicity *in vivo* in the tissues assessed The Committee concluded that 2,3-DCP can be regarded as having no significant genotoxic potential *in vivo*.

Carcinogenicity

18. Further advice on the carcinogenicity of 2,3-DCP was sought from the COC at the June 2004 meeting in the light of the updated advice on mutagenicity from COM.

19. Although there are no carcinogenicity studies available for 2,3DCP, the World Health Organisation's International Agency for Research on Cancer (IARC) evaluated the brominated analogue, 2,3 dibromo-propanol (2,3 DBP) and considered that "there is sufficient evidence in experimental animals for the carcinogenicity of 2,3 dibromopropan-1-ol". In addition skin application of 2,3 DBP produced multisite tumours in both rats and mice.[34] However, the Committee considered this information in 2001 and agreed that no conclusions could be drawn from the studies on 2,3 dibromo propan-1-ol in respect of the carcinogenicity of 2,3 DCP.

20. Thus no conclusions regarding the carcinogenicity of 2,3-DCP can be reached on the available information on this compound.

Conclusions

21. The Committee concluded

1,3-DCP: The COC concurs with its previous advice that 1,3-DCP should be regarded as a genotoxic carcinogen. It is not possible to exclude a genotoxic mechanism for the induction of the tumours of rat tongue seen in a long-term drinking water study with 1,3-DCP. The Committee recommended that further investigations regarding the mechanism of 1,3-DCP carcinogenicity in the rat tongue should include information on contact-irritancy, cell proliferation and formation of adducts in tongue tissue using ^{32}P-postlabelling in animals treated with suitably high doses of 1,3-DCP.

2,3-DCP: The available evidence is consistent with the conclusion that 2,3-DCP does not posses genotoxic activity in-vivo. There are no appropriate carcinogenicity bioassays of 2,3-DCP available. No conclusions regarding carcinogenicity of 2,3-DCP can be reached.

COC/04/S2 June 2004

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Olfactory neuroblastoma: evidence for an elevated incidence among dentists and dental nurses?

Introduction

1. Olfactory neuroblastoma (ONB. The alternative name is esthesioneuroepithelioma) is estimated to comprise approximately 3% of nasal neoplasms excluding benign polyps. The incidence in N. America/Western Europe is estimated to be approximately 0.15/million/year. There is no evidence for a sex difference in incidence. It occurs in all ages (but is rare below 10 y and over 70 y)[1]. It has been reported to have bimodal incidence, with peaks in the 2nd -3rd decade and later in the 6th and 7th decades of life[2]. It has also been estimated there have only been 950 cases cited in the scientific literature from 1924, when ONB was first cited in the literature, up to 1997[3]. Thus the available evidence suggests that ONB is a very rare tumour.

2. ONB is described as a neuroectodermal neoplasm showing predominantly neural features[4]. The most common symptoms in patients presenting with ONB are nasal obstruction (93%), epistaxis (55%) and rhinorrhea (30%). Other symptoms such as headache and anosmia occur at an incidence of below 10%[2]. Diagnoses is based on clinical presentation, CT/MRI* screening and histology with the need for a battery of immunohistochemical stains to differentiate from other closely related head and neck cancers[5,6,7].

Published information: Association of ONB with occupation or chemical exposure

3. There is no published evidence to associate ONB with any particular occupation or chemical exposure. The only published case-report of ONB where an occupational exposure aetiology has been suggested refers to a woodworker exposed to wood dust for 25 years[8]. The Committee was aware that adenocarcinoma of the nasal cavities and paranasal sinuses is clearly associated with exposure to hard wood dust. The published evidence on wood dust had been thoroughly reviewed by the World Health Organisation's International Agency for Research on Cancer (IARC) in 1995 and no evidence for an association between exposure to wood dust (hard or softwoods) and ONB had been documented[9]. The Committee agreed that it was highly improbable that the researchers investigating wood workers would have misdiagnosed ONB as adenocarcinoma of the sinuses.

Association of ONB with dentists/dental nurses

Presentation from Professor Valerie Lund (Institute of Laryngology and Otolaryngology)

4. Professor Lund presented details of four individuals with ONB, two of whom had worked as dentists, and two who had been employed as dental nurses. Members heard that two pathologists had independently verified the diagnoses. Full details of these case reports have been submitted to a peer reviewed journal.

* Computerised Topography/Magnetic Resonance Imaging

COC discussion

5. Members reviewed the available information and considered the data on the case-series held by the Institute of Laryngology and Otolaryngology in the context of information identifiable though the Office for National Statistics (England and Wales) for the past 10 years. No dentists of dental nurses had been identified in the limited review of ONS data. Members acknowledged that details of occupation were underreported to ONS. The Committee felt that there was no evidence of referral bias of dentists/dental nurses to the Institute. The Committee agreed that the finding of 4 dentists/dental nurses with ONB out of a series of 52 cases of ONB referred to the Institute over a period of 23 years was likely to be a statistically significant association.

6. The Committee considered available information on potential chemical exposures of dentists/dental nurses (e.g. to metallic mercury, oil of cloves (principle ingredient eugenol) and methymethacrylate) (a copy of the covering paper can be found on http://www.advisorybodies.doh.gov.uk/pdfs/cc0337.pdf). It was agreed that there was no evidence to associate exposure to these chemicals with ONB in dentists/dental workers.

7. The Committee noted a report of cytogenetic damage in nasal tissue from dental technicians.[10] It was agreed that dental technicians were a separate and distinct group from dentists/dental nurses with regard to chemical exposures. Thus data from dental technicians was not helpful in identifying relevant chemical exposures of dentists/dental nurses.

8. The Committee considered that the first priority for further work would be to consider additional epidemiological investigations to confirm the finding reported by the Institute of Laryngology and Otolaryngology. This might include evaluation of case-reports of ONB from other countries or detailed evaluation of information held by centres of excellence (for head and neck tumours) and pathology departments from the U.K., Europe and elsewhere.

COC Conclusion

9. The Committee concluded that the finding of 4 dentists/dental nurses with ONB by the Institute of Laryngology and otolaryngology was likely to be a statistically significant association. Additional epidemiological data are needed to substantiate this observation. No definite conclusions on the potential association between dentists/dental nurses and olfactory neuroblastoma can be reached at this point in time.

COC/04/S1 April 2004

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Prostate cancer

Introduction

1. Prostate cancer is the most common cancer in men in the UK, with over 24,700 new cases a year (2000 data). Prostate cancer is the second largest cause of death from cancer in the U.K. There were 9,900 deaths reported in 2002 accounting for around 13% of cancer deaths in men. Around 70% of these deaths are in men aged over 70 years. The mortality rate for prostate cancer peaked in the early 1990s and has now fallen to 25 per 100,000 population at risk. The lifetime risk for being diagnosed with prostate cancer is 1 in 14. The cancer develops from cells within the prostate gland. The majority of prostate cancers are slow growing and many men are unaware that they have this cancer. However, a small number of prostate cancers grow more quickly and may spread to other parts of the body. Cancer Research UK reported a 57% increase in prostate cancer incidence in Great Britain between 1991 and 2000[1-3].

2. The Committee was asked to review the available epidemiological and other research to identify if there were any potential chemical exposures which might be associated with prostate cancer.

3. The Committee initially considered the evidence for an increasing incidence of prostate cancer in order to elucidate if there were diagnostic and registration changes which might be important in interpreting the documented increased incidence of prostate cancer. The second phase of the review concerned an evaluation of the epidemiological and other data regarding occupational groups (such as farmers/farm workers) and chemical exposures which have been proposed as being associated with prostate cancer.

4. The Committee considered an overview drafted by the DH Toxicology Unit (http://www.advisorybodies.doh.gov.uk/pdfs/annex1cc0335.pdf) and evaluated additional commissioned papers published studies. The DH Toxicology Unit overview and additional commissioned papers list the full set of references considered during the COC discussions. The Committee considered the evidence regarding chemical causation of prostate cancer at its November 2003 and April 2004 meetings. The additional discussion papers on prostate cancer from the DH Toxicology Unit on the evidence regarding a possible association between PAH exposure (http://www.advisorybodies.doh.gov.uk/pdfs/Cc0412.pdf) and occupation in the rubber industry (http://www.advisorybodies.doh.gov.uk/pdfs/Cc0413.pdf) were reviewed at the June 2004 meeting.

Trends in Prostate cancer in U.K.

5. Age-adjusted rates for prostate cancer increased in all age groups in England and Wales during the 1970s and 1980s. A marked increase occurred after this, rates peaked in 1994 and subsequently decreased in some, but not all, age groups[4]. The Committee agreed that increased use of trans-urethral resection of the prostate (TURP) for benign prostatic hyperplasia accounted in part for increased reporting of prostate cancer during the 1970-80s. The adoption of Prostate-Specific Antigen (PSA) testing during the 1990s partly explained the subsequent increased reporting of prostate cancer. Similar patterns were observed in Scotland, where the increases in incidence were closely correlated with rates of TURP (up to 1988) and, subsequently, PSA testing (1989-1996)[5].

6. The Committee reviewed a Small Area Health Statistics Unit (SAHSU) study on geographical variation in the incidence of prostate cancer in the U.K. at the June 2002 meeting[6]. The Committee agreed that the study showed no evidence for significant geographical variation in prostate cancer in the U.K. This would suggest there were no major environmental factors affecting incidence of prostate cancer in the U.K.

7. The Committee agreed that the impact of screening for prostate cancer using Prostate Specific Antigen (PSA) on recording of incidence and to a lesser degree mortality data severely complicated the interpretation of epidemiological studies and time trends in incidence in particular.

Risk factors associated with prostate cancer

8. There are a number of suspected risk factors for prostate cancer. The most important two are age and family history. Clinical prostate cancer is rare in men under 40 years of age[7]. The risk of prostate cancer increases by 2-3 fold in men who have a first-degree relative with the disease[8]. It is estimated that high penetrance familial prostate cancer accounts for 5-10% of all cases and a higher proportion of cases identified before the age of 55 y[9,10].

9. A number of other risk factors have been suggested including vasectomy[12,16], sexual activity[12,16], viral exposure[17] and physical activity[18]. However, the evidence for these factors is uncertain and no conclusions can be drawn. There is some limited evidence that smoking is associated with prostate cancer[11,12,16] but no convincing evidence regarding alcohol consumption[19].

10. The evidence for an association between diet and risk of prostate cancer was reviewed fully by the Working Group on Diet and Cancer of the Committee on Medical Aspects of Food and Nutrition Policy in 1998[15]. The Working Group concluded that the limited data were weakly consistent with the hypothesis that higher total fat intakes are associated with higher risks of prostate cancer. The Working Group also concluded that the limited evidence was moderately consistent that higher vegetable consumption, especially raw and salad vegetables, is associated with a lower risk of prostate cancer. The evidence for an association between consumption of fruit and risk of prostrate cancer was

inconsistent. There were insufficient data on intakes of soya products to reach a conclusion on the association of soya products with risk of prostate cancer. Advice on nutritional factors is the responsibility of the Scientific Advisory Committee on Nutrition (http://www.sacn.gov.uk/).

11. Other potential risk factors include ethnicity[11,12], a number of genetic polymorphisms (for example genes involved in androgen metabolism and signalling pathways)[12], and endocrine factors (such as low testosterone levels, and elevated IGF-1 levels)[11,13,14]. These observations have led to the suggestion that androgenicity may influence prostate cancer risk.

Chemical exposures associated with prostate cancer

Cadmium

12. Occupational exposure to cadmium was associated with an increased incidence of lung cancer and was considered by the World Health Organisation's International Agency for Research on Cancer (IARC) to be carcinogenic to humans (i.e. Group 1)[20]. Chronic dietary administration of 50 ppm cadmium in the diet to rats has been reported to be associated with proliferative responses of the prostate (e.g. hyperplasia and adenoma)[21]. The finding of increased incidence of prostate cancer in rats given a single subcutaneous injection of cadmium[22] was considered by members to be dependent on functioning of the testes and androgen production. Subcutaneous administration of higher cadmium doses, which induced testicular toxicity and thus reduced androgen production, resulted in no evidence for prostate cancer. It was noted that prostate cancer had been induced following direct injection of cadmium into the prostate of rats but members considered that this route of administration was of limited relevance[23].

13. The Committee considered one published paper[24] which reported evidence that low concentrations of cadmium chloride could interact with androgen receptor *in vitro* and could also produce an androgenic response (e.g. increased prostate weight) *in vivo* in rats given relatively low intraperitoneal doses. This suggests a plausible mechanism by which cadmium might be associated with prostate tumours in rats.

14. However the evidence from occupational studies regarding prostate cancer showed no association in the majority of studies including relatively large cohort studies. Thus overall there was no evidence to associate occupational exposure to cadmium with cancer of the prostate. The Committee was aware of a relatively old study of residual exposure which reported 40 years of mortality follow-up of the residents of Shipham, Somerset, England where there were high soil-levels of cadmium. No evidence for an excess mortality from prostate cancer was found, though this was only based on 2 cases[25]. The possibility that cadmium might induce androgen imbalance and thus might potentially be associated with prostate cancer should be monitored any relevant information considered in the future.

Pesticides and endocrine disrupting chemicals.

15. There is evidence from a variety of *in-vitro* studies that a number of pesticides (such as certain organochlorine insecticides (o,p'DDT, p,p'DDT, ,β-hexachlorocyclohexane (β-HCH) and the fungicide chlorothalonil) can produce androgenic effects[26,27]. However it has been noted that some of these pesticides can also induce anti-androgenic effects (e.g. vinclozolin)[27].

16. The Committee agreed that any potential androgenic effect *in vivo* following environmental exposure to pesticides and other endocrine disrupting chemicals was likely to be minimal. The Committee noted that there was some epidemiological evidence suggesting a weak association between herbicide exposure and prostate cancer[27-29]. The Committee considered the evidence for an association between farmers, farm workers and pesticide applicators and increased risk of prostate cancer. These studies are considered below in paragraphs 24-30.

17. The Committee was aware that the development of appropriate biomarker approaches to the determination of exposure might aid in the evaluation of exposure to pesticides. There was however, comparatively limited information available where biomonitoring data had been used to evaluate exposure in epidemiological studies of prostate cancer. The only retrieved publication was in abstract form[30].

Genotoxic chemicals.

18. A number of genotoxic chemicals including the polycyclic aromatic hydrocarbon benzo(a)pyrene have been found to induce prostate tumours in experimental animals (http://www.advisorybodies.doh.gov.uk/pdfs/cc0335.pdf). Co-administration of testosterone enhanced the tumourigenicity in experimental animals. Epidemiology studies investigating occupational exposure to polycyclic aromatic hydrocarbons have reported an association with prostate cancer in a number of studies[31,32].

19. A further discussion paper which presented a detailed review of the epidemiology studies of the potential association between occupational exposure to PAHs and increased risk of prostate cancer was provided by the DH Toxicology Unit. (http://www.advisorybodies.doh.gov.uk/pdfs/Cc0412.pdf)

20. The overall conclusion reached in the additional review prepared by the DH Toxicology Unit was that there are several occupational groups where relatively high exposures to PAHs could be anticipated, e.g. truck drivers, foundry workers, chimney sweeps and to a lesser extent fire-fighters. There have been a number of epidemiological investigations of the potential association between exposure to PAHs in these occupational groups and risk of prostate cancer. This has included several cohort studies in coke oven workers, fire-fighters and chimney sweeps. The adequacy of exposure data documented is very limited in most of the reports reviewed in the DH Toxicology Unit paper. Where exposure data

or information on the duration of occupational exposure were available, there was evidence from some studies of both greater exposure to PAHs and slightly higher risks of PC, but there was no compelling evidence for an increased risk of prostate cancer in any of the PAH exposed occupational groups studied.

21. The Committee agreed that overall the available studies do not provide evidence that is convincing for an association between occupations with exposure to PAHs and an increased risk of prostate cancer.

Vitamin supplements (zinc)

22. The Committee was asked to comment on the recent paper by Leiztmann M et al which investigated approximately 47,000 individuals as part of the U.S.A. based Health Professionals Follow-up study[33]. Members considered that the study had been adequately undertaken by a well respected group using the Health Professionals cohort established in the U.S.A. in 1986. There was a statistically significant increase in relative risk for advanced prostate cancer in men consuming ⩾100 mg/day supplemental zinc (RR = 2.29, 95% Confidence Interval (CI) 1.06-4.95). There was limited evidence for a dose-response relationship which was not statistically significant. There was a statistically significant association with taking supplemental zinc for ⩾10 years (RR = 2.37, 95% CI 1.42-3.95). Members were uncertain as to whether individuals who consumed high amounts of supplemental zinc would be more likely to seek PSA testing. However it was noted that the authors had considered routine screening for PSA up to the year 2000 in their evaluation. Members felt that the arguments presented by Leitzmann and colleagues regarding the role of intracellular concentrations of zinc in prostate tissue were inconsistent with the existing information on zinc and it was not possible to derive a biologically plausible hypothesis from the information reported. It was noted that a number of comments regarding the approach to statistical analysis of the data, the small number of cancer patients who reported intakes of zinc over 100 mg/day and the limited evidence to support a biologically plausible hypothesis concerning dietary supplements containing zinc and increased risk of prostate cancer had been raised in published correspondence commenting on the paper by Leiztmann M et al[34-37].

23. The Committee considered that the study results could not be dismissed. However, members heard that dietary supplements available in the U.K. each contained up to 50 mg of zinc. The Expert Group on Vitamins and Minerals had recently established a Safe Upper Level for dietary supplementation of 25 mg zinc/day based on evidence that consumption of 50 mg/day might reduce the absorption of copper across the gastrointestinal tract (http://www.foodstandards.gov.uk/multimedia/pdfs/evm_zinc.pdf)[38]. Information from the EPIC-Norfolk cohort (for first 1860 individuals entering the cohort in 1993/4) reported that 5% of subjects were consuming zinc supplements (the intake from supplements was 4.9 (ffl 4.1 mg/d). Thus the number of individuals consuming more than 50 mg zinc/day from supplements was likely to be very small. The Committee agreed that it was not possible to identify sufficient numbers of individuals for study from the EPIC cohort, and that therefore that it was not feasible to undertake any further epidemiological investigation of dietary zinc intake and prostate cancer in the UK.

Occupations associated with prostate cancer.

Farmers, farm workers and pesticide applicators

24. A number of studies have indicated a small excess of prostate cancer PC amongst farmers and farm-related workers and pesticide applicators, although other studies have failed to confirm this observation. Several reviews and meta-analyses of the epidemiological literature have been published. These generally described a slight excess of prostate cancer[39-47].

25. The COC considered a systematic review on occupational related pesticide exposure and cancer by Van Maele-Fabry and Willems[47] in detail. This meta-analysis produced an overall relative risk of 1.13 (95% C.I. 1.04-1.22) for prostate cancer in workers exposed to pesticides in pesticide related occupations (from 11 cohort, 4 Proportional Mortality Ratio, and 7 case control studies). Members noted that for all studies (excluding proportional mortality ratio Studies) the relative risk was 1.09 (95% C. I. 1.00 – 1.19) and that the risk estimates were for all farming occupations and not just for pesticide applicators. North American studies tended to show higher prostate cancer risk than European studies. The Committee considered that pesticide exposure was likely to be lower in Europe. The separate risk ratio for pesticide applicators (Relative risk 1.64 95% C.I. 1.23 – 2.38) was greater than the overall risk ratio for all studies.

26. The Committee also considered the large retrospective cohort study reported by Morrison et al[29] in detail. This study comprised male farmer aged 45 or more at 1971 identified through the Canadian National Mortality Database during the period of June 1971 up to the end of 1987. A total of 1,148 prostate cancer deaths and over two million person years were observed. The analyses reported were based on a one third sample from this cohort who had completed the more extensive census questionnaire thus allowing for better classification of exposure. A relative risk of 2.23 (95% C.I. 1.30-3.84) for prostate cancer was reported for farmers (aged 45-69 y) who sprayed herbicides on to 250 or more acres ($p<0.01$ test for trend). The Committee noted this analysis was based on younger farmers who were more likely to have applied the herbicides themselves. A subsequent analysis using data for mortality from 1981-1987 reported no evidence for a dose-related effect of herbicide use on prostate cancer[29]. It was possible that changes in herbicides used by Canadian farmers may account for this finding.

27. The Committee agreed that these two studies provided some evidence for increased prostate cancer risk for farm workers most exposed to pesticides and with some evidence suggesting an association between increased risk of prostate cancer and exposure to pesticides and in particular herbicides.

28. The COC also noted two separate cohort studies of cancer incidence from the U.S.A. (a retrospective analysis of licensed pesticide applicators in Florida and a prospective analysis of pesticide applicators from Iowa/North Carolina)[48,49]. The Florida study showed no association between prostate cancer and year of first licence (a proxy measure for duration of exposure). The Iowa/North Carolina study found no evidence for a trend with increasing exposure to herbicides, fumigants and fungicides but did report

a trend regarding organochlorine pesticides and older age. No trend was documented for individual organochlorine pesticides in this study. Overall these two studies provided some limited evidence for an association between pesticide exposure and prostate cancer but provided no convincing evidence regarding any specific pesticide exposures.

29. The Committee was aware of a review of prostate cancer undertaken by the Health and Safety Executive[50] published in 1998 which had concluded that the potential association between farmers/farm workers and prostate cancer merited further monitoring of the literature.

30. Overall the Committee agreed there was some evidence to suggest an association between farmers/farm workers, exposure to pesticides and increased risk of prostate cancer. The possibility of such an association could not be discounted and the published literature should continue to be monitored for further studies. Members commented on the need for improved measures of exposure to pesticides and in particular herbicides. It was considered that the potential association between herbicide use by farmers and farm workers should be kept under review.

Rubber workers

31. The further review undertaken by the DH Toxicology Unit at the request of the COC identified epidemiological studies undertaken at rubber manufacturing plants in the U.S.A., Europe and the U.K. as well as two studies where the location of the rubber manufacturing plant was not reported. (http://www.advisorybodies.doh.gov.uk/pdfs/Cc0413.pdf)

32. Overall there was no convincing evidence to associate employment in the rubber industry with prostate cancer. A number of the studies investigated the association between employment in particular jobs and prostate cancer. The suggestion for such an association came from studies in rubber manufacturing plants in the U.S.A. where the task of compounding and mixing was highlighted, but no definite conclusions could be drawn. On the basis of the limited available studies, there was no convincing evidence to associate prostate cancer with any particular chemical exposure at rubber plants.

33. The Committee concluded that the information from the available epidemiological studies are consistent with the view that overall, there is no evidence convincing of an increased risk of prostate cancer in rubber workers as a whole.

Other occupations

34. The Committee agreed that the evidence regarding other occupations and prostate cancer did not suggest any hypotheses that required further investigation.

COC conclusions

35. The Committee agreed the following overall conclusions;

i) The increase in incidence of prostate cancer reported over the past 2-3 decades is largely accounted for by improved identification of cases due to increased numbers of individuals undergoing surgery for benign prostatic conditions and the use of Prostate Specific Antigen Screening.

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

iii) The information from the available epidemiological studies are consistent with the view that overall, there is no convincing evidence of an increased risk of prostate cancer in rubber workers as a whole.

iv) There is no convincing evidence to associate other occupations with prostate cancer.

v) There is no convincing evidence to associate occupational exposure to cadmium with cancer of the prostate. The possibility that cadmium might induce androgen imbalance and thus might potentially be associated with prostate cancer should be monitored and relevant new information considered in the future.

vi) The one available epidemiological study on dietary zinc supplementation and risk of prostate cancer dose found increased risk of prostrate cancer at high levels of supplementation (>100 mg/day). Further epidemiology studies are unlikely to provide sufficient numbers of individuals regularly consuming high doses of supplements for a study to be undertaken in the U.K. The Committee agreed that it could not identify a biologically plausible rationale as to why zinc should be associated with prostate cancer.

COC/04/S6 December 2004.

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Cancer Biomarkers and Prevention Group, Biocentre, University of Leicester

Professor David Forman BA PhD FFPHM
Professor of Cancer Epidemiology, Unit of Epidemiology and Health Services Research,
School of Medicine, University of Leeds

Mrs Rosie Glazebrook
Non-specialist Member

Professor David Harrison BSc MB ChB MD FRCPath FRCP(Edin) FRCS(Edin)
Professor and Head of Department of Pathology, University of Edinburgh Medical School

Ms Denise M Howel BSc MSc CStat FIS
Senior Lecturer in Epidemiological Statistics, School of Population and Health Sciences,
University of Newcastle

Dr Sandra Jane Kennedy BSc PhD FRCPath CBiol FIBiol
Vice-President of Safety Assessment UK, GlaxoSmithKline

Professor David H Phillips BA PhD DSc FRCPath
Professor of Environmental Carcinogenesis, Institute of Cancer Research

Dr Ruth Roberts BSc PhD
Director of Toxicology, Safety Assessment, AstraZeneca

Professor David E G Shuker BSc ARCS PhD DIC CChem FRSC
Professor of Organic Chemistry and Head of Department of Chemistry, The Open University

Dr Nicola Wallis BSc MBChB MRCPath MFPM
Safety and Risk Management, Pfizer Global Research & Development

SECRETARIAT

Mr J Battershill BSc MSc Scientific Secretary
Dr D Benford BSc PhD Scientific Secretary – Food Standards Agency
Mr K Mistry Administrative Secretary
Dr R Fielder BSc PhD Dip RCPath (until August 2004)
Ms F Pollitt MA Dip RCPath

Declaration of interests during the period of this report

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
Professor P G Blain (Chairman)	NONE	NONE	NONE	NONE
Dr C Allen	NONE	NONE	NONE	NONE
Professor A Boobis	Abbey National	Shareholder	Servier	Research support
	Barclays Bank	Shareholder		
	BG Group	Shareholder		
	BT Group	Shareholder		
	Centrica	Shareholder		
	Marks and Spencers	Shareholder		
	National Grid Transco	Shareholder		
	Scottish Power	Shareholder		
Dr P Carthew	Provalis	Share Holder	NONE	NONE
	Unilever	Salary		
Professor P B Farmer	Abbey National	Shareholder	American Chemistry	Research Support
	Bradford & Bingley	Shareholder	Council	
	Celltech	Shareholder	CEFIC	
	Foreign & Colonial	Shareholder		
	Friends Provident	Shareholder		
	Health Effects Institute	Research Committee Member		
	Torotrak	Shareholder		
Professor D Forman	Barclays	Shareholder		
	Friends Provident	Shareholder		
	HBOS	Shareholder		
	Woolwich	Shareholder		
Mrs R Glazebrook	Dr Foster Ltd	Salary	NONE	NONE
	BT Group	Shareholder		
	Lloyds TSB	Shareholder		
	National Grid	Shareholder		

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
Professor D Harrison	Medical Solutions	Shareholder	NONE	NONE
	Quintiles	Consultant		
	Scottish Medicine	Consultant		
Ms D Howel	NONE	NONE	NONE	NONE
Dr S J Kennedy	Unilever	Shareholder	NONE	NONE
Professor D Phillips	Aviva	Shareholder	NONE	NONE
	Banco Santander	Shareholder		
	BG Group	Shareholder		
	Bradford & Bingley	Shareholder		
	Centrica	Shareholder		
	Lattice Group	Shareholder		
	National Grid	Shareholder		
	Takeda	Shareholder		
Dr R Roberts	AstraZeneca	Salary	NONE	NONE
		Shareholder		
	P & O	Shareholder		
Professor D Shuker	NONE	NONE	NONE	NONE
Dr N Wallis	Pfizer	Salary	NONE	NONE
		Shareholder		