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

Preface

The Committee on Mutagenicity (COM) provides advice on potential mutagenic activity of specific chemicals at the request of UK Government Departments and Agencies. Such requests generally relate to chemicals for which there are incomplete, non-standard or controversial data sets for which expertise of independent committee members is required to provide recommendations on potential hazards and risks and frequently suggestions for further studies.

During 2002, the Committee finalised its review of dichlorvos and initiated a review of another insecticide, malathion. Reviews of the veterinary medicine dimetridazole, the incapacitant substance pelargonyl vanillylamide (PAVA), and the possible nitrosation of nicotine from nicotine patches were completed.

The Committee also reviewed its procedures in the light of new guidance from the Office of Science and Technology on a code of practice for Scientific Advisory Committees and the Government's response to the BSE enquiry report. The Committee adheres to most of the recommendations but agreed to publish more of the substantive background papers to discussions at the earliest opportunity. The COM devised a template showing its methods of working and expertise, which clarifies this for health professionals and members of the general public.

The Committee has an ongoing responsibility to provide Government Department's and Regulatory Authorities with advice on developments in procedures for the evaluation and risk assessment of mutagens. In this regard the Committee assessed new information from the ILSI/HESI (see below for definition) research initiative on the use of the Syrian Hamster Embryo (SHE) cell transformation assay as an *in-vitro* test for identifying potential mutagens. The COM confirmed its earlier views that this test is not suitable for screening or regulatory assessment of chemical mutagens. The Committee's views on the SHE assay have been published in the scientific literature (Toxicologic Pathology 2002 Jul-Aug;30(4):536-8).

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Dichlorvos

2.1 Dichlorvos (O-(2,2-dichlorovinyl)-O,O-dimethylphosphate, DDVP) is an organophosphorous insecticide. The COM provided advice to the Advisory Committee on Pesticides on the mutagenicity of dichlorvos during 2001. A full report was published in the 2001 Annual Report. The COM considered dichlorvos at three meetings in 2001 including an extraordinary meeting where industry made a presentation. A Judicial Review was sought by the data holder regarding the regulatory review of dichlorvos pesticides products. The Judicial Review took place during 5-9 November 2001. Mr Justice Crane handed down his judgement on the case held in the High Court between AMVAC Chemicals UK Ltd (Claimants) and Secretary of State for Environment, Food and Rural Affairs (DEFRA) and Secretary of State for Transport, Local Government and Regions (DTLR) (Defendants) on 3rd December 2001. Essentially the Claimants (AMVAC Chemical UK Ltd) won on one of the three issues they had raised, namely that the decision to suspend pesticide approvals was flawed in relation to the amount of notice given to the claimant and the decision was therefore quashed. Mr Justice Crane saw no reason why those advising ministers should not review their advice, taking into account all the Claimants submits, without significant delay.

2.2 This meant that the COM was asked to consider the relevant material submitted to the court by AMVAC to ascertain whether this warranted any revision of the COM statement on dichlorvos. This information essentially comprised exhibits from a number of independent scientific experts and a number of papers on the generic issues of evaluation of various types of mutagenicity assays. In addition other pesticide approval holders were asked to forward any further data by 4 January 2002.

2.3 A further extraordinary meeting of COM was arranged for the 9 January 2002 to consider these data.

2.4 The Committee considered all of the relevant information provided to the court and concluded that dichlorvos should be regarded as an *in vivo* mutagen at the site-of-contact (i.e at the initial sites of exposure, the COM felt there was no evidence for systemic mutagenic effects.) High doses of dichlorvos induced mutagenic effects in the skin following topical application and in the liver following intraperitoneal dosing. The Committee noted the limited evidence for a carcinogenic effect of dichlorvos. This related to tumours of the forestomach in mice after gavage dosing and also the oesophageal tumours seen after dietary administration. There was no satisfactory explanation proven for the mechanisms of these tumours and the Committee felt, given the available mutagenicity data on dichlorvos, that it would be prudent to assume a genotoxic mechanism. The Committee agreed that in the absence of appropriate mechanistic data a precautionary approach should be adopted and no threshold could be assumed for the mutagenic and carcinogenic effects of dichlorvos.

2.5 The Committee considered a request from the Advisory Committee on Pesticides on what investigations might assist in further considering the potential for dichlorvos to act as a site of contact mutagen. Members suggested that good quality studies in transgenic animals using repeat dosing to investigate mutagenic activity in the skin following dermal application and in the gastrointestinal tract following oral administration would be appropriate.

2.6 The COM statement was published in January 2002 and is included at the end of this report.

Dimetridazole

2.7 Dimetridazole (DMZ) is an antiprotozoal substance that is used to maintain the health of certain farm animals. In the UK it has been permitted for use as a feed additive for turkeys and guinea-fowl and as a veterinary medicine for game birds (pheasants and partridges only). The European Commission was considering whether to suspend use as a feed additive, but this would not directly affect veterinary medicinal use. In the last few years, DMZ has been assessed by the EU's Committee on Veterinary Medicinal Products (CVMP)and by the EU's Scientific Committee on Animal Nutrition (SCAN). These two committees disagreed with one another over the interpretation of the mutagenicity data. The CVMP considered that more information was needed before it could conclude on mutagenicity, whereas the SCAN considered that there was sufficient information to allow it to conclude that there was no genotoxic hazard to consumers of foods derived from animals given DMZ. The specialist expert advice of COM was sought by the Food Standards Agency (FSA).

2.8 The COM reached the following conclusion regarding the mutagenicity of DMZ.

2.9 Dimetridazole (DMZ) has mutagenic activity *in vitro*. The Committee was provided with full reports of *in vivo* studies to investigate the ability of DMZ to induce micronuclei in bone marrow of mice, UDS in primary hepatocytes of male rats, and dominant lethal mutations in the germ cells of male mice. In all cases the oral route was used, with dose levels up to about 1 gram/kg per day. Negative results were consistently obtained. However the Committee concluded that the rat liver unscheduled DNA synthesis (UDS) assay had not been adequately conducted and recommended that a further rat liver UDS assay conducted in accordance with OECD guidelines (but with their recommendation to use 4 animals per dose/sampling time point) was required to provide full reassurance that DMZ (or its metabolites) does not have significant mutagenic activity in mammals in vivo.

2.10 The COM statement is included at the end of this report.

Malathion

2.11 Malathion is an organophosphorus insecticide. It has been marketed in the UK for use in agriculture and horticulture since 1956. There were three products with approvals for use in agriculture and horticulture, home garden and use in pigeon lofts at the time when this review was initiated in January 2002. A number of products containing malathion are also licensed as human medicines for use in the control of head lice.

2.12 The Advisory Committee on Pesticides was reviewing the available toxicological information on malathion as part of its ongoing review of organophosphorus compounds. The ACP asked for advice from COM and COC on mutagenicity and carcinogenicity at its 289th meeting on 17 January 2002. The Chairs of COM and COC agreed that a joint statement was required in view of the need for a full review of all mutagenicity and carcinogenicity data.

2.13 The COM undertook an initial consideration of the in confidence mutagenicity data provided by the pesticide data holder and the available published information provided by the data holder at its 25 April 2002 meeting. A number of additional published papers on malathion and impurities present in technical grade malathion were also considered at this meeting. At its meeting of 10 October 2002 the COM considered some additional information provided in confidence by the pesticide data holder (a report of one additional *in vivo* study and information on the potential for variation in impurities between different sources of malathion) together with a number of published studies not previously reviewed.

2.14 The Committee agreed a number of conclusions, which were forwarded to the pesticide data holder. Additional data on the conduct and results of the *in vivo* oral rat liver UDS assay were submitted by the pesticide data holder and were to be considered at February 2003 meeting of COM.

2.15 Malathion was also considered at the COC meeting of 27 June 2002. A full statement from COC and COM is in preparation.

PAVA: use as an incapacitant spray

2.16 Sussex Police Force have started to use an incapacitant spray based on pelargonyl vanillylamide (PAVA) as an alternative to CS spray. PAVA is the synthetic equivalent to capsaicin the active ingredient of natural peppers. It is permitted as a food flavour (at up to 10 ppm). It is also used in human medicine topically as a rubifacient. The Home Office had asked the COT for advice on the health effects of PAVA spray. The COT gave initial consideration to this at its meeting on 4th December 2001, and requested that the COM provide advice on the mutagenicity data. This comprised a package of 3 *in vitro* studies and one *in vivo* study that had been commissioned by Sussex Police.

2.17 The Committee agreed the following conclusions for inclusion in the COT statement:

i. The structure of PAVA suggests the possible formation of reactive oxygen species from the phenol moiety, and other possible active metabolites which may be mutagenic.

ii. Data are available from 3 *in vitro* studies done to current standards. The assay for gene mutation in bacteria gave negative results. Equivocal/weakly positive results were obtained in the mouse lymphoma assay. A clear positive result was however obtained in the assay for chromosome damage in CHO cells in the presence of the exogenous metabolic activation system which was not limited to concentrations producing excessive toxicity. These *in vitro* data indicate that PAVA has mutagenic potential.

iii. Negative results were obtained in a bone marrow micronucleus test, PAVA being given orally at up to dose levels that produced marked toxicity (some lethality).

iv. As noted in the COM guidelines (http://www.doh.gov.uk/com/guidance.pdf) , in the case of substances positive *in vitro* a negative result in a single tissue will not provide sufficient data to conclude that the chemical is inactive *in vivo*. Thus data from a second *in vivo* assay are necessary to provide adequate reassurance that the mutagenic potential identified in the *in vitro* studies cannot be expressed *in vivo*. In this regard members felt that data from an *in vivo* liver UDS assay would be appropriate in this case and that negative results in this assay would provide the necessary reassurance.

2.18 A full statement is included in the COT section of this report.

Possible nitrosation of nicotine from nicotine patches

2.19 A member of COM requested the views of the Medicines Control Agency (MCA) on the possible nitrosation of nicotine derived from nicotine patches applied to the skin, and any mutagenic and subsequent carcinogenic risk. MCA presented a paper to the Committee in response to this request.

2.20 Members heard that nicotine from patches is absorbed through the skin and passes into the systemic blood system, and is distributed throughout the body. Blood plasma concentrations rise more slowly from the use of these products than from cigarettes. Nicotine is continually released throughout the time of exposure. Nicotine has not been shown to be carcinogenic to animals. There was the possibility that nicotine could be demethylated and subsequently (or concomitantly) nitrosated to form N-nitroso-nornicotine, which is a genotoxic carcinogen. Although the amount of nitrosamine generated in this way was unknown, the MCA considered that it was likely to be minimal and very much less than the levels of other nitrosamines and other carcinogens present in tobacco smoke. In the licensing of a medicinal product one aspect to be considered was the benefit to health which had to be compared with any risk attributed to the use of the medicinal product. The MCA view was that the benefits clearly outweighed the risks in this case.

2.21 Members agreed that any concern over the risk of nicotine related mutagenicity and cancer from skin patches due to nitrosation is likely to be very small or insignificant in tobacco users who are or have been exposed to high concentrations of many carcinogens. It was noted that similar arguments also applied to chewing gum containing nicotine.

Review of Committee Procedures

OST Code of Practice for Scientific Advisory Committees and Committee procedures in the light of the Government's response to the BSE enquiry report

2.22 The Committee agreed to consider these two reports together as many of the topics were common in both reports. Members agreed that in general the COM procedures complied with most of the guidance given by OST.

2.23 The Committee agreed that it was difficult to publish a detailed forward plan, as much of the work of the Committee was reactive in response to requests for advice from other Government Department/Agencies, often at short notice. It was noted that the agenda was normally set by the secretariat in response to such requests but that members could make suggestions for consideration at anytime. Regarding 'horizon scanning' members believed that generic issues were often identified by the secretariat and members, but acknowledged that systematic searching of the literature to identify all relevant research was not possible.

2.24 The Committee considered that improving communications of its advice to the public was difficult because of its specialist and very technical nature. The Chairs of the COC/COM had both agreed with the proposal in the OST report to publish more background papers. A 'what's new' section had also been placed on the COM website, which would help improve communication. Members agreed that lay summaries of completed statements should be drafted as appropriate when particularly complex subjects were under discussion. It was agreed that a glossary of technical terms could help with public understanding and that COM would contribute to a joint COT/COC/COM glossary. With respect to dealing with dissenting views members agreed that it should be made clear in the minutes and statements when consensus had not been reached, and the dissenting view published alongside the statement agreed by the majority.

COM Template

2.25 The COM agreed a template diagram which provided an overview of how COM undertakes risk assessment of carcinogens and the interaction of COM with its sister Committees (COT and COC) and with Government Departments, Regulatory Agencies and the Chief Medical Officer Professor Sir Liam Donaldson. For ease of reference this template is reproduced at the end of this section of the Annual Report.

Test Strategies and Evaluation

ILSI/HESI research programme on alternative cancer models: results of Syrian hamster embryo cell transformation assay

2.26 The International Life Sciences Institute (ILSI) and the Health and Environmental Science Institute (HESI) have co-ordinated a multinational research programme from 1996 – 2001 to more fully characterise the responsiveness of several alternative cancer models. The research has focused predominantly on a number of proposed short-term *in vivo* test models for assessment of potential carcinogenic activity carcinogenicity in mice (in particular ras H2, Tg.AC, p53 +/-,Xpa-/-, Xpa-/-/p53+/- double knockout, neonatal mouse) but also included the *in vitro* cell transformation assay using Syrian hamster embryo cells (SHE cell transformation assay) The overall objective of the work was to evaluate the ability of these models to provide useful information for human cancer risk assessment. The research involved input from over 50 industrial, governmental (USA, Denmark, Netherlands and Japan) and academic laboratories and cost around $35M. The COC has considered all of the data submitted by ILSI/HESI

except for the results of the investigations using the SHE cell transformation assay. These data have been considered by Committee on Mutagenicity on Chemicals in Food, Consumer Products and the Environment (COM) whose conclusions are given below.

2.27 In 1994 the COM considered a number of cell transformation assays including the modified SHE method, and had agreed that transformation assays using Syrian Hamster cells were not yet ready for routine use, but warranted further work on both their validation and providing an understanding of the underlying mechanisms. The Committee considered a draft proposal for an OECD guideline for cell transformation using the modified SHE method (low pH culture). A number of supporting publications and papers claiming a predictive correlation between cell transformation in this test system and carcinogenicity were also reviewed. In 1996, the Committee agreed that there were no mechanistic data available which gave an insight into the relationship between cell transformation in the SHE assay and the carcinogenic process. Although apparently high correlations had been reported in trials using a range of animal carcinogens including non-genotoxic carcinogens, only a very limited number of laboratories were involved and little value could be attributed to these results in the absence of appropriate supporting mechanistic data. The COM concluded at the end of its 1996 review that it was not possible to support the proposed OECD guideline.

2.28 The Committee reached the following conclusions:

i) The SHE cell transformation assay should not be used for regulatory screening of chemicals for potential carcinogenicity.

ii) There are insufficient data on validation of the SHE cell transformation assay to justify the development of an OECD test guideline for this assay.

iii) The Committee has considerable reservations regarding the mechanistic basis underpinning the rationale for using the SHE cell transformation assay to screen for chemical carcinogenesis.

iv) The Committee has considerable reservations regarding the validity of using morphological assessment alone to define transformed foci in the SHE cell transformation assay. The development of an objective molecular marker is essential before validation work can proceed.

2.29 The COM statement is included at the end of this report.

In vitro micronucleus test

2.30 The 3rd International Workshop on Genotoxicity Testing (IWGT) was held in Plymouth in June 2002 and included a Working Group on the *In vitro* Micronucleus test. There was international consensus that this method was adequately validated, and also on the methodology for a guideline. The COM has a remit to advise on the development of test methods and strategies. Members welcomed the development of the *in vitro* micronucleus test. Members queried the consensus point that the experimental unit for statistical analysis was the cell and not the culture and noted that this did not

conform to the approach taken in other previously validated *in vitro* tests. The secretariat would raise this aspect with the IWGT on behalf of the committee.

Ongoing Reviews

Flunixin, Flunixin-meglumine, meglumine

2.31 Flunixin in the form of the meglumine salt is a non-steroidal anti-inflammatory (NSAID) drug and a non-narcotic analgesic drug with antipyretic activities. It dissociates to Flunixin and meglumine in the body. It is used in veterinary medicine (including food-producing animals). The FSA have asked for advice on the mutagenicity of Flunixin, Flunixin-meglumine, meglumine. The COM has evaluated the available mutagenicity data and is to consider a presentation from the data holder regarding a mutagenicity testing strategy at the February 2003 meeting.

Significance of in vivo mutagenicity at high doses

2.32 The COM has previously agreed that it is prudent to assume that there is no threshold for mutagenicity unless appropriate mechanistic data can be provided to identify a threshold related mechanism. *In vivo* studies in the bone marrow provide key data in identifying compounds as *in-vivo* mutagens. In some cases the only data available to indicate such *in vivo* activity is from mutagenicity studies using excessively high doses (by current guidelines) associated with severe toxicity/lethality, and there is no evidence from carcinogenicity bioassays to suggest that a compound is a genotoxic carcinogen. Due to the importance of these data in risk assessment, where positive results normally lead to a 'non-threshold' approach being adopted by regulatory agencies, it is important that the observed effects are not secondary to toxicity. The Committee considered a paper drafted by the Secretariat at its October 2002 meeting which presented "in-confidence" data from submissions received by regulatory authorities. These were to be used as examples in order to draft generic guidance which could be published. A further paper is to be considered at the February 2003 meeting.

Glossary of Terms

2.33 A document is in preparation.

Statements of the COM 2002

Mutagenicity of dichlorvos

Dimetridazole

Malathion

PAVA: use as an incapacitant

Possible nitrosation of nicotine from nicotine patches

Mutagenicity of dichlorvos

Introduction

Background to COM review

1. Dichlorvos (O-(2,2-dichlorovinyl)-O,O-dimethylphosphate, DDVP) was first introduced into the UK as an agricultural pesticide in 1962. Non-agricultural uses were first assessed under the voluntary Pesticides Safety Precaution Scheme in 1975-78. A review by the ACP of approvals issued under the Control of Pesticides Regulatory (COPR 1986) was undertaken in 1994. Currently dichlorvos is widely used by amateur and professional users as a public hygiene insecticide (e.g. use of hand held aerosols for surface/space spray and slow release products e.g. strips, cassettes). A relatively small number of products are approved for use in animal husbandry and in agriculture and horticulture on edible crops (e.g. cucumbers) and on non-edible crops (e.g chrysanthemums). Dichlorvos is currently used in a veterinary medicinal product for control of fleas in cats and dogs. The use of dichlorvos in pesticide products and in veterinary medicines is currently being reviewed.

2. The COM considered generic aspects arising from the paper by Sasaki YF et al[1] on the performance of the *in vivo* COMET assay with respect to the newly published strategy in the COM guidelance at its 8 February 2001 meeting. The Committee agreed that the positive results reported in the COMET assay using dichlorvos suggested that a full review of all the mutagenicity data was required.

COM reviews

3. The toxicokinetics, mutagenicity and carcinogenicity data sections from the draft evaluation prepared by HSE for the Advisory Committee on Pesticides meeting on 5 April 2001 were made available to the COM. The Committee evaluated the data from all of the mutagenicity studies cited in the HSE review.[1-102] The COM also considered additional information and mutagenicity data submitted by industry to HSE prior to the COM meeting on 26 April 2001.[103-107] A further meeting was held on 23 July 2001 to consider additional submitted information and to hear a presentation from industry. The COM advice was forwarded to the regulatory authorities (the Biocides and Pesticides Authorisation Unit (BPAU) at HSE and the Pesticides Safety Directorate (PSD)) at the end of July 2001 and was subsequently published in December 2001 after a judicial review of the regulatory decisions regarding dichlorvos. An extraordinary meeting of COM was held on 9 January 2002 to consider the new information submitted to the High Court during a judicial review of the regulatory decision on the pesticide products containing dichlorvos and data provided to regulatory authorities up to 4 January 2002 and to decide whether this warranted any revision of the COM statement on dichlorvos.

Overall Assessment of In vitro mutagenicity studies

4. Members agreed that dichlorvos is a weak methylating agent (compared to methyl methanesulphonate; MMS). The Committee concurred with the following assessment of the *in vitro* mutagenicity studies.

i) Dichlorvos is mutagenic, both in the presence and absence of exogenous metabolism, to bacteria, yeast cells and in mammalian cell gene mutation assays, chromosome aberrations assay, the *in vitro* micronucleus test and sister chromatid exchange assays.

ii) Positive results have been reported in *in vitro* UDS assays using human lymphocytes and human epithelial-like cells.

iii). Dichlorvos has been shown to methylate nucleophiles and to induce strand breaks in isolated DNA.

5. Members agreed that DNA methylation induced by dichlorvos contributed towards the mutagenicity reported in *in vitro* test systems but noted that other mechanisms might also be involved. Members considered that the positive results obtained in *in vitro* mutagenicity tests with dichlorvos in the presence of an exogenous metabolising fraction and in the assay for single strand breakage of DNA also suggested that dichlorvos and/or its metabolites were genotoxic. This might include dichloroacetaldehyde although the available evidence was insufficient to identify all potential mutagenic metabolites of dichlorvos.

6. The Committee concluded that dichlorvos is an in vitro mutagen

Assessment of *in vivo* mutagenicity studies

7. The Committee noted that there were a large number of *in vivo* studies available. Dichlorvos was negative in most published *in vivo* mutagenicity assays where it was administered as a single dose. These included mouse bone-marrow micronucleus (using i.p route)[70,90,94] and bone-marrow chromosome aberration studies in mice[23,60] and hamsters[22] using oral and, in two studies (mice/hamster) inhalation exposure. Negative results were also reported in SCE in mice[44,53,95] and UDS assays [liver (rats)/forestomach (mice)][9,55,99,101]. A negative result was also reported in an adequately conducted bone-marrow chromosome aberration study where mice were given daily oral doses of dichlorvos by gavage for five days.[100]

8. Members also noted that there were a number of positive studies and these are discussed below.

9. The Committee agreed that dichlorvos has been reported to induce micronuclei in keratinocytes in mice following the topical application to skin.[81] Members agreed that the approach used in this study had not been fully validated but agreed the authors had used an appropriate positive control chemical and that the results with dichlorvos were indicative of an in-vivo site-of-contact mutagenic effect. Members also noted a positive response in a nuclear anomaly assay in hair follicles of mice following topical application.[75] Although the latter is not considered to be a definitive genotoxicity assay, the results might be indicative of a biological effect in the skin.

10. Members agreed that the positive results reported in an abstract by Majeeth et al in a mouse bone-marrow micronucleus assay could not be interpreted, as insufficient information on the methods and results were available.[52] The Committee considered that equivocal evidence of chromosomal aberrations in bone-marrow smears had been reported in a study where hamsters were given a single oral dose of up to half the LD50 of the formulation.[30]

11. The Committee agreed that evidence for the induction of changes in chromosome number had been documented in the bone-marrow of rats following repeated oral dosing with dichlorvos for 6 weeks (5 days/week).[63] Members considered that the methods used were satisfactory and noted that, although the adequacy of reporting was limited, the results indicated a positive effect for the induction of numerical chromosome aberrations. It was noted that a clear dose-response would not be expected in this study as the dose range selected was relatively narrow.

12. Regarding the recently published COMET assay[1], Members considered that the approach adopted by Sasaki and colleagues to the mutagenicity testing of several hundreds of chemicals had a number of drawbacks, for example, limited reporting of signs of toxicity seen in animals. Members considered that the appropriateness of the isolated nuclei method used by Sasaki and colleagues had not been established and noted that there was no cellular measure of cytotoxicity or apoptosis in this study. In respect of the study on dichlorvos, members agreed that the dose level chosen (ca 80% of the LD50) was too high. Members agreed that in view of these limitations, little weight could be placed on this study. The positive data in all tissues examined was unexpected given all the available mutagenicity data on dichlorvos. Members considered that it was not possible to conclude that dichlorvos had mutagenic effects in a wide range of tissues on the basis of these data. Thus, although the authors suggested that dichlorvos had an *in vivo* genotoxic effect, the data were uninterpretable.

13. Members considered the in-vivo mutagenicity study in l lacZ transgenic (Muta™ Mouse) undertaken by Plesta and colleagues.[102] The authors had reported a statistically significant (3-fold) increase in mutant frequency in the liver and a slight non-statistically significant increase in mutant frequency in the bone-marrow following repeated dosing with dichlorvos (5 x 11 mg/kg) given intraperitoneally. Members noted that the dose levels used in this study were high and did induce severe toxicity in the animals. They agreed that although the methods used and standards of reporting used in this study had limitations, the data were indicative of a mutagenic effect of dichlorvos *in vivo* at the site-of-contact i.e. the liver. The Committee noted that the authors had failed to identify any O(6) and N-7 methylguanine adducts in tissue DNA from transgenic mice given a single intraperitoneal dose of either 4.4 mg/kg bw or 11 mg/kg dichlorvos bw but agreed that the methods used by the authors were of inadequate sensitivity and it was unlikely that any alkyl adducts could have been detected. In support of this conclusion Members commented that the levels of DNA adducts (O(6) and N-7 methylguanine) in transgenic mice (Muta™ Mouse) following repeated dosing with dimethyl sulphate (10 x 6 mg/kg bw i.p) were only approximately 4-fold higher than the limit of detection. Members considered that evaluation of DNA adducts in dichlorvos treated animals after the repeat dosing regime might have provided valuable information but these analyses had not been undertaken.

14. The Committee concluded that a consistent pattern of mutagenic effects had been documented in the in-vivo studies in which dichlorvos induced mutagenic effects at high doses in the skin following topical application[81], and in the liver following repeated intraperitoneal dosing[102], suggesting a potential site-of-contact effects (i.e. at initial sites of exposure).

Additional data submitted by industry: AMVAC (for 26 April 2001)

15. A number of papers had been submitted just prior to the COM meeting. Members agreed that no substantive new mutagenicity data had been submitted.[103-105] The additional data from the mouse lymphoma test undertaken as part of the US NTP assessment of dichlorvos was consistent with other assays and indicated a positive result in this assay. Regarding the specific comments on the most recent in-vivo mutagenicity assays, members agreed with the reservations proposed by industry regarding the interpretation of COMET assay[106] but did not agree with the views expressed regarding the conduct of the mutagenicity study in transgenic animals[107]. Members considered that the mutagenicity study in transgenic mice indicated a potential mutagenic hazard at the site-of-contact.

16. The Committee commented on the "Blue-Ribbon" evaluation of dichlorvos completed in July 1998[105] and noted that differences in the rate of methylation compared to the rate of phosphorylation could not be used to discount a potential in-vivo mutagenic hazard of dichlorvos. Additionally the role of phosphorylation in the induction of genotoxic effects could not be discounted.

COM review of submission from industry (23 July 2001)

17. A further meeting of the Committee was held on the 23 July 2001 to consider a presentation from industry on the mutagenicity of dichlorvos. This consisted mainly of a critique of the four positive in-vivo studies underpinning the COM statement (referred to in paragraphs 9-13 above), and of the Committee's approach to weight-of-evidence considerations. No additional information was provided to support the reference submitted by industry to the Committee on the possibility of oxidative damage (108) as a mechanism for the induction of mutations seen in the Muta™ mouse study.

COM consideration of additional information (9 January 2002)

18. The COM considered the new information submitted to the High Court during a judicial review of the regulatory decision on the pesticide products containing dichlorvos (held between 5-9 November 2001) and additional data provided to regulatory authorities up to 4 January 2002 to see if any revision of the COM statement on dichlorvos was warranted.

19. The COM considered the documents listed under reference 111 of this statement. Members only considered the information relating to the scientific assessment of dichlorvos and did not consider information of a legal nature. There were a number of topics raised in the documents.

20. Members agreed that mutagenicity studies that had not been subject to full international validation could be used to inform hazard assessment and regulatory decision making, This was particularly relevant when considering in-vivo activity at sites of initial contact for compounds shown to be direct acting mutagens in-vitro. The COM guidance (published in December 2000; See http://www.doh.gov.uk/com/guidance.pdf) recognised that such situations needed to be approached on a case-by-case basis. The current COM guidance listed a number of non-standard test methods which could be used including the use of transgenic animal models. Members concluded that the information available to the Committee to assess the potential for site-of-contact mutagenicity for dichlorvos was very limited, namely in-vivo skin micronucleus test, the intraperitoneal Muta™ Mouse study and forestomach UDS assay. The design of all these studies had limitations which had been noted by the COM. However in the absence of more definitive data, the results of these tests can be used to provide a provisional hazard assessment and could not be dismissed. Members considered the comments put forward on the conduct of the Muta™ Mouse study undertaken by Plesta and colleagues and reaffirmed that this study was acceptable for hazard identification and had given a positive result.

21. A number of the documents commented on the possibility that a threshold existed for the mutagenic efects of dichlorvos. Members reaffirmed their view (see COM statement COM/01/S3 published June 2001 http://www.doh.gov.uk/comivm.htm) that in the absence of specific investigations concerning mechanisms and possible thresholds, the prudent assumption was that there was no threshold for *in-vivo* mutagens. Members recalled that sufficient data had been provided to determine the existence of a threshold for aneugens that acted by inhibition of the mitotic spindle and also in the case of rapid detoxification of hydroquinone after oral administration; however this was not the case with dichlorvos.

22. COC Members attending the COM meeting of 9 January 2002 reviewed the available information from the carcinogenicity bioassays reviewed in the HSE review (submitted to ACP in April 2001) and in the documents submitted to the court and most recently to the regulatory authorities as part of the data call in up to 4 January 2002. COC members considered that it was extremely difficult to assess the extent of exposure from the available information. However the evidence suggested that some exposure of the skin would have occurred during the inhalation study undertaken by Blair et al in 1974. Regarding the other studies in rats, COC members considered there were limitations in all of the studies (e.g. age of study, numbers of animals used, extent of pathology investigations) and that, apart from evidence of mononuclear cell leukaemia in F344 male rats in two studies, there was no evidence for a carcinogenic effect in rats. It was noted that a Pathology Working Group (PWG) had subsequently discounted the finding of mononuclear cell leukaemia in the NTP bioassay in rats, but the report presenting the basis for this decision was not available to COC members. Regarding other studies in mice, COC members considered that there were limitations in the conduct of these studies similar to those undertaken in the rat. Members considered that it was not possible to undertake a comparison of the studies in mice where dichlorvos had been administered in corn oil and those where dichlorvos had been administered in the drinking water or as an aqueous solution by gavage. COC members reaffirmed, however that when the NCI and NTP bioassays in mice were considered together there was limited evidence for an effect on squamous epithelium of the forestomach and oesophagus in mice.

However the latter study should be viewed in terms of its age and small number of oesophageal tumours. On considering the overall package of carcinogenicity bioassays COC members felt that there was no consistent evidence for a genotoxic carcinogenic effect. COC members noted that there was no agreed mechanism for the forestomach tumours.

COM Discussion

23. The Committee agreed that there is clear unequivocal evidence that dichlorvos can induce DNA damage, chromosomal breakage and mutations in mammalian cells from *in vitro* studies. The compound has been shown to interact with DNA via methylation, however several other mechanisms are theoretically possible. *In vivo* dichlorvos can be rapidly detoxified by hydrolysis before it reaches the systemic circulation. Members noted from the HSE review that retention of 14C-vinyl-labelled dichlorvos in skin was recorded in a study where radiolabelled dichlorvos was applied to the skin on the backs of male rats. Several non-standard *in vivo* mutagenicity assays have indicated that dichlorvos can induce genetic damage when systemic detoxification mechanisms are bypassed, e.g. following exposure to the skin and exposure to the liver following intraperitoneal dosing. The COM agreed that there was a potential risk of mutagenicity at site of contact tissues, i.e. at the initial sites of exposure. The COM felt there was no evidence for systemic mutagenic effects. The Committee agreed that until evidence was provided to the contrary and in the absence of appropriate mechanistic data, a precautionary approach should be adopted and no threshold could be assumed for the mutagenic activity of dichlorvos.

24. Members were aware that there was some limited evidence for a carcinogenic effect in mice from standard bioassays.[109,110] This related to an increase in squamous cell papillomas of the forestomach in mice and carcinomas of the forestomach in female mice given gavage doses of dichlorvos[110] together with the finding of squamous cell papilloma and carcinoma of the oesophagus in a small number of mice[109] Members noted there was no evidence for carcinogenicity from a number of other carcinogenicity bioassays including an inhalation bioassay in the rat, although there were limitations with all of these studies.

25. Members noted that negative results had been obtained with dichlorvos in a single dose UDS assay in the forestomach of mice using gavage dosing.[9,99,101] An increase in replicative DNA synthesis had been reported in this study. Members noted that there were a number of proposals regarding the mechanism of dichlorvos tumourigenicity in the mouse forestomach including localised irritancy of dichlorvos in corn oil. The Committee agreed that this proposal had not been proven and considered that it was not possible to exclude a genotoxic effect from these data given the relative insensitivity of the method used as indicated by the response with the positive control chemical; they felt that repeat dosing would most likely be required to identify any mutagenic effect of dichlorvos in this assay.

Conclusion

26. The Committee concluded that dichlorvos should be regarded as an *in-vivo* mutagen at the site-of-contact (i.e. at the initial sites of exposure. The COM felt there was no evidence for systemic mutagenic effects.) High doses of dichlorvos induced mutagenic effects in the skin following topical application and in the liver following intraperitoneal dosing. The Committee noted the limited evidence for a carcinogenic effect of dichlorvos. This related to tumours of the forestomach in mice after gavage dosing and also the oesophageal tumours seen after dietary administration. There was no satisfactory explanation proven for the mechanisms of these tumours and the Committee felt, given the available mutagenicity data on dichlorvos, that it would be prudent to assume a genotoxic mechanism. The Committee agreed that in the absence of appropriate mechanistic data a precautionary approach should be adopted and no threshold could be assumed for the mutagenic and carcinogenic effects of dichlorvos.

January 2002

COM/02/S2

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111. Additional information submitted to high court during judicial review (5-9 November) and to BPAU/PSD up to 4 January 2002.

New Documents (AMVAC)

1. Cancer summary – 'Dichlorvos: An Assessment of Carcinogenic Potential'.

2. Letter to Ian Chart from J A MacGregor dated 7 December 2001.

3. Letter from Dr. Ward Richter, Director of Pathology Southern Research Laboratory, dated 4 December 2001.

New Documents (Other data holders)

1. Submission from Denka.

2. Submission from Product Safety Assessment Ltd.

Documents previously submitted during the Judicial Review proceedings

1. Written Comments submitted on 11 May 2001 to COM following the first draft COM Statement (F3 920-942).

2. Written summary submitted on 28 June 2001 prior to presentation to the 23 July 2001 COM Meeting (D1 86-93).

3. Written comments submitted on 26 July 2001 following the second draft COM statement (D1 98-104).

4. Expert opinion of David Brusick August 2001 (D1 117-122).

5. Expert opinion of John Ishmael August 2001 (D1 147-157).

6. Expert opinion of Karel de Raat August 2001 (D1 167-180).

7. Expert opinion of John Mennear August 2001 (D1 184-197).

8. First witness statement of J. A. MacGregor August 2001 (D1 217-243).

9. Second witness statement of J. A. MacGregor August 2001 (D1 312-326).

10. Third witness statement of J. A. MacGregor (D2 674-677).

11. Affidavit of Anju Sanehi (D1 1-7 paragraphs 13-18).

Dimetridazole (DMZ)

Background to COM review

1. Dimetridazole (DMZ) is an antiprotozoal substance that is used to maintain the health of certain farm animals. In the UK it is permitted for use as a feed additive for turkeys and guinea-fowl and as a veterinary medicine for game birds (pheasants and partridges only). The European Commission is currently considering whether to suspend use as a feed additive, but this would not directly affect veterinary medicinal use.

2. In the last few years, DMZ has been assessed by the EU's Committee on Veterinary Medicinal Products (CVMP)[1,2] and by the EU's Scientific Committee on Animal Nutrition (SCAN)[2]. These two committees disagreed with one another over the interpretation of the mutagenicity data. The CVMP considered that more information was needed before it could conclude on mutagenicity, whereas the SCAN considered that there was sufficient information to allow it to conclude that there was no genotoxic hazard to consumers. The specialist expert advice of COM was sought by the Food Standards Agency (FSA). The FSA is particularly concerned about the safety of consumers of foods derived from animals given DMZ.

Assessment of mutagenicity data

In vitro data

3. DMZ was mutagenic in bacteria.[4-6] Studies using nitroreductase proficient and deficient strains of *Salmonella typhimurium* TA100 showed that this pathway accounted for a proportion but not necessarily all of the mutagenicity seen in bacteria.[7] Positive results were reported in *Saccharomyces cerevisiae* D4 demonstrating that DMZ was mutagenic in eukaryotic cells.[8] Members noted that there was inconsistency in the interpretation of the data for the *in vitro* mutation assays in the mouse lymphoma assay. For the cytogenetics assay in CHO-K1 cells the data were reported as negative but were not traceable. In addition there were very limited details available regarding the *in vitro* UDS assay in V79 Chinese hamster lung fibroblasts and no conclusions could be reached on the results of this test.

4. However sufficient details were available to assess the genotoxicity of DMZ in human lymphocytes using the comet assay.[9] It was established that DMZ was genotoxic under aerobic conditions in the absence of exogenous metabolic activation. The addition of Aroclor 1254 induced rat liver S-9 fraction abolished the genotoxicity of DMZ in this test system. Using the same treatment concentration of DMZ, the magnitude of the response (mean tail moment derived from 200 cells) was reduced under anaerobic conditions and abolished by the addition of anti-oxidants (8-hydroxyquinoline, vitamin C, catalase or superoxide dismutase). Thus, DMZ was genotoxic in the *in vitro* comet assay in human lymphocytes and that the activity observed in this assay was consistent with oxidative DNA damage.

5. The Committee agreed that DMZ was mutagenic *in vitro*.

In vivo data

Insects

6. Members agreed that no weight could be given to the negative results reported in the sex-linked recessive lethal mutation assay in *Drosophila melanogaster*.[10]

Mammals

7. Negative results were reported in published *in vivo* micronucleus assays in the mouse using intraperitoneal and oral routes of administration.[11] However no conclusions could be reached by the Committee in view of the limited details of these tests that were available.

8. The full reports made available to the Committee of the three *in vivo* studies form the basis for the Committee conclusions regarding the ability of DMZ to express the mutagenic potential shown in vitro in mammals.

9. Negative results were obtained when DMZ was investigated in an adequately conducted bone marrow micronucleus test in the mouse, DMZ being given orally at 2 daily doses up to 915 mg/kg.[12] Negative results were also obtained in an *in vivo* liver UDS assay when DMZ was given orally to male rats at single doses up to 1000 mg/kg but the Committee noted that this study had not been performed to current standards since the analyses were limited to examination of primary hepatocytes at a single harvest time (15 hours).[13] [The OECD guideline (486) adopted in 1997, recommends an early sampling time (at 2-4 hours) as well as a later sampling time (12-16 hours). Compounds such as dimethylnitrosamine would not be detected as positive if only the later sampling time point was used.] Negative results were also obtained when DMZ was examined for its ability to induce mutations in germ cells in a dominant lethal assay in male mice.[14] Animals were given 5 daily doses of up to 1000 mg/kg and then subjected to sequential mating over 8 weekly periods.

10. The Committee agreed that the further data were needed to provide adequate reassurance that the mutagenic activity seen *in-vitro* was not expressed *in vivo*. This would comprise a liver UDS assay in rats conducted in accordance with the OECD guideline; it was however recommended that 4 animals should be analysed at each dose level and time point.

Carcinogenicity data

11. The Committee agreed that the available long-term carcinogenicity bioassays in rats had not, from the limited data available, been conducted to contemporary standards.[15] Benign mammary tumours had been documented in two of these studies and some limited evidence was available to support a hormonal mechanism for the induction of these tumours. However, the blood concentration of progesterone was raised in female rats but not in males, whereas benign mammary tumours had been produced in both sexes. Overall, no reassurance regarding the absence of genotoxicity could be derived from the available carcinogenicity bioassays.

Conclusion

12. Dimetridazole (DMZ) has mutagenic activity *in vitro*. The Committee was provided with full reports of *in vivo* studies to investigate the ability of DMZ to induce micronuclei in bone marrow of mice, UDS in primary hepatocytes of male rats, and dominant lethal mutations in the germ cells of male mice. In all cases the oral route was used, with dose levels up to about 1 gram/kg per day. Negative results were consistently obtained. However the Committee concluded that the rat liver UDS assay had not been adequately conducted and recommended that a further rat liver UDS assay conducted in accordance with OECD guidelines (but using 4 animals per dose/sampling time point) was required to provide full reassurance that DMZ (or its metabolites) does not have significant mutagenic activity in mammals in vivo.

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ILSI/HESI research programme on alternative cancer models: results of Syrian hamster embryo cell transformation assay

Background

1. The International Life Sciences Institute (ILSI) and the Health and Environmental Science Institute (HESI) have co-ordinated a multinational research programme from 1996 – 2001 to more fully characterise the responsiveness of several alternative cancer models. The research has focused predominantly on a number of proposed short-term *in-vivo* test models for assessment of potential carcinogenic activity carcinogenicity in mice (in particular ras H2, Tg.AC, p53 +/-,Xpa-/-, Xpa-/-/p53+/- double knockout, neonatal mouse) but also included the *in-vitro* cell transformation assay using Syrian hamster embryo cells (SHE cell transformation assay). The overall objective of the work was to evaluate the ability of these models to provide useful information for human cancer risk assessment. The research involved input from over 50 industrial, governmental (USA, Denmark, Netherlands and Japan) and academic laboratories and cost around $35m.[1]

2. The Committee on Carcinogenicity of Chemicals on Food, Consumer Products and the Environment (COC) has considered all of the data submitted by ILSI/HESI except for the results of the investigations using the SHE cell transformation assay. These data have been considered by Committee on Mutagenicity on Chemicals in Food, Consumer Products and the Environment (COM) whose conclusions are given below.

Previous considerations of the SHE cell transformation assay by COM

3. The assessment of the SHE *in vitro* test system was considered by the COM in 1994 and in 1996. Full details of these considerations can be found in the relevant Annual reports.[2,3]

4. In 1994 the COM considered a number of cell transformation assays including the modified SHE method, and had agreed that transformation assays using Syrian Hamster cells were not yet ready for routine use, but warranted further work on both their validation and providing an understanding of the underlying mechanisms. The Committee considered a draft proposal for an OECD guideline for cell transformation using the modified SHE method (low pH culture). A number of supporting publications and papers claiming a predictive correlation between cell transformation in this test system and carcinogenicity were also reviewed.

5. In 1996, the Committee agreed that there were no mechanistic data available which gave an insight into the relationship between cell transformation in the SHE assay and the carcinogenic process. Although apparently high correlations had been reported in trials using a range of animal carcinogens including non-genotoxic carcinogens, only a very limited number of laboratories were involved and little value could be attributed to these results in the absence of appropriate supporting mechanistic data.

6. The COM concluded at the end of its 1996 review that it was not possible to support the proposed OECD guideline for the reasons given below:

   (i) The current draft of the guideline was poorly referenced and the text was vague and could apply to several different methods.

   (ii) The mechanisms underlying the changes observed in SHE cells were unknown.

   (iii) There were no objective criteria to define the end point (quantification of transformed foci) which is subjective.

   (iv) Data from a validation exercise involving a number laboratories testing compounds blind should be undertaken before consideration could be given to the proposed draft OECD guideline.

ILSI/HESI Alternative Cancer Test research

7. The Committee considered a draft paper by Mauthe RJ and colleagues which had been submitted to *Toxicologic Pathology*. The Committee had considerable reservations on several aspects of the ILSI study relating to the assay system, the study design, the data obtained and the data analyses. There is still no mechanistic basis to underpin the assay and the endpoint (transformed foci) remains subjective as there is a lack of a clear, objective definition of transformed foci. There were reservations about the selection and categorisation of test chemicals, concentration ranges were considered to be too narrow for reasonable analysis of dose-response and, concerns about the extent of repeat testing. Control values were unsatisfactorily low (0 to 6) and in some tests there was a lack of consistency of result between closely spaced doses. Finally, the definition of positive and negative results relied on statistical analyses that seemed inappropriate to the data. Most importantly, there was no correction for multiple comparisons. Also methods had been used (Fisher exact and binomial-based) that assume uniformity of sampling circumstance (i.e. that all cells have an equal chance of transformation under fixed experimental conditions). This is unlikely to be true for the mixture of cell types derived from embryos. No tables of historical negative and positive control ranges (and/or confidence limits) were given to enable general variability, test validity and biological importance to be assessed. Some members of the committee considered that two-sided (-tailed) statistical analyses would be more appropriate as it is probable that compounds may have negative as well as positive effects on transformation. Thus the Committee felt that the results of some tests reported as positive were most likely to be either equivocal or negative. Members also considered that the difficulties in objectively identifying transformed cells combined with the limited number of repeat trials suggested that interpretation of the ILSI/HESI data was particularly problematic. The results for a number of the chemicals tested are considered in detail below.

8. Phenacetin was included in the study as a definite human carcinogen, but was considered by the World Health Organisations International Agency for Research on Cancer (IARC) to be a probable human carcinogen. The IARC conclusions indicated that phenacetin was carcinogenic in rodents inducing malignant tumours of the urinary tract in rats and mice and nasal tumours in rats. IARC had noted that Phenacetin was mutagenic *in vitro* in Chinese hamster cells but gave equivocal results in *in-vivo* tests in rodents for chromosomal aberrations and micronuclei. Overall the data on phenacetin suggested that a positive response would have been expected in the SHE cell transformation assay whereas a negative response had been obtained with phenacetin. There was a need for further consideration of this result.

9. The COM's evaluation suggested that the positive responses obtained with melphalan (included as a human carcinogen) and sulphamethoxazole (rodent carcinogen) were equivocal and needed further trials to confirm the response obtained with this assay. Members noted that ampicillin had given a statistically significant increased response at the highest dose tested (13 transformed foci at 3000 mg/ml) whereas a dose level of 2450 mg/ml had not yielded any transformed cells. Overall ampicillin was classified by the authors as giving a positive response in the SHE assay. However, members considered that the outcome was equivocal or negative and that further testing was required to elucidate the response of ampicillin in this assay.

10. Members felt that the critical problem preventing the use of the SHE assay in a regulatory context was the difficulty in the morphological identification of transformed foci.

Use of SHE assay for regulatory screening of chemicals

11. The Committee considered on the basis of all the available information that some important generic comments could be made on the SHE cell transformation assay.

12. Members felt there was little prospect in obtaining reproducible results with the SHE cell transformation assay as a screen for the identification of chemical carcinogens in the absence of an objective molecular marker to identify cell transformation. Members stressed that there was a need to explain on a mechanistic basis why chemical carcinogens with disparate mechanisms of action should be expected to produce cell transformation in an embryonic cell line.

13. Members considered that whilst positive results could be obtained for benzo(a)pyrene indicating that SHE cells (and or its feeder layer) could activate carcinogens there was very little information available to define the metabolic competency of SHE cells and the feeder layer used.

14. Members noted that there was a tendency to report positive results for a diverse range of chemicals in the SHE cell transformation assay thereby demonstrating good sensitivity. However, there was a lack of chemicals reported to give negative data so that neither the specificity nor the accuracy of the test can be properly assessed. This problem had been illustrated by the data set from the ILSI/HESI trial. However, Members felt that no particular value could be currently ascribed to either positive or negative results obtained in the SHE cell transformation assay in the absence of an objective endpoint to measure, and an understanding of, the mechanism underlying the process of cell transformation. Many of the chemicals selected for this trial are rodent carcinogens that are not human carcinogens. There are concerns that this assay has poor specificity for the detection of human carcinogens.

Conclusion

15. The Committee agreed that the SHE cell transformation assay should not be used for regulatory screening of chemicals for potential carcinogenicity.

16. There are insufficient data on validation of the SHE cell transformation assay to justify the development of an OECD test guideline for this assay.

17. The Committee has considerable reservations regarding the mechanistic basis underpinning the rationale for using the SHE cell transformation assay to screen for chemical carcinogenesis.

18. The Committee has considerable reservations regarding the validity of using morphological assessment alone to define transformed foci in the SHE cell transformation assay. The development of an objective molecular marker is essential before validation work can proceed.

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2002 Membership of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

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K N Mistry (Administrative)

J M Battershill BSc MSc

Declaration of COM members' interests during the period of this report

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Prof P B Farmer (Chairman)	Celltech	Share Holder	NONE	NONE
	Abbey National	Share Holder		
	Bradford & Bingley	Share Holder		
	Friends Provident	Share Holder		
	Torotrak	Share Holder		
	SBS Group	Share Holder		
Prof J Ashby	Zeneca	Employee, Salary, Share option	NONE	NONE
	ML Labs	Share Holder		
	Phytopharm	Share Holder		
Dr G Clare	Huntingdon Life Sciences	Employee, Salary, Share option	NONE	NONE
	AstraZeneca	Share Holder		
	Syngenta	Share Holder		
	HBOS	Share Holder		
Dr J Clements	Covance	Employee Salary Share Option Share Holder	NONE	NONE
Prof C Cooper	HBOS	Share Holder	NONE	NONE
	Norwich Union	Share Holder		
Dr N Gooderham	Abbey National	Share Holder	GlaxoSmithKline	BBSRC Collaborative Studentship
	Friends Provident	Share Holder		
	Game	Share Holder		
	ML Laboratories	Share Holder		
	Northern Rock	Share Holder		
	Proctor & Gamble	Consultant		
	Protherics	Share Holder		
	Sunderland AFC	Share Holder		

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Ms M Langley	BT	Share Holder		
	Business Consolidating Services	Director		
	Ciebel	Share Holder	NONE	NONE
	CREE Research	Share Holder		
	Cyber Care	Share Holder		
	Eshelon	Share Holder		
	HBOS	Share Holder		
	MMO_2	Share Holder		
	Quelcom	Share Holder		
	Wibex	Share Holder		
Dr I Mitchell	Kelvin Associates	Associate Consultant		
	IM Enterprises	Director/Creditor		
	GlaxoSmithKline	Pension Option and Share Holder Consultant		
	Bass	Share Holder	NONE	NONE
	Cable & Wireless	Share Holder		
	Cadbury Schweppes	Share Holder		
	Marconi	Share Holder		
	Nokia	Share Holder		
	Pfizer	Share Holder		
	RTZ	Share Holder		
	Shell	Share Holder		
	Unilever	Share Holder		
	Vodafone	Share Holder		
	Whitbread	Share Holder		
	British Telecom	PEP Holder		
	Centrica	PEP Holder		
	Scottish Power	PEP Holder		
	Shire	PEP Holder		

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Dr E M Parry	Invesco	PEP Holder		
	Fleming	PEP Holder	NONE	NONE
	Legal & General	PEP Holder		
Prof D Phillips	Abbey National	Share Holder		
	BG Group	Share Holder		
	Bradford & Bingley	Share Holder	NONE	NONE
	Centrica	Share Holder		
	CGNU	Share Holder		
	Lattice Group	Share Holder		
	National Grid	Share Holder		
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Prof D J Tweats	GlaxoSmithKline	Salary Employee Consultant Share Option Holder		
	Boots Healthcare	Consultant	NONE	NONE
	Charterhouse	Consultant		
	Therapeutic Ltd	Consultant		
	Gentronix Ltd	Consultant		
	Theravance Inc	Consultant		
	Watford FC	Share Holder		

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

DRAFT TEMPLATE FOR COM 2002

The template is designed to show the breadth of expertise available to the Committee and is intended to aide members in discussing future needs with regard to expertise necessary to fulfil the terms of reference of the COM. The compliment of COM is 10 members (9 specialists and one lay member) and one chair. A deputy chair has not been appointed at October 2002.