Committees on *Toxicity* *Mutagenicity* *Carcinogenicity* of Chemicals in Food, Consumer Products and the Environment

1994 Annual Report

HMSO

1994
ANNUAL REPORT OF THE COMMITTEES ON
TOXICITY
MUTAGENICITY
CARCINOGENICITY
OF THE CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

LONDON: HMSO

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ISBN 0 11 321912 1

If you require any information about the references used in the preparation of this report please write to the committee's administrative secretary at the following address:

Department of Health
Room 679D
Skipton House
80 London Rond
Elephant and Castle
London SE1 6LW

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About the Committees

This is the fourth joint annual report of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) and the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC). The aim of these reports is to provide the toxicological background to the Committees' decisions for the concerned professional. Those seeking further information on a particular subject can obtain relevant references from the Committees' administrative secretary.

Members of the COT, COM and COC are appointed by the Chief Medical Officer (CMO). The Committees advise the CMO and, through the CMO, the Government.

Committee members are appointed as independent scientific and medical experts on the basis of their special skills and knowledge. They are appointed for fixed time periods, generally three years, and are eligible for reappointment at the end of their terms. The terms of reference are at Annex 1.

The report also contains the commercial interests of committee members. Members are required to declare any commercial interests on appointment and, again, during meetings if a topic arises in which they have an interest. If a member declares a specific interest in a topic under discussion, he or she may, at the Chairman's discretion, be allowed to take part in the discussion, but they are excluded from decision making. Guidance on this is at Annex 2.

For the first time this year, the report contains, at Annex 4, an alphabetical index to subjects and substances considered in this and the previous three reports. A second index, at Annex 5, contains details of the subjects on which the COT has given advice since 1987 as part of its consideration of the results of surveillance for chemicals in the UK diet. These considerations are published in the Food Surveillance Papers which report this surveillance work, rather than in the Committee's annual reports.

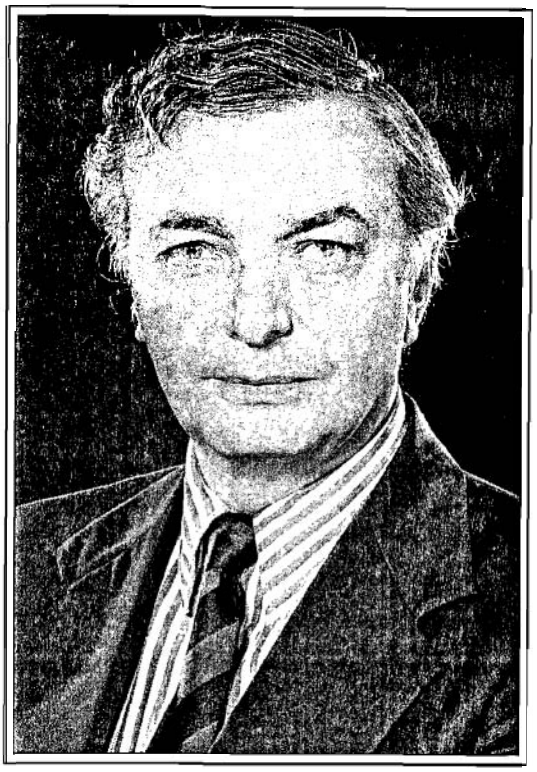
The usual way in which committee reviews are conducted is that the relevant secretariat critically assesses all the relevant data and prepares papers for the Committee. These normally consist of appendices giving detailed summaries of

the studies reviewed – methodology and results – and a covering paper in which the available data are briefly summarised, the most important points highlighted and recommendations presented for discussion by the Committee. Although original study reports are not routinely circulated to members, they are made available on request, and are circulated if the study is particularly complex. Definitive summaries are necessary because documentation on any one chemical can amount to many hundreds of pages.

Many of the reviews conducted by the Committees are done so at the request of other Government Departments and the Committee secretariats liaise closely with colleagues in these Departments. The Committees offer advice independent of each other in their area of expertise but will, if need be, work closely together. This is helped by the close working relationships of the secretariats. If, for example, during a review of a particular chemical by the COT, it becomes clear that there is need for expert advice on mutagenicity or carcinogenicity aspects, it will be referred to COM or COC as appropriate. These three Committees also provide expert advice to other advisory committees, such as the Advisory Committee on Novel Foods and Processes and the Food Advisory Committee. There are also links with the Veterinary Products Committee, the Advisory Committee on Pesticides and the Steering Group on Chemical Aspects of Food Surveillance.

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

Professor H F Woods
(Chairman)
BSc MB BCh WIRCP
D Phil FRCP(Lon) FFPM
FRCP(Edin) FFOM



Preface

The is a sustained and growing public interest in the safety aspects of chemicals in food and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has, during the last year, continued to play a key role in the network of committees and working groups which assess chemical risks and benefits. This role is exemplified by the range of individual topics presented in this report.

In my preface to last year's report I made reference to the continuing development of more refined ways of using numerical assessment data as presented in the form of an Acceptable Daily Intake (ADI). Through the publication of statistics relating to the dietary intake of food additives in the United Kingdom published by the Steering Group on Chemical Aspects of Food Surveillance, it is possible to see how the ADI for a particular compound is working in practice so far as the consumer population is concerned.

During the year the policy of having a wide range of expertise available on the Committee has been shown to be a great advantage. In addition, we have been very well served by our administrative and scientific secretariats.

One topic covered in this report brings to attention a problem of toxicology which may increase in both prevalence and importance in future years. This is the issue of Unlicensed Traditional Remedies. The Committee recognises the useful role that traditional remedies can play in the treatment of illness. However, toxicological data collected by the Poisons Unit at Guy's Hospital has caused the COT to be concerned about some preparations containing persistently dangerous concentrations of toxic heavy metals. We are also concerned about the presence of wrongly identified herbs and extraneous materials added to remedies that have caused widespread illness in countries outside the United Kingdom.

The varied topics covered in this report and the difficulty of many questions posed to us made 1994 a challenging year for the Committee.

FRANK WOODS

Azodicarbonamide

1.1 This chemical is used as a flour improver by the breadmaking industry. It is used mainly to overcome certain difficulties in breadmaking which can be caused by natural variations in the quality of the available flour, facilitating the production of bread of a consistent quality. It is not used routinely in the UK other than for the production of certain speciality breads.

1.2 The Committee had considered this flour treatment agent on a number of occasions prior to 1994. Its discussions centred on two issues: 1. whether there was adequate evidence that no detectable levels of azodicarbonarnide remained in the bread after baking and the identity of a compound or compounds.to which it was converted (breakdown products) and 2. whether its use gave rise to higher levels of the contaminant ethyl carbamate than those normally found in bread. Ethyl carbamate is produced naturally during fermentation in the production of various foods and alcoholic beverages. It is a genotoxic carcinogen in experimental animals and is therefore regarded as a potential carcinogen in humans. As with other genotoxic, naturally-occurring food contaminants, the COT advises that levels should be kept to the lowest technologically achievable.

1.3 During its initial considerations in previous years, the COT had been largely reassured that no detectable levels of azodicarbonarnide remained after commercial baking of bread. It had, however, asked for confirmation of the breakdown products, the main one of which had been identified tentatively as the compound biurea. It had also asked for information on the particle size distribution in commercial grade azodicarbonarnide to ensure that this variable had been adequately considered in the breakdown studies, and had indicated that some toxicity testing was likely to be requested on biurea, although it had not yet decided on the extent of testing required. The COM had asked for a further study to confirm that the mutagenic activity seen in some *in vitro* mutagenicity tests on azodicarbonarnide was due to the induction of oxidative free radicals rather than a mutagenic action of azodicarbonarnide *per se*. This was important because even if no azodicarbonarnide residues are detected in bread, it could still be present at levels less than the analytical detection limit. The COT had also reviewed two surveys on the levels of ethyl carbamate in bread made using azodicarbonarnide and was of the opinion that these contained too few samples and that a further survey was necessary to identify a level of addition of azodicarbonarnide to flour which did not cause a significant increase in levels of ethyl carbamate.

1.4 No further data had been forthcoming from industry on this subject and so, in 1994, officials of the Ministry of Agriculture, Fisheries and Food sought clarification of its current position from the Federation of Bakers regarding the outstanding data requests from the COT. The federation replied that the further work requested appeared to its members to be of doubtful validity in assessing the safety-in-use of azodicarbonamide. It indicated that it did not intend to undertake the work requested.

1.5 The COT gave careful consideration to the arguments presented by the Federation of Bakers. On the issue of particle size, it accepted the Federation's case that the 5 micron specification for the commercially used grade of azodicarbonarnide would not leave detectable residues in bread. However, on the other points of detail, which related to confirming the identity of breakdown

products, the need for further mutagenicity studies on azodicarbonamide and the increased levels of ethyl carbamate, the Committee did not accept the arguments presented. The Committee decided that without data which satisfactorily addressed its outstanding concerns or a commitment from industry to provide such data, it had to advise the Food Advisory Committee that azodicarbonamide should no longer be permitted for use as a flour treatment agent.

Comfrey

1.6 The COT published its assessment of the safety-in-use of comfrey and comfrey products in its 1992 Annual Report. This included a recommendation that concentrated forms of comfrey such as tablets and capsules should no longer be available and this advice was subsequently acted on by the suppliers of these preparations. During 1994 the Society for the Promotion of Nutritional Therapy submitted to the COT the results of a survey of comfrey users which it had carried out. The survey had collected information on the amounts and types of comfrey preparations used, and had asked respondents to supply details of any health benefits they considered had resulted from use of these preparations and any adverse health effects they had experienced.

1.7 The results of the survey were considered by the COT as part of a review of its advice on comfrey. The Committee concluded that they provided insufficient new scientific information to cause it to modify its previous advice, as set out in the 1992 Annual Report.

Emulsifier YN (Ammonium Phosphatides)

1.8 This food additive is used as an emulsifier and viscosity reducing agent in the manufacture of chocolate products and is produced from rapeseed oil. It was reviewed by the Committee some years ago as part of the FAC/COT review of The Emulsifiers and Stabilisers in Food Regulations, the report of which was published in 1992. At that time the Committee classified Emulsifier YN as provisionally acceptable for use in food, subject to the provision of teratology studies in two species within two years of publication of the report. The reason for asking for these studies was to bring the toxicological data set on this additive up to present day standards.

1.9 At its June 1994 meeting, the Committee considered a new teratology study on Emulsifier YN, which had been carried out in rats. It concluded that the study was well-conducted and showed no adverse effects of Emulsifier YN at levels up to 5% in the diet of the test animals. The Committee also used the opportunity to review its outstanding data requirements for this additive and decided that a second teratology study was no longer required. In making this decision it took into account the innocuous nature of the emulsifier, what is known about its manufacture, composition and metabolism, and the uniformly negative toxicity results so far reported even after administration of very high doses. The Committee set an Acceptable Daily Intake (ADI_{1994}) for Emulsifier YN of 0–30 milligrams per kilogram

bodyweight (mg/kg bw), based on a NOAEL from a long-term study in the rat of 3000 mg/kg bw/day and a safety factor of 100.

Epoxidised soya bean oil

1.10 Epoxidised soya bean oils (ESBO) are used as heat stabilisers, plasticisers and lubricants in a wide range of plastics, including a number of cling films. The Committee reviewed the available toxicology on ESBO in 1989 when it considered a report on plasticiser levels in food contact materials prepared by the Working Group on Chemical Contaminants from Food Contact Materials of the Steering Group on Chemical Aspects of Food Surveillance. At that time the Committee requested further genotoxicity, teratology and fertility studies in order to complete the evaluation of ESBO. Appropriate studies were subsequently submitted by a consortium of manufacturers.

1.11 The COT reviewed the reports of these new studies and concluded that ESBO showed no genotoxic potential and that a teratology and a multigeneration study in rats gave no cause for concern about the safety of ESBO. Additional data supplied on a two year feeding study in rats confirmed the Committee's previous conclusion, based on a summary report of this study, that the No Observed Adverse Effect Level (NOAEL) was 100mg/kg bw/day.

1.12 The COT recommended a tolerable daily intake (TDI) for ESBO of 1 mg/kg bw which was derived by applying a safety factor of 100 to the NOAEL seen in the two year feeding study in rats. (A TDI was appropriate in this case, rather than an ADI, as ESBO would be present as a contaminant in food rather than an additive).

Hemicellulase from *Aspergillus Niger*

1.13 During 1994 the COT considered submissions of data from a number of companies on hemicellulase preparations produced by culture of the microorganism *Aspergillus niger* (A. niger). All preparations were intended for use in the manufacture of bread. The submission for each enzyme was assessed with respect to the Committee's guidelines for the safety assessment of microbial enzyme preparations used in food, which were discussed in the 1991 and 1992 annual reports. In only one case – a submission for a spray dried hemicellulase preparation – did the COT consider that the submission complied sufficiently well with its guidelines to enable it to recommend approval at this stage. The Committee was satisfied as to the safety-in-use of this preparation subject to the provision of an acceptable specification and the submission of further data within one year of the Committee's advice being forwarded to the company concerned. This provisional approval did not, however, extend to an ultra filtered product derived from the same preparation. The further data requested were: data on the type of other subsidiary enzyme activities present in the product in addition to endoxylanase activity, data on the variation in the level of activity of these enzymes from a number of batches of product, and results of TOS/E[1] estimations (endoxylanase activity) prior to ultrafiltration. The Committee also asked for justification of the use of

1. TOS/E = The ratio of total organic solids to the actual enzyme present.

germ filters with a pore size of 0.4μm instead of 0.22μm which is the standard grade used in the pharmaceutical industry.

1.14 The COT considered representations from manufacturers of enzyme preparations on the requirement in its guidelines to deposit the production culture with an independent reference culture collection. The identification of these cultures is commercially sensitive information and some manufacturers have expressed concern that deposition in a reference culture collection might enable rival companies to gain access to the cultures. The COT decided to seek further advice on this issue.

Hydrocarbon Propellants

1.15 In **1993** the Committee was asked to consider the safety-in-use of an aerosol propellant consisting of a mixture of the low molecular weight hydrocarbons propane, n-butane and isobutane. The propellant was intended for use in a range of products based on vegetable oils dispensed from aerosol cans. The manufacturers were intending to market the sprays for three purposes: as a pan spray, as a garlic flavoured spray for making garlic bread, or for spraying on to uncooked food as a salad dressing. Limited residue studies had been carried out. These indicated that no residues of hydrocarbon were detected in a sample of food fried using the pan spray. However, significant amounts of hydrocarbon were detected in a sample of lettuce coated with oil dispensed from the aerosol containing the salad dressing some time after spraying. This prompted the Committee to ask for further information on residue levels and on the rate of disappearance of these gases from foods.

1.16 The manufacturer was apprised of the COT's view and decided to withdraw the application for use of the propellants in the product to be marketed as a salad dressing. The Committee reconsidered the application in **1994** and was satisfied that for the other two products, which are intended for use in processes involving heating, most of the propellant gases will be driven off. Consequently, it advised that there were no toxicological concerns associated with the use of the propellants in these products.

Immobilised Lipase from *Rhizopus Niveus*

1.17 The Committee was asked to consider the safety-in-use of an immobilised lipase (an enzyme) prepared by fermentation of the fungus *Rhizopus niveus.* The enzyme was intended for use in the production of interesterified fats for use as cocoa butter substitutes. The COT considered that the data presented for this enzyme, while not fully satisfying the requirements of its guidelines for the safety assessment of microbial enzyme preparations used in food, provided sufficient evidence of safety and consistency. It agreed a temporary clearance for one year and asked for the following data to be submitted in that time: a more extensive specification, clarification of the variation in protease activity values, a test for

pathogenicity of the production strain, and an assay for chromosome aberrations on a concentrated extract of the enzyme prepared using an organic solvent which simulates the reaction mixture of fatty acid esters and vegetable oil.

Potassium and sodium ferrocyanides

1.18 These additives are used as anticaking agents in salt and as fining agents in wine and cider. Intakes are very low compared to most food additives (a few hundred micrograms per day). They were last considered by the COT in 1988 when they were classified as provisionally acceptable for use in food subject to the provision of an appropriate set of mutagenicity studies, the full report of a two-year rat study on sodium ferrocyanide which had been carried out in the early 1970s and a teratology study on one of the salts. These data were submitted to the COT for review in 1994.

1.19 The Committee accepted the advice of the secretariat of the COM that the mutagenicity studies were well conducted and were consistently negative. The teratology study of sodium ferrocyanide indicated no adverse effects up to a limit dose of 1 g/kg bw/day. The COT noted that the two-year rat study was carried out before the introduction of Good Laboratory Practice and had not been performed to current day standards. Nevertheless, it was considered to be an adequate study and to show no evidence of carcinogenicity. The only finding of note was an increased cell excretion rate in two-hour urine samples. This was considered not to be serious in the absence of an increased rate of kidney damage in ferrocyanide-treated rats compared to controls.

1.20 The Committee decided that, in view of the low intakes of these additives by man and the reassuring results of the available toxicity studies, no further testing was required. It set a group $ADI_{„}$ for ferrocyanides of 0–50 µg/kg bw. This was calculated from a NOAEL in the long-term rat study of about 5 mg/kg bw/day and a safety factor of 100.

Unlicensed Traditional Remedies

1.21 During 1994, the COT saw the results of a survey carried out by the National Poisons Unit, Guy's Hospital on the occurrence of adverse effects in individuals consuming unlicensed traditional remedies. After considering these data, the Committee gave its advice on this issue in the form of the following statement:–

(i) The Committee recognises that traditional remedies can play a useful role as part of the armamentarium against illness. Indeed many allopathic drugs have their antecedents in therapeutic traditional remedies. The use of allopathic medicines is based on the administration of known amounts of an active principle which has to conform to established standards of quality, safety and efficacy. Traditional remedies should conform to similar standards. Until they do so, inherent variability of content, dependent on conditions of growth of constituents, as well as variability in prescribing practice and the expertise of traditional practitioners, will continue to increase the difficulty of investigating and demonstrating the presence or

indeed the absence, of adverse effects. The result is that reports of positive adverse associations have been restricted largely to major or life threatening events and there is little information on the overall safety of traditional remedies.

(ii) We are agreed that the clinical toxicological data collected by the Poisons Unit, Guy's Hospital give sufficient cause for concern and suggest that the use of some traditional remedies poses a serious threat to health.

Recommendations

(iii) We are concerned that preparations containing potentially dangerous concentrations of toxic heavy metals are widely available. Strong efforts should be directed to prevent the importation of such products if possible and to minimise their sale and prescription to the public.

(iv) We are concerned that wrongly identified herbs and extraneous materials added to remedies can and have caused widespread illness in countries other than the UK. Quality control of both the raw materials and the finished product are required. .

(v) We wish to see more investigations on the extent of systemic exposure especially in those communities which may be most at risk.

(vi) Health care professionals and the public should be made aware of the wide use and the potential for toxicity that traditional remedies may pose.

Topics Still Under Consideration

1.22 The following topics, which were discussed by the COT at meetings held in 1994, are under review:

Acetyl Tributyl Citrate
Alitame
Boron in drinking water
Certain microbial enzyme preparations
Health aspects of manganese exposure from the use of Methylcyclopentadienyl Manganese Tricarbonyl in fuel
Polychlorinated biphenyls
Sucrose polyesters of fatty acids

1994 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

DECLARATION OF INTERESTS DURING THE PERIOD OF THIS REPORT

	Personal Interest		Non Personal Interest	
Member	Company	Interest	Company	Interest
Prof H F Woods (Chairman)	Cadbury Schweppes Edinburgh Investment Trust Foreign & Colonial Investment Trust Hanson Smith & Nephew	Share Holder Share Holder Share Holder Share Holder Share Holder	Wide range of national & international food & chemical companies	Dean of the Faculty of Medicine, University of Sheffield, which has extensive activity in teaching and research in nutrition and toxicology and in topics related to and supported by many companies in the food and chemical industry. Trustee of Hallamshire Therapeutic Research Trust Ltd, Harry Bottom Charitable Trust and Special Trustees for the former United Sheffield Hospitals.
Dr P J Aggett	Milupa	Occasional Fee	Nestlé Nutricia Milupa	Research Support Research Support Research Support
Dr V Beral	NONE	NONE	NONE	NONE
Dr N A Brown	American Petroleum Glaxo Styrene Tate & Lyle Zeneca	Occasional Fee Occasional Fee Occasional Fee Occasional Fee Occasional Fee	EC (DGXII) Glaxo Wellcome Trust Zeneca	Research Support Research Support Fellowship & Research Support Research Support
Prof A D Dayan	British Petroleum ICI Proctor & Gamble Schering Plough Smith Kline Beecham TI Wellcome Foundation	Consultant Consultant Consultant Consultant Consultant Share Holder Pension	Glaxo	Research Fellowship
Prof G G Gibson	NONE	NONE	Unilever plc	Research Studentship
Dr G Hawksworth	NONE	NONE	Glaxo Group Research Pfizer Central Research Servier Research & Dev Smith Kline Beecham Solvay Pharma Zeneca	Research Support Research Support Research Support Research Support Research Support Research Support
Dr I Kimber	British Airways British Petroleum ICI Zeneca Zeneca	Share Holder Share Holder Share Holder Share Holder Employee	Unilever plc	Grant for Research

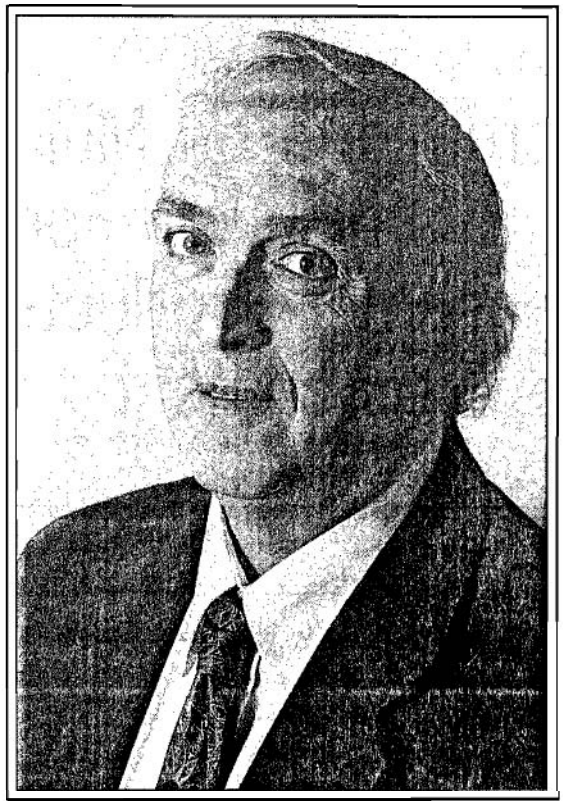
COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

DECLARATION OF INTERESTS DURING THE PERIOD OF THIS REPORT

	Personal Interest		Non Personal Interest	
Member	Company	Interest	Company	Interest
Dr D Prentice	Ciba Gensia Hoechst Veterinar Hoffman-La Roche Nestle Rhone-Poulenc Rorer Sandoz Schering-Plough Syntex Synthelabo (LERS) TAP Pharmaceuticals Wyeth-Ayerst	Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant	NONE	NONE
Dr A G Renwick	International Sweeteners Association Smith Kline Beecham	Consultant Consultant	Bayer Ciba-Geigy Glaxo Hoffman-La Roche Solvay-Duphar	Research Support Research Support Research Support Research Support Research Support
Mr F Sullivan	Borax Ltd Chiroscience Cocensys Frauenhofer Research Rank Hovis McDougall Rothmans International Sandoz Wyeth-Ayerst	Consultant Occasional Fee Occasional Fee Consultant Consultant Occasional Fee Occasional Fee Occasional Fee	EC Community (DGV)	Grant
Dr A Thomas	NONE	NONE	NONE	NONE
Prof D Walker	Amersham British Petroleum Boehringer FEDESA Sandoz Solvay Duphar	Share Holder Share Holder Occasional Fee Occasional Fee Occasional Fee Occasional Fee	Robens Institute, Univ of Surrey	Retaining Fee
Prof R Walker	Cadbury Beverages Europe Coffee Science Info Centre Food Safety Advisory Centre IDV Ltd Proctor & Gamble	Consultant Consultant Consultant Consultant Consultant	Nestlé	Research Studentship

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

Professor J M Parry
(Chairman)
BSc PhD DSc



Preface

When mutations occur in human genes they may lead to both somatic diseases, such as cancer, and to a variety of inherited birth defects. Chemicals which interact with the genetic material, DNA, or some of the components of the cell division apparatus may potentially induce mutations and thus impact upon human health. To prevent mutagenic chemicals entering the environment and thus exposing the human population to genetic damage, a variety of test methods have been developed to detect the mutagenic activity of chemicals. Information from such tests may be used to regulate the safety of chemicals used for industrial, agricultural, medical or other purposes.

The function of the COM is to provide advice to Government Departments on the mutagenic potential of chemicals. This involves the detailed evaluation of published and unpublished data to determine the mutagenic activity and, where necessary, to identify those missing pieces of information which may clarify the Committee's evaluation. The Committee's evaluation of activity of a chemical is then made available to the appropriate Governmental Departments or Agencies with regulatory responsibility.

To ensure adequate standards of chemical testing there is a need for the development of methods with high sensitivity and reliability An ongoing role of the COM is to evaluate test methods and to provide advice on the status of individual methods and their suitability for routine usage. During 1994 the COM evaluated three test methods namely; cell transformation assays, in *vitro* micronucleus assays and dominant lethal assays, and provided advice on their suitability for current use, needs for development and appropriate methods for data evaluation. General advice on the suitability of tests were provided for the development of guidelines for chemicals in general and human medicines.

JAMES PARRY

Dithiocarbamates in Latex Products

2.1 Dithiocarbamates are used as accelerators in latex surgical examination gloves. The Medical Devices Directorate (MDD) requested advice on 3 specific compounds namely zinc dimethyl- (ZDMC), zinc diethyl- (ZDEC) and zinc dibutyl-dithiocarbamate (ZDBC). Available data showed that ZDMC was mutagenic both *in vitro* and *in vivo*. MDD sponsored a number of studies to investigate the mutagenic potential of ZDEC and ZDBC in comparison with ZDMC. The studies commissioned were *in vitro* assays for gene mutation in Salmonella typhimurium and in mammalian cells (the mouse lymphoma assay), an *in vitro* assay for clastogenicity in mammalian cells (metaphase analysis) and an *in vivo* bone marrow assay (a micronucleus test in the mouse). It was hoped that the higher homologues in the series, ie ZDEC and ZDBC would have significantly less mutagenic potential than ZDMC.

2.2 These data were considered by the COM at meetings in 1993 and 1994 and the following conclusions were drawn regarding ZDEC and ZDBE:–

(i) ZDEC. There was clear evidence of mutagenic activity *in vitro* both in bacteria and in a cytogenetics assay in human lymphocytes. The *in vitro* mouse lymphoma assay was unlikely to detect all clastogenic activity (most small colonies not counted).

(ii) ZDBC. There was no mutagenic activity in bacteria. However, there was evidence of mutagenicity in an *in vitro* cytogenetics assay in human lymphocytes. The *in vitro* mouse lymphoma assay was unlikely to detect all clastogenic activity for the reason given above.

(iii) Negative results were obtained for both compounds in an *in vivo* micronucleus test in mice.

2.3 The results of additional liver UDS assays using ZDMC, ZDEC, ZDBC, commissioned by the MDD were considered during 1994.

(i) ZDMC appeared to be negative in the liver UDS assay when given orally to male rats, but the significance of the compound related increase in both nuclear and cytoplasmic grain counts is unclear, and therefore the compound should be regarded as having demonstrated an equivocal result in this assay.

(ii) ZDEC gave some indication of an increase in a liver UDS assay 16 hours after treatment; the effects were too small to be regarded as a clear positive, but the result should be considered as equivocal.

(iii) ZDBC gave negative results in the *in vivo* liver UDS assay when given orally to male rats.

(iv) The available data on ZDBC was considered to provide adequate reassurance that this substance does not have *in vivo* mutagenic potential. The use of this accelerator (rather than ZDMC or ZDEC) in the manufacture of latex gloves would significantly reduce any remaining concerns arising from the potential mutagenic effect of the small residual amounts of this accelerator present in latex gloves.

Polycyclic Aromatic Hydrocarbons

2.4 Polycyclic aromatic hydrocarbons (PAHs) are a group of highly lipophilic chemicals that are present ubiquitously in the environment as pollutants. The PAHs are compounds with structures made up of two or more fused benzenoid rings. The principal source of PAHs in the atmosphere are the combustion of fossil fuels, refuse burning and coke ovens; vehicle emissions are also a major source in developed countries. Humans are exposed to a mixture of PAHs from inhalation of air pollution and ingestion through food and drinking water. Workers in industries such as aluminium production, coal gasification, coke production and iron and steel founding are exposed to higher levels occupationally. Cigarette smoke is also a major source of PAHs for those individuals who smoke.

2.5 The COM and the COC were asked for advice by DoE and MAFF on evaluation of the individual compounds so that priority or representative compounds could be identified for monitoring and/or surveillance. DoE's urban air monitoring programme will monitor 21 members of the class, and the Expert Panel on Air Quality Standards is to consider options for regulatory control of these compounds. In a similar fashion MAFF's Working Party on Organic Environmental Contaminants in Food is concerned with the presence of 18 PAHs reported to be present in food. Many of these PAHs are the same as those monitored in air. The COM and COC were asked for advice on the priorities for surveillance within the group of compounds, based on carcinogenic activity, Conclusions were reached for 16 out of the 25 PAHs considered.

2.6 The COM concluded that the PAHs could be grouped into 4 classes:

1 – Clear *in vivo* mutagens.

2 – Compounds with some indication of mutagenic potential.

3 – Compounds with no significant *in vivo* mutagenic potential.

4 – Compounds on which there were inadequate data and no decision could be made.

2.7 With regard to category 2, it was felt that *in vitro* assays using exogenous metabolic activation systems such as 'S–9' could not be used as definitive information in the ranking system for PAHs and that category 2 should be used when there was some indication of *in vivo* activity or *in vitro* activity using cell mediated activation assays.

2.8 Of the PAHs considered the groupings based on mutagenicity data were as follows:

1: Benzo(a)pyrene, Dibenz(ah)anthracene, Benzo(a)anthracene

2: Chrysene, Cyclopenta(cd)pyrene, Benzo(b)fluoranthene, Benzo(ghi)perylene, Benzo(k)fluoranthene, Indeno[1, 2, 3-cd]pyrene, Benzo(b)naph[2, 1-dlthiophene.

3: Pyrene, Benzo(e)pyrene, Anthracene, Phenanthrene, Fluoranthene.

2.9 The data on the remaining 9 PAHs indicated that they fell into category 4. A further review of these compounds would be undertaken at a future date.

Hydroquinone and Phenol

2.10 HSE asked for advice on the interpretation of the mutagenicity data on hydroquinone and phenol. The principal use for hydroquinone is in the manufacture of black and white film developers. Other uses included the manufacture of antioxidants and polymerisation inhibitors; as a chemical intermediate in the manufacture of pharmaceutical, agrochemicals and dyes; in the production of cosmetics and topical creams; and as a laboratory reagent. Phenol is mostly used during the manufacture of phenolic resins, but is also used in the manufacture of disinfectants, some shampoos and in the preparation of soaps.

2.11 The following conclusions were agreed:

Hydroquinone

(i) Hydroquinone was an in vivo mutagen in somatic cells, but there was no convincing evidence for effects in germ cells in vivo. Any risk to human health by ingestion would be likely to be greatly reduced because of two protective mechanisms, namely rapid conjugation and detoxification via the glutathione pathway. Mutagenicity also appeared to be related to peroxidase activity and catalase could have a protective role. Actual systemic exposure levels would be very much lower than levels at which positive results had been achieved in studies in animals.

(ii) The Committee concluded that by the oral route there was potential for a threshold of activity based on the protective mechanisms outlined at (i). Because of this, regulatory authorities could adopt a safety factor approach. The situation regarding dermal exposure was less clear. Toxicokinetic studies would be needed in skin and if similar protective mechanisms were demonstrated the same threshold approach would be appropriate. It is not possible with the presently available data to assume a threshold existed for activity on the respiratory tract following exposure by inhalation.

(iii) A recent epidemiology study of hydroquinone workers (employed during 1949–1990) was considered. Certain limitations of the study were noted: small numbers, inadequate description of a major change in operating procedure during the period of interest and deficiencies in the exposure measurements; however, these observations did not detract from the overall conclusion that there was no significant increase in cancer incidence in workers exposed to hydroquinone.

Phenol

(i) In vitro mutagenicity data on phenol were of poor quality and results difficult to interpret, but in vivo data showed phenol to be a somatic cell mutagen at very high dose levels. Data from germ cell studies in vivo were inadequate to allow any definite conclusions to be drawn. It was noted that negative results had been obtained in long term carcinogenicity bioassays in both rats and mice.

(ii) Any risk to human health by ingestion would be likely to be greatly reduced because of two protective mechanisms, namely rapid conjugation and detoxification via the glutathione pathway. Mutagenicity also appeared to be related to peroxidase activity and catalase could have a protective role.

Actual systemic exposure levels would be very much lower than levels at which positive results had been achieved in studies in animals.

(iii) The Committee concluded that by the oral route there was potential for a threshold of activity based on the protective mechanism outline at (ii). Because of this, regulatory authorities could adopt a safety factor approach. The situation was less clear with regard to dermal exposure. Toxicokinetic studies would be needed in skin and if similar protective mechanisms were demonstrated the same threshold approach would be appropriate. It is not possible on the presently available data to assume a threshold existed for activity on the respiratory tract following exposure by inhalation.

Polychlorinated Biphenyls (PCBs)

2.12 The Committee was asked for advice on the mutagenicity of PCBs by the COT Secretariat who were reviewing the toxicity of these compounds. The following conclusions were reached;

(i) The majority of the available data on the mutagenicity of PCBs relates to commercial preparations principally Aroclor 1254 but also Aroclor 1242 and Kanechlor 500. These products consist of mixtures of a large number of compounds, and trace amounts of other chemical contaminants, such as polychlorinated dibenzofurans. Very limited data are available on specific PCBs.

(ii) Extensive studies on Aroclor 1254 using the Salmonella assay for gene mutation in bacteria were consistently negative. Negative results were also obtained with Aroclor 1221 and 1268. Data from other *in vitro* tests are too limited to draw any definite conclusions.

(iii) Commercial PCBs (Aroclor 1254,1242 and Kanechlor 500) have been fairly extensively investigated for induction of clastogenic effects in bone marrow of rodents *in vivo*. Negative results were consistently obtained. In addition, negative results were also obtained when Aroclor 1254 was investigated for DNA adduct formation in the liver by 2 groups using the ^{32}P-postlabelling technique. Negative results were also obtained with both Aroclor 1254 and 1242 in assays to detect genotoxic effects in germ cells using both cytogenetic analysis and the dominant lethal assay.

(iv) Commercial PCBs do not have mutagenic effects in the Salmonella assay nor was there any evidence of genotoxicity *in vivo* in studies in bone marrow, liver or male gonads. They can be regarded as essentially 'non-genotoxic' and any carcinogenesis in animal studies is likely to be produced by 'non-genotoxic' mechanisms.

(v) Very little mutagenicity data are available on specific congeners. There is limited evidence that 3, 4, 3', 4'-tetrachlorobiphenyl and mixtures of 3, 4, 3', 4'-tetrachlorobiphenyl and 2, 5, 2', 5'-tetrachlorobiphenyl, but not the pure form of 2, 5, 2', 5'-tetrachlorobiphenyl, have clastogenic potential in an *in vifro* assay using human lymphocytes. There are, however, no adequate *in vivo* data on specific congeners and the absence of activity with

the commercial PCBs in this regard would suggest that these congeners do not have significant mutagenic potential.

(vi) The commercial PCBs (Aroclor 1254 and Kaneclor 500) have been investigated by several groups for promoting effects in 2 stage *in uiuo* models of chemically induced hepatocarcinogenesisin rats. In all cases evidence of promoting activity was obtained. There is also evidence in animals that PCBs act as complete carcinogens.

Trihalomethanes in Drinking Water

Chloroform, Bromodichloromethane [BDCM], Chlorodibromomethane [DBCM] and Bromoform

2.13 The Committee was asked to consider these four trihalomethanes by the Department of the Environment's Drinking Water Inspectorate. These compounds arise in drinking water largely as the result of disinfection, although they may also occur individually as the result of contamination. The following conclusions were reached;

Chloroform

(i) Chloroform had been extensively investigated for its mutagenic potential *in uitro.* Essentially negative results were obtained in standard tests for point mutation in bacteria, and in limited tests for chromosome aberrations in mammalian cells. Equivocal results were obtained in a recent poor quality mouse lymphoma assay, but all earlier studies for gene mutation in mammalian cells gave negative results. The weight of evidence from the *in uitro* data was negative.

(ii) Conflicting results had been reported *in uiuo.* Positive results had been claimed in assays for clastogenicity (metaphase analysis) in rats and SCE induction in mice and also for a low level of DNA binding in the liver and kidney of rats. However, the Committee had strong reservations about the quality of these studies and the results reported. In contrast, negative results had been obtained in four good quality micronucleus tests in mice, in a DNA binding study in the mouse and in *in uiuo* liver UDS studies in rats and mice. In conclusion, the Committee agreed that there was no convincing evidence that chloroform was genotoxic.

Brornodichloromethane

(i) Bromodichloromethane has shown some mutagenic activity when investigated in the Salmonella assay under conditions which minimised vapour loss. Positive results were obtained with TA100 in the presence and absence of S-9. Negative results were obtained in plate incorporation assays in Salmonella where no attempt had been made to prevent vapour loss. Positive results were also obtained in the mouse lymphoma assay in the presence of S-9 and in a metaphase analysis for clastogenicity using Chinese hamster lung cells. These *in uitro* data indicate that bromodichloromethane has mutagenic potential.

(ii) Negative results were obtained in a bone marrow micronucleus test using a comprehensive protocol and the intraperitoneal route. No conclusions can be drawn from a reported result in a bone marrow metaphase analysis study due to the questionable nature of the data available. In addition, the very small increase in SCEs seen in a separate bone marrow study was not significant. The bone marrow data were therefore considered essentially negative.

(iii) However, results are needed from an assay using a second tissue *in vivo* before the mutagenic potential seen *in vitro* can be discounted; an *in vivo* liver UDS assay was recommended. Until such data are available it would be prudent to assume that this compound is a potential *in vivo* mutagen.

Chlorodibromomethane

(i) Chlorodibromomethane has shown some mutagenic activity when investigated in the Salmonella assay under conditions which minimised vapour loss. Positive results were obtained with TA100 in the presence and absence of S-9 and with TA98 in the presence of S-9. Negative results were obtained in plate incorporation assays in Salmonella where no attempt had been made to prevent vapour loss. Positive results were also obtained in a metaphase analysis for clastogenicity in Chinese hamster lung cells. These *in vitro* data indicate that chlorodibromomethane has mutagenic potential.

(ii) Negative results were obtained in a bone marrow micronucleus test using a comprehensive protocol and the intraperitoneal route. No conclusions can be drawn from a reported positive study due to the questionable nature of the data available. The very small increase in SCEs seen in a separate bone marrow study was not significant. The bone marrow data were therefore considered essentially negative.

(iii) However, results are needed from an assay using a second tissue *in vivo* before the mutagenic potential seen *in vitro* can be discounted; an *in vivo* liver UDS assay was recommended. Until such data are available it would be prudent to assume that this compound is a potential *in vivo* mutagen.

Bromoform

(i) Bromoform has been shown to induce gene mutation in Salmonella TA98 in the presence of S-9 and in TA100 in the absence of S-9 when using a system that prevented loss of vapour. Negative results were obtained in plate incorporation assays in Salmonella where no attempt had been made to prevent vapour loss. Equivocal results were obtained in the mouse lymphoma assay and in a metaphase analysis for chromosome damage in Chinese lung cells in the presence of S-9. The *in vitro* data indicate that bromoform has mutagenic potential.

(ii) Bromoform has been subjected to a number of *in vivo* assays to investigate clastogenicity in bone marrow. Negative results were obtained in a micronucleus test using a comprehensive protocol and the intraperitoneal route. A slight increase in micronuclei was seen in an oral micronucleus study at the top dose used, and this study was regarded as equivocal. There is one report of a positive metaphase analysis but these data are questionable. No conclusions can be drawn from the very small increase in SCEs seen in another study using the oral route.

(iii) In light of the equivocal nature of the *in vivo* bone marrow clastogenicity studies, it is recommended that bromoform be studied for further clastogenic activity in a micronucleus assay in the bone marrow. If this is negative, results from a second tissue would be needed to provide adequate reassurance that bromoform does not have *in vivo* activity. An *in vivo* liver UDS assay was considered appropriate. Until such data are available it would be prudent to assume that this compound is a potential *in vivo* mutagen.

Sucralose

2.14 In 1989 the company manufacturing this proposed new sweetener had been asked for further data on the potential in *vitro* mutagenicity of its hydrolysis product. The COM advised, in 1993, that an *in vitro* liver UDS assay should be undertaken in the first instance. The study reports were considered by the COM during 1994 who concluded that a negative result had been obtained and agreed that no further work was required.

Acetyl Tributyl Citrate (ATBC)

2.15 ATBC is used as a plasticiser in polyvinylidene chloride cling films, and was considered by the COM in June 1989 when further data were requested, namely a repeat *in vitro* metaphase study using either rat or human lymphocytes conducted to an adequate protocol with the results confirmed in an independent experiment; in addition, an *in vitro* study to investigate gene mutation in mammalian cells had been requested in view of the widespread exposure to relatively low levels of the compound. The COM considered reports of the further studies requested which had been submitted by a consortium of manufacturers.

2.16 The Committee agreed' that following conclusions:

(i) ATBC has given negative results in studies to investigate gene mutation in Salmonella and negative results were also obtained when the clastogenic potential of ATBC was investigated by metaphase analysis in rat peripheral lymphocytes. In addition, the compound does not have chemical structural alerts.

(ii) A study to investigate gene mutation in mammalian cells using the CHO/HGPRT assay could not be evaluated due to the inadequate protocol used (relatively small number of cells, large variation in spontaneous mutation frequency and inconsistencies in cytotoxicity data [apparently 100% cytotoxicity at several concentrations]). No conclusions could be drawn from the negative data reported and the Committee thus recommended that a further gene mutation assay in mammalian cells conducted to an adequate protocol (preferably a mouse lymphoma assay) should be undertaken.

Furocoumarins in the Diet

2.17 The COM was asked to advise on the mutagenic risk arising from the levels of 8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP) and psoralen in food which are naturally occurring constituents of several plant species including a number of food plants (eg parsnip, celery citrus fruits and peas). The Committee was aware that MAFF were currently in the process of collating the results of surveillance data on furocoumarins for a future Food Surveillance Paper. The COM was also asked to consider whether the review should be limited to these 3 linear bifunctional psoralens or whether data on angular monofunctional furocoumarins (eg angelicin) and other linear furocoumarins present in food should also be reviewed.

2.18 The Committee was aware that there were extensive data available on the photomutagenicity of 8-MOP as this compound has been widely used in PUVA therapy for psoriasis. The following conclusions were agreed.

(i) The mechanism of the photomutagenicity of the bifunctional psoralen 8-MOP plus UVA is well established. For practical purposes 5-MOP and psoralen can be regarded as having similar activity. The monofunctional angelicin is a significantly less potent photomutagen (by an order of magnitude).

(ii) In view of the very weak mutagenic potential of 8-MOP, and related compounds, in the absence of W A, the low levels of exposure arising from the diet (a few µg8-MOP/mg total furocoumarin) are unlikely to be of concern with regard to systemic mutagenic effects.

(iii) The possibility of a local photomutagenic effect on the skin due to a combination of the psoralen plus W A exposure cannot be totally excluded but blood levels arising from dietary intakes are likely to be very low; around an order of magnitude below those resulting from PUVA treatment. Exposure to W A from natural sunlight is also considerably less. Any risk is thus likely to be very small.

Test Methods

2.19 The Committee continued to provide advice on test methods particularly in the context of the international guidelines developed by the OECD which are currently being updated. Advice was provided prior to an OECD nominated expert meeting held in Rome in September 1994 to finalise the updating of 7 existing guidelines and to consider 2 new guidelines. In particular the Committee recommended the acceptance of the peripheral blood inicronucleus test in mice as an acceptable alternative to the bone marrow assay and agreed that a combined guideline covering both approaches could be accepted. Advice was also provided for input into discussions by the Genotoxicity Working Party of the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

2.20 In addition, consideration was given to a number of areas relating to specific test method development. These are considered in the following sections;

Cell Transformation Assays

2.21 The COM reviewed the use of cell transformation assays using cultures prepared from rodents in evaluating the potential genotoxicity of chemicals. The Committee focused its' review on the Syrian Hamster embryo assay and the Syrian Hamster Dermal assay (SHD) but also considered mechanistic studies on transformation in SHD cells. The COM agreed that transformation assays using Syrian Hamster cells were not yet ready for routine use, but warranted further work on both validation and understanding of the underlying mechanisms. It was noted that there were many problems with the murine assays with regard to their use in general screening and it was agreed that further work on the murine cell transformation assays was not a priority at the present time.

In *Vitro* Micronucleus Test

2.22 An *in vitro* micronucleus test, if adequately validated as a general screening test, would have significant advantages in costs compared to metaphase analysis. The COM considered the progress in the development of the in *vitro* micronucleus test. The Committee concluded that the *in vitro* micronucleus assay should be validated as an alternative *in vitro* assay for screening for potential clastogenicity by an inter-laboratory collaborative study, and agreed that more data were needed before the additional value of this assay in screening chemicals for aneugenic potential could be fully assessed.

Presentation on Dominant Lethal Assay

2.23 Professor Ashby gave a brief presentation on the rodent dominant lethal assay, drawing attention to a draft paper for publication on the topic. He outlined the basis of the assay, and discussed some of the parameters and problems that might obscure the assay endpoint. He concluded that there was a need to present data from dominant lethal studies in a logical manner and proposed a graphical presentation of total implants/female, number of post implantation losses, and percentage of pregnant females (data analysed on a weekly basis). The possibility of false positives due to toxic rather than genotoxic effects should be recognised, di-2-ethylhexyl phthalate being noted as an example where positive results were associated with a marked reduction in the number of pregnant females.

Topics Still Under Consideration

2.24 The following topics which were discussed by the COM at meetings, held in 1994, are under review;

Ethanol, acetaldehyde and alcoholic beverages
Phenol and hydroquinone
Polycyclic aromatic hydrocarbons

1994 Membership of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

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COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

DECLARATION OF INTERESTS DURING THE PERIOD OF THIS REPORT

	Personal Interest		Non Personal Interest	
Member	Company	Interest	Company	Interest
Prof J M Parry (Chairman)	BAT Grants Committee British Telecom Compass Catering Fisons Pharmaceuticals Glaxo Group Research JIB Insurance Smith Kline Beecham South Wales Electricity Wellcome Foundation	Consultant Share Holder Share Holder Consultant Grant Share Holder Consultant Share Holder Consultant	Amersham International Pfizer Smith Kline Beecham Welsh Water	Grant Studentship Studentship Studentship
Prof J Ashby	ZENECA	Employee	NONE	NONE
Prof R L Carter	NONE	NONE	NONE	NONE
Dr J Cole	NONE	NONE	NONE	NONE
Dr C Cooper	NONE	NONE	NONE	NONE
Prof D S Davies	Clinical & Biochemical Pharmacology Consultancy Ltd ICI plc ML Laboratoris plc Scheming Plough, USA Zeneca plc	Director Share Holder Non Executive Director Consultancy Share Holder	Astra Boots Fisons Glaxo Hoechst Kali Chemi Lilly ML Laboratories Plc Pfizer Phacmacia Roche Products Sanofi Winthrop Smith Kline Beecham Stirling Upjohn Wellcome Foundation Zeneca	Fellowship Research Research Research & Studentship Research Research Research Fellowship, Studenship & Research Research Research Research Research Travel grant Research Research Research Research
Prof H J Evans	British Petroleum British Telecom Croda Fisons ICI plc Merck, Sharpe & Dohme Scottish Power Southern Electric Y Water W Water Zeneca	Share Holder Share Holder Share Holder Share Holder Share Holder Consultant Share Holder Share Holder Share Holder Share Holder Share Holder	NONE	NONE
Prof R F Newbold	NONE	NONE	NONE	NONE
Dr D J Tweats	Glaxo	Salary Share Option Holder	NONE	NONE
Dr S Venitt	Abbey National plc	Share Holder	NONE	NONE
Dr R M Winter	NONE	NONE	NONE	NONE

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

Professor R L Carter
(Chairman)
MA DM DSc FRCPath
FFPM

Preface

The COC evaluates chemicals for human carcinogenic potential at the request of the Department of Health and other Government Departments. This years' work amply demonstrates the wide range of topics which the Committee can be asked to consider. The Department of the Environment (DoE) requested advice on guideline values for arsenic, four individual trihalomethanes, and benzo(a)pyrene in drinking water and on the potential carcinogenic risk of fluoranthene in water. The Committee was also asked to undertake further reviews of polyurethane coated breast implants by the Medical Devices Directorate (MDD) and certain Man Made Mineral Fibres (MMMFs) by the Health and Safety Executive (HSE). Regarding chemicals in food, the Committee assessed the carcinogenicity data on polychlorinated biphenyls at the request of the COT, gave advice to MAFF on the carcinogenic risk of certain naturally occurring furocoumarins in the diet, and considered a toxic equivalency approach to mixtures of polycyclic aromatic hydrocarbons in food. In addition to its work on specific substances, the Committee was also asked for advice from the Ethnic Minorities Section of the Department of Healths' Health Promotion section on whether the chewing of betel nut and areca products without tobacco was a carcinogenic risk.

On a more general issue, the Committee agreed a scheme for the prioritisation of carcinogenic chemicals. The scheme is intended to aid MAFF and DH in prioritising action on putative carcinogenic chemicals in food. Future work will involve testing the appropriateness of the prioritisation scheme by considering known chemical carcinogens.

RICHARD CARTER

Arsenic in Drinking water

3.1 The Department of the Environment asked the COC for its opinion on the revised guideline value of 10 µg/l reported in the second edition of the WHO guidelines on drinking water quality published at the end of 1993. The COC views would assist the Drinking Water Inspectorate's review of domestic regulations and negotiations within the European Commission.

3.2 The Committee concluded that:

(i) Inorganic arsenic compounds have clastogenic potential and are human carcinogens. It is prudent, in the absence of further data, to assume that they are genotoxic carcinogens and that there is no threshold for such effects.

(ii) Levels of arsenic in drinking water should be lowered as far as is reasonably practicable. The proposed reduction of the regulatory limit in drinking water from 50 µg/litre to 10 µg/litre was welcomed.

Trihalomethanes in Drinking Water

Chloroform, Bromodichloromethane [BDCM], Chlorodibromomethane [DBCM] and Bromoform

3.3 The Committee was asked to consider this group of trihalomethanes by the Department of the Environment's Drinking Water Inspectorate. The COC was also asked whether the four compounds could be considered as a single group. The mutagenicity of these trihalomethanes was considered by the COM (see paragraph 2.13). The COC came to the following conclusions.

(i) It is unlikely that adequate epidemiological data will become available in the near future for the evaluation of these compounds in drinking water and thus risk assessments will have to be based on animal studies.

(ii) In considering concentrations of trihalomethanes in drinking water, it is appropriate to proceed as if each individual 'compound carried a potential carcinogenic hazard. Their pattern of tumour induction in animal bioassays, mechanism of carcinogenic action and level of potency are not sufficiently similar to justify consideration as a single group.

(iii) These compounds arise in drinking water largely as a result of disinfection, although they may also occur individually as the result of contamination. In public water supplies in England and Wales, the total concentration of the four trihalomethanes rarely exceeds 100 microgrammes per litre (100 µg/1). Thus for a 60 kg individual, daily ingestion of each trihalomethane would normally be considerably lower than 3 microgrammes per kilogram body weight (3µg/kg bw).

Chloroform

(iv) Chloroform induced renal adenomas and carcinomas in rats and mice. Administration of 38 mg/kg bw/day or more *via* the drinking water for 104 weeks produced a dose related increase in renal tumours in male but

not female rats; both genotoxic and non-genotoxic mechanisms have been demonstrated for renal tumours occurring exclusively in male rats due to other chemicals. The lowest reported carcinogenic dose in mice was 60 mg/kg bw/day in an experiment where male mice were given oral doses of chloroform by gavage, 6 days per week for 80 weeks. The reported increase in hepatocellular adenomas and carcinomas noted in carcinogenicity bioassays where chloroform was given by gavage in corn oils is uninterpretable, with respect to assessing human hazard, due to the pronounced liver toxicity. There is no convincing evidence of genotoxicity, and thus chloroform should be regarded as a non-genotoxic animal carcinogen.

BDCM

(v) BDCM induced renal adenomas and carcinomas in rats and mice and there is some evidence for induction of adenomas and carcinomas of the large intestine in rats. The lowest reported dose that gave rise to a carcinogenic effect in rats was 100 mg/kg bw/day in male and female rats given oral doses of BDCM by gavage, 5 days per week for 102 weeks. The lowest reported carcinogenic dose in mice was 50 mg/kg bw/day in an experiment where the animals were given oral doses of BDCM by gavage, 5 days per week for 102 weeks. BDCM was mutagenic *in vitro* but was negative in an *in vivo* bone marrow micronucleus assay. Results are needed from an *in vivo* assay using a second tissue in order to complete the evaluation of the mutagenicity of BDCM. It is prudent, at the present time, to assume that BDCM is a potential *in vivo* mutagen and hence provisionally a genotoxic carcinogen.

DBCM

(vi) DBCM induced a small increase in the incidence of hepatocellular adenomas and carcinomas in male and female mice after gavage administration of 100 mg/kg bw/day, 5 days per week for 104–105 weeks. This result is uninterpretable, with respect to assessing human hazard, due to the pronounced liver toxicity resulting from the administration of DBCM by gavage in corn oil. There was no evidence of carcinogenicity in rats given DBCM by gavage (at up to 80 mg/kg bw/day, 5 days per week for 102 weeks) or in mice given DBCM via the drinking water (at up to 400 mg/litre for 102 weeks). DBCM was mutagenic *in vitro* but was negative in an *in vivo* bone marrow micronucleus assay. Results are needed from an *in vivo* assay using a second tissue in order to complete the evaluation of the mutagenicity of DBCM. It is prudent, at the present time, to assume that DBCM is a potential *in vivo* mutagen and hence provisionally a genotoxic carcinogen.

Bromoform

(vii) Bromoform induced adenomas and carcinomas of the large intestine in male and female rats dosed by corn oil gavage at 200 mg/kg bw/day, 5 days per week for 105 weeks. There are no published studies of bromoform administered in the drinking water which could be used to clarify the significance of this result. Bromoform was mutagenic *in vitro* and gave an equivocal response in an *in vivo* bone marrow micronucleus assay. Results

are required from a further bone marrow assay and, if this is negative, from an *in vivo* assay using a second tissue in order to complete the evaluation of the mutagenicity of bromoform. It is prudent, at the present time, to assume that bromoform is a potential *in vivo* mutagen and hence provisionally a genotoxic carcinogen.

(viii) Levels of BDCM, DBCM and Bromoform in drinking water should be kept as low as is compatible with adequate disinfection of drinking water.

3.4 The Committee agreed that these conclusions should be reviewed when the results from additional studies requested by the COM are available.

Polycyclic Aromatic Hydrocarbons (PAHs)

Carcinogenicity Evaluation and Use of Toxic Equivalency Factors to Assess Mixtures

3.5 The PAHs had been previously considered by the COM and had been classified, into four broad groups: clear *in vivo* mutagens, compounds with some mutagenic potential, compounds with no significant *in vivo* mutagenic potential, and compounds on which there were inadequate data and no decision could be made (see paragraph 2.4-2.9 above). The COC was asked to prioritise the 25 PAHs previously considered by the COM. The COC considered comparative carcinogenicity studies on groups of PAHs, and developed a classification using an approach based on toxic equivalency factors (TEF). MAFF had approached the DH for an opinion on the suitability of TEFs and on the size of the factors suggested.

3.6 It was concluded that the use of TEFs, despite a number of limitations, were appropriate for ranking the carcinogenic potential of PAHs and interpreting the results of monitoring surveys of these compounds in food. The Committee agreed a prioritisation for 16 out of the 25 PAHs (see below). The remaining PAHs would be considered at a future date.

Concern (TEF)	*Compound*
High (1.0)	Dibenz(a, h)anthracene, benz(a)pyrene
Medium (0.1)	Benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno[1,2,3-cd]pyrene, benzo(ghi)perylene, chrysene, cyclopenta(cd)pyrene, anthanthrene, benzo(b)naph[2,1-d] thiophene.
Low (0.001)	Fluoranthene, pyrene, phenanthrene, anthracene, benz(e)pyrene

Fluoranthene in drinking water

3.7 Fluoranthene, was also considered individually. The Department of the Environment had asked for specific advice on this compound which was the biggest single PAH contaminant in drinking water.

3.8 The following conclusions were reached:

(i) Fluoranthene showed mutagenic activity *in vitro* with exogenous metabolic activation and formed low levels of DNA adducts *in vivo* in various tissues in the rat. Fluoranthene had not been adequately tested for *in vivo* mutagenic activity, and should therefore be regarded for the moment as a potential *in vivo* mutagen.

(ii) The available data were inadequate for a definite conclusion to be drawn on the carcinogenicity of fluoranthene. Data from skin-painting carcinogenicity studies in mice were negative, although the numbers tested were small. A positive result was obtained in a short term lung tumour assay in neonatal mice, but the predictive value of this test is questionable. In view of the chemical structure of fluoranthene and its mutagenic potential, it would be prudent to assume that fluoranthene has carcinogenic potential.

(iii) The Committee recommended that *in vivo* mutagenicity studies such as a bone marrow assay for chromosome damage and a liver UDS assay, should be performed using oral administration. If these tests gave negative results fluoranthene, could be regarded as having no significant genotoxic potential in *vivo* and hence would not be regarded as a genotoxic carcinogen.

3.9 It was agreed that the Committee would reconsider the levels of fluoranthene in drinking water when the additional *in vivo* data were available.

Quantitative risk assessments of benz(a)pyrene in drinking water

3.10 Particular consideration of the maximum admissible concentration (MAC) of benzo(a)pyrene [BaP] in drinking water in the UK was requested by the Drinking Water Inspectorate. At present, the prescribed concentration of BaP in drinking water in the UK under the Water Supply (Water Quality) Regulations 1989 is 10 ng (0.01 µg)/litre as an annual average. This standard was based on the WHO (1984) guideline value for drinking water of 0.01 µg/litre for BaP. In 1993 the WHO had set a new higher guideline value of 0.7 µg/litre: this was based on a different mathematical model, but used the same inadequate experimental data, as the earlier value. The major reason for the increase in the guideline value was that the new WHO estimate made no correction for the difference in body surface area between mice and humans.

3.11 The Committee agreed the following conclusions:

(i) Benzo(a)pyrene is a potent genotoxic animal carcinogen and should be assumed to be a human carcinogen.

(ii) Varying estimates of the carcinogenic risk associated with exposures to BaP, based on differing data sets and using differing assumptions, demonstrate. the problems of mathematical modelling of such risks and the inadvisability of relying exclusively on such estimates for the setting of regulatory limits.

(iii) Since BaP is a genotoxic carcinogen and levels in UK drinking water conform to the present regulatory limit of 0.01 µg/litre as an annual average, levels should not be allowed to rise (ie the regulatory limit should not be raised) and efforts should be made to decrease concentrations wherever possible.

Polyurethane Coated Breast Implants

3.12 The Committee had previously considered this topic in 1991 when studies from the USA became available which suggested that polyurethane (polyesterurethane) used in the manufacture of breast implants had the potential to degrade in vitro to form the probable carcinogen 2, 4-toluenediamine (2, 4-TDA). At that time, the COC had concluded that:

(i) 2, 4-TDA should be regarded as a probable genotoxic carcinogen.

(ii) There was evidence that small ainounts of 2, 4-TDA could be released from polyurethane foam in vitro.

(iii) There was indirect evidence that implanted polyurethane foam broke down in vivo in rats, but the identity of the breakdown products had not been established and their possible effects on local tissues were not known.

(iv) There was no information on the breakdown of implanted polyurethane foam in human tissues.

(v) There were no data on the possible release of harmful substances other than 2, 4-TDA from implanted polyurethane foam either in vitro or in vivo.

(vi) There was no direct evidence that 2, 4-TDA was released from polyurethane-coated breast implants in vivo in women. If it were released, a carcinogenic risk could not be excluded but it was not possible to estimate the size of any such risk.

3.13 The Committee considered new information on the degradation and the pharmacokinetics of polyurethane foam in vivo.

3.14 The following conclusions were agreed:

(i) The Committee's advice remained that 2, 4-toluenediamine (2, 4-TDA) should be regarded as a probable genotoxic carcinogen when administered orally.

(ii) Direct evidence had showed that small amounts of 2, 4-TDA (estimated at less than 100 µg per day) were released in vivo from polyurethane coated breast implants in women. Since 2, 4-TDA can be metabolished to a genotoxic metabolite, this release might represent a potential carcinogenic hazard. The effects might occur locally around the implant, or elsewhere in the body, following absorption into the systemic circulation. It was not possible to estimate the size of the potential risk from this exposure.

(iii) Information on the breakdown of implanted polyurethane foam in human tissues suggested that breakdown occurred over a period of several years.

Betel Quid, Pan Masala and Areca Nut Chewing

3.15 The Committee was asked for advice from the Ethnic Minorities Section of the DH Health Promotion section on whether the chewing of betel nut and areca products **without** tobacco was a carcinogenic risk.

3.16 The Committee reached the following conclusions:

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

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

(iii) The Committee concluded that the use of these products without tobacco was possibly carcinogenic in humans.

Polychlorinated Biphenyls (PCBS)

3.17 The Committee was asked to review the carcinogenicity of PCBs by the COT who were reviewing the toxicology of these chemicals. The COM had previously considered the mutagenicity of these compounds, and concluded that PCBs were not genotoxic (see paragraph 2.12). The Committee considered that there was some evidence that PCBs acted as tumour promoters by a variety of mechanisms, possibly involving the **Ah** receptor or by stimulating cell proliferation and enzyme induction. Little information was available on specific PCB congeners. The following conclusions were agreed:

(i) Polychlorinated biphenyls (PCBs) are manufactured by the progressive chlorination of biphenyl, such that all commercial products are a mixture of several different congeners. Almost all commercial PCB mixtures contain small quantities of polychlorinated dibenzofurans. All the epidemiological data and carcinogenicity tests considered by the Committee were based on commercial mixtures, so it was not possible to draw conclusions on any individual congeners. PCBs have very long half lives within the human body.

(ii) Commercial PCBs did not have mutagenic effects in the Salmonella assay, nor was there any evidence of *in vivo* genotoxicity in bone marrow, liver or testes. They could be regarded as essentially non-genotoxic and any carcinogenic effects in animals were likely to be produced by non-genotoxic, but at present ill-defined, mechanisms.

(iii) A number of commercial PCBs have been shown to be carcinogenic in rats; Aroclor **1254** and **1260** and Clophen **60** induce hepatocellular carcinomas. Limited studies in mice indicated that Aroclor **1254** and Kanechlor **400** and **500** induce liver tumours in this species.

(iv) There were few data available on the carcinogenicity of PCBs in humans. Investigations on patients who consumed PCB-contaminated rice oil suggested that there was an increased incidence of liver cancer. Mortality studies in workers exposed to PCBs at capacitor manufacturing plants in the USA also suggested an increase in mortality from liver cancer. A report from a manufacturing site in Italy was uninterpretable because of the use of unrepresentative controls and lack of exposure data. In all the available studies the numbers involved were small and the results very difficult to interpret. Because of these inadequacies it was not possible to reach a definite conclusion from the epidemiological data.

(v) Commercial PCBs (Aroclor 1254 and Kanechlor 500) have been investigated by several groups for promoting effects in 2 stage *in vivo* models of chemically induced hepatocarcinogenesis; in all cases evidence of promoter activity was obtained.

(vi) It would be prudent to assume that all PCB congeners are potential human carcinogens.

Man Made Mineral Fibres (MMMFS: Glass Fibres, Rock and Slag Wool, but not Refractory Ceramic Fibres)

3.18 Man Made Mineral Fibres is a generic term denoting fibrous organic substances made primarily from rock, clay, slag or glass. These fibres can be classified into 3 general groups of glass fibres (glass wool and glass filament), rock wool or slag wool, and refractory ceramic fibres (RCFs). It is the first two types that are widely used in industrial and domestic insulation, with RCFs only being used for more specialised industrial purposes. The Committee provided advice to HSE and DoE on the MMMFs used in domestic insulation (ie glass fibres, rock and slag wool – but not RCFs) in 1986. The European Union was now considering the classification of MMMFs on the basis of their potential carcinogenicity (under the Dangerous Substances Directive 67/548/EEC) and HSE requested advice from the COC specifically on the classification question. The IARC published a review of MMMFs in 1988, which had reached broadly the same conclusions as the earlier COC consideration. Since then there have been little new epidemiology but there have been some new information from well conducted inhalation bioassays in rats using the respirable fraction from commercial fibres as the test material.

3.19 The Committee reached the following conclusions:

(i) The Committee noted that occupational exposure to rock/slag wool or glass wool in the early technological phase of the use of these materials showed a link with an increase in lung cancer although other confounding factors may have been present. There was no evidence of a risk of lung cancer associated with occupational exposure to rock/slag wool under modern working conditions, but the data are inadequate to reach a firm conclusion. There are no recent epidemiological data and, in view of the possibility of long-term effects of such exposures, there should be continued monitoring (including for mesothelioma) of workers exposed under modern conditions. The Committee understood that further epidemiological data would be

available from the European multisite study during 1995. The results will be considered by the COC.

(ii) Some doubts still remain and thus it would be prudent to act on the basis that sufficient exposure to any form of MMMFs in the production of user industries may increase the risk of lung cancer among the workforce. The information is insufficient to indicate a particular level of exposure to these fibres at which no adverse affects would be apparent. Current evidence confirms the appropriateness of the present limits for exposure.

(iii) Well conducted inhalation studies exposing rats to high levels of respirable rock and slag wool and glass fibres for two years showed no increase in lung tumours.

(iv) The MMMFs considered in this review (ie rock/slag wool and glass wool) should not be classified for carcinogenicity under the criteria laid out in the Dangerous Substances Directive (67/548/EEC), in view of the negative results in inhalation studies in animals.

Furocoumarins in the Diet

3.20 Furocoumarins are naturally occurring constituents of several plant species including food plants. They occur particularly in the Umbelliferae (e.g. parsnip, celery, parsley and coriander) but also in the Rutaceae (e.g. citrus fruits) and the Legumionosae (e.g. peas, beans, peanuts). The most commonly detected linear furocoumarins are 8-methoxypsoralen (8-MOP, xanthotoxin), 5-methoxypsoralen (5-MOP, bergapten) and psoralen itself.

3.21 The Committee was asked to advise on the carcinogenic risk posed by the concentrations of 8-MOP, 5-MOP and psoralen in certain foods to be reported in a forthcoming MAFF Food Surveillance Paper and to confirm whether there was a lower carcinogenic risk from angular furocoumarins such as angelicin in food. The advice applies to oral rather than skin exposure and to the usual concentrations of furocoumarins in the diet i.e. derived from normal vegetables and fruit. However, higher concentrations have been reported after extreme fungal contamination.

3.22 The Committee noted that many of the studies on 8-MOP were designed to assess the risk of PUVA therapy, used in the treatment of psoriasis and other skin diseases. Treatment consists of an oral dose of a psoralen (usually 8-MOP) of 0.5 – 0.6 mg/kg bw (around 40 mg) followed, 2 hours later, by UVA exposure at 0.5 – 11 J/cm^2 according to skin type or minimum erythemic dose. For comparison, dietary intakes are 0.02 mg/kg bw (1.4 mg) at most and daily UVA exposure is around 1 J/cm^2 in the summer in the north of the UK.

3.23 The Committee came to the following conclusions:

(i) PUVA therapy (8-MOP with UVA) clearly causes and increase in squnmous cell carcinomas of the skin in humans. The evidence for an increased incidence of other cancers with PUVA therapy is unconvincing.

(ii) Assessing the carcinogenic risk from the levels of furocoumarins in the diet is more difficult. There are no adequate epidemiologicalstudies of exposure

to furocoumarins other than by PUVA therapy; most studies have only examined 8-MOP and most pharmacokinetic data are based on patients with psoriasis rather than healthy volunteers.

(iii) The mutagenicity of the furocoumarins has been considered by the COM who concluded that 8-MOP plus UVA was photomutagenic. Psoralen and 5-MOP plus UVA could be regarded as having similar activity but angelicin was a significantly less potent photomutagen. In the absence of UVA, 8-MOP and related compounds had very weak mutagenic potential. The risk of a local photomutagenic effect at dietary exposures was considered to be very small.

(iv) There are few adequate data on the carcinogenicity of furocoumarins after oral exposure in animals. In one carcinogenicity study in rats, which used high doses (37.5 and 75 mg/kg bodyweight) of 8-MOP by gavage in corn oil, an increased incidence of neoplasms was seen only in males. There was a significant increase in malignant tumours in males at only one site (the Zymbal gland), and this increase was not dose-related. There was a non-significant increase in renal adenocarcinomas and significantly increased incidences of renal adenomas, subcutaneous fibromas and alveolar/bronchiolar adenomas. Thus, for 8-MOP without UVA, there is limited evidence for weak carcinogenic potential in male rats but it is difficult to base any conclusions with regard to human risk on these results.

(v) Although there are no oral carcinogenicity studies using 5-MOP, psoralen or angelicin, there are topical application studies comparing these three furocoumarins with 8-MOP. With UVA, 5-MOP and psoralen are similar to 8-MOP in terms of induction of skin tumours in animals after topical application but the incidence of skin tumours with angelicin and UVA was only two-thirds of the incidence with the other furocoumarins. None of the furocoumarins produced skin tumours by topical application without UVA.

(vi) The carcinogenic risk resulting from consumption of linear furocoumarins in food and exposure to UVA in sunlight is likely to be minimal for the following reasons.

- extreme dietary intakes of linear furocoumarins are estimated to be 25 fold lower than the doses used in PUVA therapy.

  high and variable blood concentrations of 8-MOP (0 to 600 ng/ml) are present following oral doses of 8-MOP given as tablets as part of PUVA therapy, which employs doses which saturate first-pass metabolism. In contrast, linear furocoumarins were not found at a detection limit of 2 – 4 ng/ml in the blood of a small number of volunteers (14) consuming large amounts of celery (300 – 700g). This difference between PUVA therapy and dietary intake is considered to arise from differences in the dose given and the rate and extent of absorption from a drug formulation and from a food matrix. Thus, blood concentrations of linear furocoumarins after eating celery are likely to be at least 75 fold lower than average blood concentrations during PUVA therapy.

- the intensity of UVA lamps used in PUVA therapy is approximately twice that of summer sunlight.

- the total area of the skin exposed to UVA is greater during PUVA therapy than during typical sun exposure.
- PUVA therapy is designed to ensure maximum 8-MOP levels in the skin at the same time as maximum UVA exposure. This will not necessarily occur with food consumption and sunlight exposure.

(vii) In summary, any carcinogenic or photocarcinogenic risk arising from linear furocoumarins in the diet is likely to be very small.

A Scheme for the Prioritisation of Carcinogenic Chemicals

3.24 The scheme was intended to aid MAFF and DH in prioritising action on putative carcinogenic chemicals in food. The COC had assessed polycyclic aromatic hydrocarbons (PAHs) using a draft scheme as model compounds. The Committee considered that three areas should be developed further; improvement in assessing population exposure, indication of potency, and how to address important information gaps. A paper dealing with these issues was considered.

3.25 Members concluded that:

(i) They would be content to operate the prioritisation scheme in conjunction with the Secretariat. This scheme would constitute a useful guide to assigning broad priorities for putative food carcinogens, and would help to focus official attention and resources where they were most needed.

(ii) A measure of potency might be included within the scheme (for example when comparing genotoxic carcinogens). It should be based on the best available data which allowed a comparison to be made, including epidemiological data, comparative studies in animals, and TD50 estimations. The Maximum Tolerated Dose (MTD) could be used as a surrogate for carcinogenic potency when ranking chemicals in circumstances where no other data were available.

(iii) The PAHs could be taken further through the scheme by the Secretariat and a final prioritisation presented to the Committee. Other compounds which have been considered by the Committees in the recent past such as benzene, and chlorinated hydrocarbons could also be ranked and prioritised in order to provide model or index classifications to test the appropriateness of results of the prioritisation scheme.

Topics Still Under Consideration

3.26 The following topics which were discussed by the COC at meetings held in 1994, are under review:

Alcoholic beverages, ethanol and acetaldehyde
Prioritisation of remaining polycyclic aromatic hydrocarbons.

1994 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

Professor R L Carter MA DM DSc FRCPath FFPM

MEMBERS

Professor P G Blain BMedSci MB PhD FRCP(Lon) FRCP(Edin) MFOM CBiol FIBiol
Professor R A Cartwright MA MB PhD FFPHM
Professor C E D Chilvers BSc(Econ) MSc Hon MFPHM
C Cooper BSc PhD DSc
Professor A D Dayan BSc MD FRCP FRCPath FFOM FFPM CBiol FIBiol

P B Farmer MA DPhil CChem FRSC
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I F H Purchase BVSc MRCVS PhD FRCPath CBiol FIBiol
A G Renwick BSc PhD DSc
S Venitt BSc PhD
Professor G T Williams BSc MD FRCP FRCPath

SECRETARIAT

T C Marrs MD MSc FRCPath FIBiol Dip RCPath (Medical) (Until March 1994)
R J Fielder BSc PhD Dip RCPath (Scientific from March 1994)
Mrs A McDonald BSc MSc (Scientific) (Until July 1994)
J M Battershill BSc MSc (Scientific) (From October 1994)
K N Mistry (Administrative)

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

DECLARATION OF INTEREST DURING THE PERIOD OF THIS REPORT

	Personal Interest		Non Personal Interest	
Member	Company	Interest	Company	Interest
Prof R L Carter (Chairman)	NONE	NONE	NONE	NONE
Prof P G Blain	NONE	NONE	ICI plc Unilever plc	Research Studentship Research Studentship
Prof R A Cartwright	Central Electricity Generating Board National Grid Co Medico-Legal Consultancies	Consultant Consultant Consultant	NONE	NONE
Prof C Chilvers	British Gas ICI plc Tomkins Zeneca	Share Holder Share Holder Share Holder Share Holder	Merck, Sharp & Dohme	Research Support
Dr C Cooper	NONE	NONE	NONE	NONE
Prof A D Dayan	British Petroleum ICI Proctor & Gamble Schering Plough Smith Kline Beecham TI Wellcome Foundation	Share Holder Consultant Consultant Consultant Consultant Share Holder Pension	Glaxo	Research Fellowship
Dr P B Farmer	British Gas National Power Powergen	Share Holder Share Holder Share Holder	Amersham BAT DOW Orion Pharma SKB Zeneca	Research Support Research Studentship Research Studentship Research Support Collaborative – Studentship Collaborative – Studentship
Prof R F Newbold	NONE	NONE	NONE	NONE
Prof J M Parry	RAT Grants Committee British Telecom Compass Catering Fisons Pharmaceuticals Glaxo Group Research JIB Insurance Smith Kline Beecham South Wales Electricity Wellcome Foundation	Consultant Share Holder Share Holder Consultant Grant Share Holder Consultant Share Holder Consultant	Amersham International Pfizer Smith Kline Beecham Welsh Water	Grant Studentship Studentship Studentship
Dr I F H Purchase	ICI plc Zeneca	Consultant Employee	NONE	NONE
Dr A G Renwick	International Sweetners Association Smith Kline Beechan	Consultant Consultant	Bayer Ciba-Geigy Glaxo Hoffmann-La Roche Solvay-Dulphar	Research Support Research Support Research Support Research Support Research Support
Dr S Venitt	Abbey National plc	Share Holder	NONE	NONE
Prof G T Williams	NONE	NONE	NONE	NONE

Terms of Reference

To advise at the request of:

Department of Health
Ministry of Agriculture, Fisheries and Food
Department of the Environment
Department of Trade and Industry
Department of Transport
Health and Safety Executive
Medicines Control Agency: Section 4 Committees and the Licensing Authority
Committee on the Medical Aspects of Food Policy
Home Office
Scottish Home and Health Department
Department of Agriculture and Fisheries for Scotland
Welsh Office
Department of Health and Social Services for Northern Ireland
Other Government Departments

1. To assess and advise on the toxic risk to man of substances which are:

(a) used or proposed to be used as food additives, or used in such a way that they might contaminate food through their use or natural occurrence in agriculture, including horticulture and veterinary practice or in the distribution, storage, preparation, processing or packaging of food;

(b) used or proposed to be used or manufactured or produced in industry, agriculture, food storage or any other workplace;

(c) used or proposed to be used as household goods or toilet goods and preparations;

(d) used or proposed. to be used as drugs, when advice is requested by the Medicines Control Agency, Section 4 Committee of the Licensing Authority;

(e) used or proposed to be used or disposed of in such a way as to result in pollution of the environment.

2. To advise on important general principles or new scientific discoveries in connection with toxic risks, to co-ordinate with other bodies concerned with the assessment of toxic risks and to present recommendations for toxicity testing.

Declaration of Interests: A Code of Practice for Members

Introduction

1. This Code of Practice is intended to act as a guide for members of these three Committees as to the circumstances in which they should declare an interest in the chemical industry.

2. The advice of these Committees concerns matters which are connected with the chemical industry and it is therefore desirable that members should have a good understanding of the work of the industry. It is also desirable that some members should have practical experience of the scientific problems of product development. To avoid any public concern that commercial interests might affect the advice of the Committees it has been decided that the arrangements which govern relationships between members and the chemical industry and information on significant and relevant interests should be on public record.

Definitions

3. In this code, 'the chemical industry' means

(a) companies, partnerships or individuals who are involved with the manufacture, sale or supply of products subject to the following legislation:–

The Food Safety Act 1990
The Medicines Acts 1968 and 1971
The Food and Environmental Protection Act 1985
The Consumer Protection Act 1987
The Cosmetic (Safety) (Amendment) Regulations 1987
The Notification of New Substances Regulations 1982

(b) trade associations representing companies involved with such products

(c) companies, partnerships or individuals who are directly concerned with research, development or marketing of a product which is being considered by the Committees on Toxicity, Mutagenicity or Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.

4. In this code 'the Secretariat' means the Secretariat of the relevant Committee.

Different Types of Interest

5. There are a number of different types of interests and the following is intended only as a guide.

A **personal interest** involves payment to the member personally. The main examples are:–

Consultancies: any consultancy, directorship, position in or work for the chemical industry, which attracts regular or occasional payments in cash or kind.

Fee-Paid Work: any work commissioned by the chemical industry for which the member is paid in cash or kind.

Shareholdings: any shareholding in or other beneficial interest in shares of the chemical industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no financial management.

A **non-personal interest** involves payment which benefits a department for which a member is responsible, but is not received by the member personally. The main examples are:–

Fellowships: the holding of a fellowship endowed by the chemical industry.

Support by industry: any payment, other support or sponsorship by the chemical industry which does not convey any pecuniary or material benefit to a member personally but which does benefit their position or department, for example:–

(i) a grant from a company for the running of a unit or department for which a member is responsible;

(ii) a grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which a member is responsible. This does not include financial assistance for students;

(iii) the commissioning of research or other work by, or advice from, staff who work in a unit for which the member is responsbile.

Trusteeship: where a'member is a trustee of a charity with investments in the chemical industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.

6. Members are under no obligation to seek out knowledge of work done for or on behalf of the chemical industry within departments for which they are responsible if they would not normally expect to be informed.

7. Members should inform the Department in writing when they are appointed of their *current personal* and *non-personal* interests. Only the name of the company and the nature of the interest is required; the amount of any salary, fee, shareholding, grant etc need not be disclosed to the Department. An interest is current if the member has an ongoing financial involvement with the chemical industry, eg if he or she holds shares in a chemical industry, has a consultancy contract, or if the member or the department for which he or she is responsible is in the process of carrying out work for the chemical industry. Members are asked to inform the Department at any time of any change in their *personal* interests, and will be invited to complete a declaration form once a year. It would be sufficient if changes in *non-personal* interests are reported in the annual

declaration form following the change. (Non-personal interests involving less than £1000 from a particular company in the previous year need not be declared to the Department.)

8. Members are required to declare relevant interests at Committee meetings, and to state whether they are personal or non-personal interests and whether they are specific to the product under consideration or non-specific.

(a) A member must declare a *personal specific* interest if he or she has *at any time* worked on the product under consideration and has personally received payment for that work, in any form, from the chemical industry. If the interest is no longer current, the member may declare it as a *lapsed personal specific* interest. The member may then only take part in the proceedings at the Chairman's discretion.

(b) A member must declare a *personal non-specific* interest if he or she has a *cuwent* personal interest in the company concerned which does not relate specifically to the product under discussion. The member may then only take part in the proceedings at the Chairman's discretion.

(c) A member must declare a *non-personal specific* interest if he or she is aware that the department for which he or she is responsible has at any time worked on the product but the member has not personally received payment in any form from the industry for the work done. The member may then take part in the proceedings unless the Chairman should decide otherwise.

(d) A member must declare a *non-personal non-specific* interest if he or she is aware that the department for which he or she is responsible is *currently* receiving payment from the company concerned which does not relate specifically to the product under discussion. The member may then take part in the proceedings unless the Chairman should decide otherwise.

9. If a member is aware that a product under consideration is or may become a competitor of a product manufactured, sold or supplied by a company in which the member has a *cuwent personal* interest, he or she should declare the interest in the company marketing the rival product.

10. A member who is in any doubt during a meeting as to whether he or she has an interest which should be declared, or whether to take part in the proceedings, should ask the Chairman for guidance. The Chairman has the power to determine whether or not a member with an interest shall take part in the proceedings.

11. If the Chairman should declare an interest of any kind he or she should stand down from the chair for that item and the meeting should be conducted by the Deputy Chairman.

Record of Interests

12. A record is kept by the Department of Health of names of members who have declared interests to the Department of Health upon appointment, as the interest first arises or through the annual declaration, and the nature of the interest.

13. It is the responsibility of individual members to declare all relevant interests. The Secretariat does not check whether members have done so. However, members can seek advice from the Secretariat if they have any doubts as to whether or not an interest should be declared.

Glossary of Terms

ADDUCT A chemical grouping which is covalently bound (strong bond formed by the sharing of a pair of electrons) to a large molecule such as DNA (qv) or protein.

ADENOCARCINOMA A malignant tumour arising from the epithelia (qv) (see 'tumour').

ADENOMA (see Tumour).

ADI Acceptable daily intake, defined as 'An estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk'.

Ah RECEPTOR The Ah (Aromatic hydrocarbon) receptor protein regulates gene expression. The identitiy of the natural endogenous chemical which bind to the Ah receptor are unknown. A range of chemical such as chlorinated dibenzodioxins and polychlorinated biphenyls bind to Ah receptor. The available research suggests that binding to the Ah receptor is an intrical part of the toxicological mechanism of these compounds.

ALKALOIDS A diverse group of nitrogen-containing substances produced by plants which may have potent effects on body function.

ANEUGENIC Inducing aneuploidy (qv).

ANEUPLOIDY The circumstances in which the total number of chromosomes witin a cell is not an exact multiple of the normal haploid (see 'Polyploidy') number. Chromosomes may be lost or gained during cell division.

ANTIOXIDANT A compound which is capable of delaying or preventing the development in food of rancidity or other flavour deterioration due to oxidation. May be used as a general term for an ingredient which prevents oxidation.

CARCINOGENICITY BIOASSAY Tests carried out in laboratory animals, usually rats and mice, to determine whether a substance is carcinogenic. The test material is given, usually in the diet, throughout life to groups of animals, at different dose levels.

CARCINOGENESIS The origin, causation and development of tumours. The term applies to all forms of tumours, benign as well as malignant (see 'Tumour') and not just to carcinomas (qv).

CARCINOGENS The causal agents which induce tumours. They include external factors (chemicals, physical agents, viruses) and internal factors such as hormones. Chemical carcinogens are structurally diverse and include naturally-occurring substances as well as synthetic compounds. An important distinction can be drawn between *genotoxic* (qv) carcinogens which have been shown to react directly with and mutate DNA, and *non-genotoxic* carcinogens which act through other mechanisms. The activity of genotoxic carcinogens can often be predicted from their chemical structure – either of the parent compound or of activated metabolites (qv). Most chemical carcinogens exert their effects after prolonged exposure, show a dose-response relationship and tend to act on a limited range of susceptible target tissues. Carcinogens are sometimes species- or sex-specific and the the term should be qualified by the appropriate descriptive adjectives to aid clarity. Several different chemical and other carcinogens may interact, and constitutional factors (genetic susceptibility, hormonal status) may also contribute, emphasising the multifactorial nature of the carcinogenic process.

CARCINOMA Malignant tumour arising from epithelial cells lining (for example) the alimentary, respiratory and urogenital tracts and from epidermis, also from solid viscera such as the liver, pancreas, kidneys and some endocrine glands. (See also 'Tumour').

CELL TRANSFORMATION ASSAY (See Transformation).

CHROMOSOMAL ABERRATION Deviation from the normal structure of chromosomes (qv) (see Clastogen).

CLASTOGEN An agent that produces chromosome breaks and other structural aberrations such as translocations (qv). Clastogens may be viruses or physical agents as well as chromosomal abchemicals. Clastogenic events play an important part in the development of some tumours.

COVALENT The type of binding formed by the sharing of an electron pair between two atoms. Molecules are combinations of atoms bound together by covalent bonds.

CYTOGENETIC Concerning chromosomes, their origin, structure and function.

DNA (DEOXYRIBOSENUCLEIC ACID) The carrier of genetic information for all living organisms except the group of RNA viruses. Each of the 46 chromosomes in normal human cells consists of 2 strands of DNA containing up to 100,000 nucleotides, specific sequences of which make up genes (qv). DNA itself is composed of two interwound chains of linked nucleotides, each nucleotide consisting of **3** elements: a pentose sugar, a phosphate group and a nitrogenous base derived from either purine (adenine, guanine) or pyrimidine (cytosine, thymine).

DOMINANT LETHAL ASSAY (See Dominant Lethal Mutation).

DOMINANT LETHAL MUTATION A dominant mutation that causes death of an early embryo.

EPIDEMIOLOGY Study of the distribution and, in some instances, the causal factors of disease in communities and populations. Originally confined to infectious diseases – epidemics – but now increasingly applied to non-infectious conditions such as cancer.

EPITHELIA The tissue covering the outer surface of the body, the mucous membranes and cavities of the body.

FREE RADICAL An unstable, highly reactive molecule which is capable of reacting with cellular proteins and DNA giving rise to adverse effects.

GENE The functional unit of inheritance: a specific sequence of nucleotides along the DNA molecule, forming part of a chromosome.

GENOTOXIC The ability of a substance to cause DNA damage, either directly or after metabolic activation (see also Carcinogens).

GERM CELL Reproductive cell eg spermatid.

GUIDELINE VALUE (For drinking water) A guideline value represents the concentration of a constituent that does not result in any significant risk to health of the consumer over a lifetime of consumption.

HEPATOCARCINOGENICITY Ability to induce liver tumours.

HEPATOCELLULAR Relating to the cells of the liver.

HYDROLYSIS The breakdown of a chemical by water into simpler products.

IN *VITRO* A Latin term used to describe effects in biological material ouside the living animal.

IN *VIVO* A Latin term used to describe effects in living animals.

LEUKAEMIA A group of neoplastic disorders (see Tumour) affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation (qv) or maturation (stage which forms final cell types). Examples include the lymphocytic leukaemias which develop from lymphoid (qv) cells and the myeloid leukaemias which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

LYMPHOCYTE Type of white blood cell.

LYMPHOMA Malignant tumours arising from lymphoid tissues. They are usually multifocal, involving lymph nodes, spleen, thymus and sometimes bone marrow and other sites outside the anatomically defined lymphoid system. (See also Tumour).

MAXIMUM TOLERATED DOSE Usually the highest dose used in a carcinogenicity bioassay (qv). Commonly chosen from a preliminary 90 day study and set at the highest dose at which there is no organ toxicity or gross functional effect. If there is no specific toxicity the dose which will cause a 10% reduction in weight gain over the life span of the animals is conventionally used.

MESOTHELIOMA A rare tumour, usually malignant (qv), which develops from the thin, flattened (mesothelial) cells which line the lung, heart and abdominal cavities. The commonest cause of mesothelioma is asbestos.

METABOLIC ACTIVATION Conversion by enzymes of a chemical from one state to another, for example by chemical reactions such as hydroxylation, epoxidation or conjugation. The term is used in a more narrow sense to describe the addition of a mammalian cell free preparation from livers of rats pre-treated with a substance which stimulates production of metabolising enzymes. These preparations are added to *in vitro* short term tests to mimic the metabolic activation typical of mammals.

METABOLITE Product formed from the original compound by enzymic reactions in the body/cell.

METAPHASE Stage of cell division (mitosis and meiosis) during which the chromosomes are arranged on the equator of the nuclear spindle (the collection of microtubule filaments which are responsible for the movement of chromosomes during cell division). As the chromosomes are most easily examined in metaphase, cells are arrested at this stage for microscopical examination for chromosome aberrations (qv) – known as metaphase analysis.

MICRONUCLEI Isolated or broken chromosome fragments which are not expelled when the nucleus is lost during cell division, but remain in the body of the cell forming micronuclei.

MICRONUCLEUS TEST (See Micronuclei).

MITOSIS The type of cell division which occurs in somatic cells when they proliferate. Each daugter cell has the same complement as the parent cell.

MOUSE LYMPHOMA ASSAY An *in vitro* assay for gene mutaion in mammalian cells using a mouse lymphoma cell line L5178Y, which is heterozygous for the gene (carries only one functional gene rather than a pair) for the enzyme thymidine kinase ($TK^{+/-}$). Mutation of that single gene is measured by resistance to toxic trifluorothymidine. Mutant cells produce two forms of colony – large, which represent mutitions within the gene and small, which represents large genetic changes in the chromosome such as chromosome aberrations. Thus this assay can provide additional information about the type of mutation which has occurred if colony size is scored.

MUTATION A permanent change in the amount or structure of the genetic material in an organism which can result in a change in the characteristics of the organism. The alternation may involve a single gene, a block of genes, or a whole chromosome. Mutations involving single genes may be a consequence of effects

on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Changes involving whole chromosomes may be numerical or structural. A mutation in the germ cells of sexually reproducing organisms may be transmitted to the offspring, whereas a mutation that occurs in somatic cells may be transferred only to descendant daughter cells.

NEOPLASM (See Tumour).

NON-GENOTOXIC See (Carcinogens).

OSTEOMAS AND OSTEOSARCOMAS Benign and malignant tumours (qv) of the bone.

PLASTICISER A substance which increases the flexibility of certain plastics.

POLYPLOIDY Having three or more times the haploid (single set of unpaired chromosomes as found in germ cells) number of chromosomes. Somatic cells from animals generally contain a diploid set of chromosomes, with pairs of equivalent chromosomes, so that twice the haploid number are present.

POLYURETHANE A thermoplastic polymer produced from the condensation of a polyisocyanate and a hydroxyl containing material. Polyurethane coatings have excellent hardness, flexibility and abrasion resistance.

PUVA THERAPY A treatment used to treat the skin disease psoriasis in which patients consume a psoralen (another word for the natural plant constituents furocoumarins) and are then exposed to UVA radiation.

RECEPTOR Part of a cell which specifically combines with an agent.

SOMATIC Occurring in cells of the body other than germ cells (see Mutation).

SQUAMOUS EPITHELIA A type of epithelium consisting of square shaped cells. Examples are the skin and the lining of the oesophagus. (see also Epithelia.)

STABILISER A type of food additive which maintains the uniform dispersion of two or more immiscible substances.

TDI Tolerable daily intake.

TERATOLOGY The study of development abnormalities and their causes.

THRESHOLD The lowest dose which will produce a toxic effect and below which no toxicity is observed.

TOXIC EQLTIVALENCY FACTOR (TEF) A measure of relative toxicological potency of a chemical compared to a well characterised reference compound. TEFs can be used to sum the toxicological potency of a mixture of chemicals which are all members of the same chemical class, having common structural, toxicological and biochemical properties. Systems have been published for chlorinated

dibenzodioxins and furans and for polycyclic aromatic hydrocarbons.

TOXICOIUNETICS The description of the fate of chemicals in the body, including a mathematical account of their absorption, distribution, metabolism and excretion.

TRANSFORMATION The process by which a normal cell acquires the capacity for neoplastic growth. Complete transformation occurs in several stages both *in vitro* and *in vivo.* One step which has been identified *in vitro* is 'immortalisation' by which a cell acquires the ability to divide indefinitely in culture without undergoing senescence (aging and death). Such cells do not have the capacity to form tumours in animals, but can be induced to do so by extended passage *in vitro,* by treatment with chemicals, or by transfection with oncogene DNA. The transformed phenotype (qv) so generated is usually, but not always, associated with the ability of the cells to grow in soft agar and to form tumours when transplanted into animals. It should be noted that each of these stages of transformation can involve multiple events which may or may not be genetic. The order in which these events take place, if they occur at all, *in vivo* is not known.

TRANSLOCATION The transfer of a region of one chromosome to another chromosome.

TUMOUR (Synonym– neoplasm) A mass of abnormal, disorganised cells, arising from pre-existing tissue, which are characterised by excessive and uncoordinated proliferation and by abnormal differentiation (qv). BENIGN tumours show a close morphological resemblance to their tissue of origin; grow in a slow expansile fashion; and form circumscribed and (usually) encapsulated masses. They may stop growing and they may regress. Benign tumours do not infiltrate through local tissues and they do not metastasise (qv). They are rarely fatal. MALIGNANT tumours (synonym – cancer) resemble their parent tissues less closely and are composed of increasingly abnormal cells in terms of their form and function. Well differentiated examples still retain recognizable features of their tissue of origin but these characterisitics are progressively lost in moderately and poorly differentiated malignancies: undifferentiated or anaplastic tumours are composed of cells which resemble no known normal tissue. Most malignant tumours grow rapidly, spread progressively through adjacent tissues and metastasise to distant sites. Tumours are conventionally classified according to the anatomical site of the primary tumour and its microscopical appearance, rather than by cause. Some common examples of nomenclature are as follows:-

> Tumours arising from epithelia (qv): *benign* – adenomas, papillomas; *malignant* – adenocarcinomas, papillary carcinomas.
>
> Tumours arising from connective tissues such as fat, cartilage or bone: *benign* – lipomas, chondromas, osteomas; *malignant* – fibrosarcomas, liposarcomas, chondrosarcomas, osteosarcomas. Tumours arising from lymphoid tissues are malignant and are called lymphomas (qv); they are often multifocal. Malignant proliferations of bone marrow cells are called leukaemias. Benign tumours may evolve to the corresponding malignant tumours; examples involve the adenoma –> carcinoma sequence in the large bowel in humans, and the papilloma –> carcinoma sequence in mouse skin.

UVA Ultraviolet light of a particular range of wavelengths (315 to 400 nm).

^{32}P-POSTLABELLING TECHNIQUE A relatively new, sensitive, but non specific, method of detecting chemical adducts between a test compound (or its metabolites) and DNA. The results give a measure of the effective dose rather than a measure of biological effect.

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Printed in the United Kingdom for HMSO
Dd 301087 C6 6/95 9385 2527

DH Committees on *Toxicity, Mutagenicity and Carcinogenicity* of Chemicals in Food, Consumer Products and the Environment **1994 Annual Report** HMSO

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