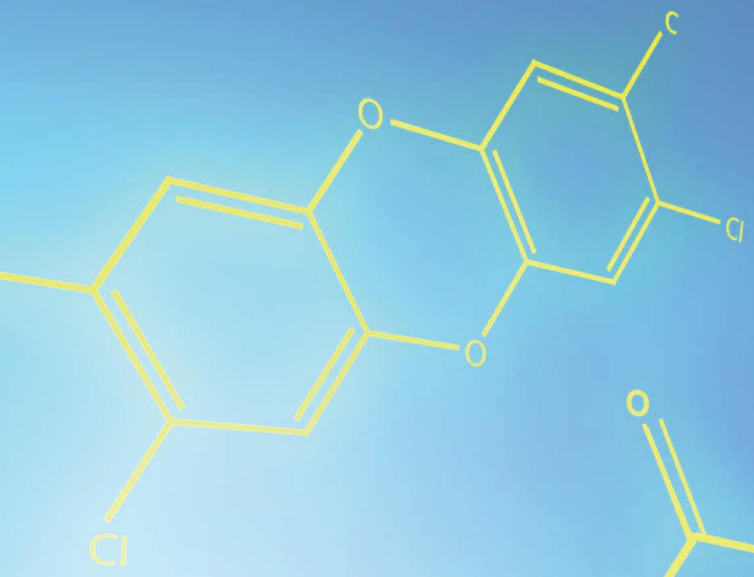
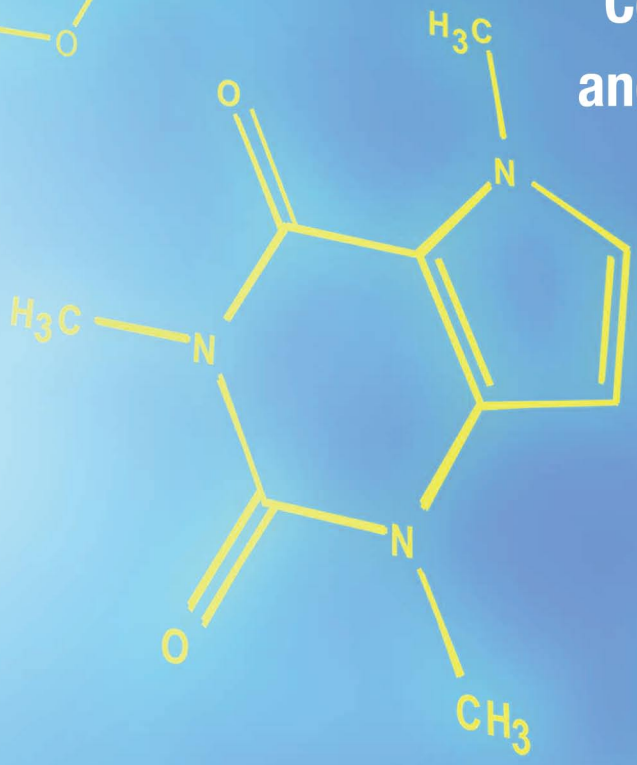
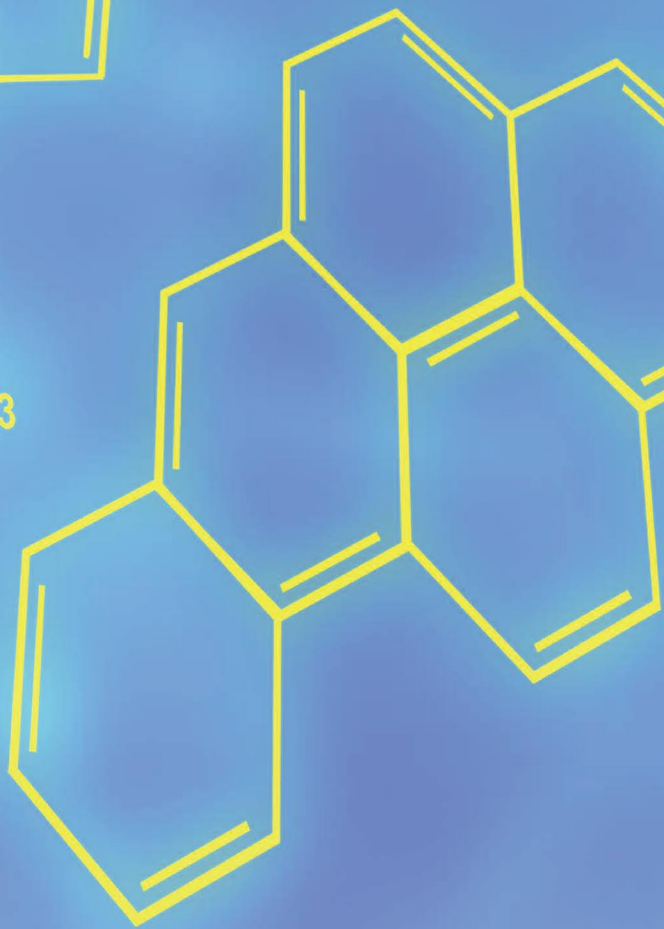
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment







Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2009

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

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Contents

About the Committees

This is the nineteenth 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 summarise the issues discussed by the Committees over the past year and provide background information on working practices. Those seeking further information on a particular subject can obtain relevant references from the Committee's administrative secretary or from the internet sites listed below.

In common with other independent advisory committees, Committee members are required to follow a Code of Conduct which also gives guidance on how commercial interests should be declared. 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. Annex 1 contains the terms of reference under which the Committees were set up. The Code of Conduct for members of advisory committees is at Annex 2 and Annex 3 describes the Committees' policy on openness. Annex 4 has the Good Practice Agreement for Scientific Advisory Committees. Annex 5 contains a glossary of technical terms used in the text. Annex 6 is an alphabetical index to subjects and substances considered in previous reports. Previous publications of the Committees are located at Annex 7.

These three Committees also provide expert advice to other advisory committees, such as the Advisory Committee on Novel Foods and Processes, and there are links with the General Advisory Committee on Science, Veterinary Products Committee and the Advisory Committee on Pesticides.

The Committees' procedures for openness include the publication of agendas, finalised minutes, agreed conclusions and statements. These are published on the internet at the following addresses:

COT: http://cot.food.gov.uk
COC: http://www.iacoc.org.uk/index.htm
COM: http://www.iacom.org.uk/index.htm

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

Preface

The Committee on Toxicity (COT) evaluates chemicals for their potential to harm human health. Evaluations are carried out at the request of the Food Standards Agency, Department of Health, Health Protection Agency and other Government Departments including the Regulatory Authorities, and are published as statements on the Internet. Details of membership, agendas and minutes are also published on the Internet.

During 2009, the Committee agreed six statements, five relating to specific chemicals or exposures (glucosamine, methylglyoxal, perfluorooctanoic acid, chloroparaffins and polychlorinated naphthalenes), and one on the more generic topic of 21st century toxicology. The last followed a workshop in which international experts were invited to present perspectives on ways in which methods for assessing the toxicity of chemicals were likely to evolve. While exciting advances in molecular biology and computational methods offer a long-term prospect of more efficient evaluation of chemical toxicity, with reduced use of experimental animals, the Committee concluded that conventional approaches are unlikely to be superseded in the short to medium term.

At the end of the year, there was a vigorous public debate about the role of scientific advisory committees, and how they should relate to Government. I am pleased to report that, at least during the terms of office of current members, the COT's sponsoring Departments (the Food Standards Agency and the Department of Health) have at all times respected our independence, and have never attempted to influence or modify our conclusions. Dialogue with our sponsors has always been constructive, helping to ensure that the value of our advice to policy-makers is maximised.

I would like to thank Joy Hinson, Peter Jackson and David Bell, who left the Committee during 2009 after valuable service, and also the administrative and scientific secretariats, who as always, have given us excellent support.

Professor David Coggon Chair
OBE MA PhD DM FRCP FFOM FFPH FMedSci

COT evaluations

Arsenic in food, opinion of the European Food Safety Authority

1.1 The European Food Safety Authority (EFSA) scientific opinion on arsenic in food was adopted on 12 October 2009[a], concluding that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) provisional tolerable weekly intake (PTWI) of 15 µg/kg body weight for inorganic arsenic was no longer appropriate; and that dietary exposure to inorganic arsenic should be reduced. This conclusion is in line with previous COT opinions. In order to refine the risk assessment of inorganic arsenic, EFSA noted that there is a need to produce speciation data for different food commodities to support dietary exposure assessment and dose-response data, for the possible health effects.

Bystander/resident exposure to pesticides

1.2 The COT initially considered this issue in April, when its advice was sought in relation to the conclusions of a judicial review concerning the current consideration of risk to bystanders and residents in the pesticide approval process. The COT subsequently considered further information provided by the Health and Safety Executive (HSE) Chemicals Regulation Directorate (CRD) at its September meeting.

1.3 "Bystander" is taken to mean people exposed to a pesticide at the time of application, whereas "residents" may be exposed later and over a longer timescale. Three exposure scenarios are considered in the UK regulatory assessments. The first is a bystander who stands upright, wearing no clothing, 8 m from the nearest part of the sprayer, during one close pass of the sprayer per day. The amounts of pesticide which might land on the skin or be inhaled are estimated. The model uses data from spraying trials that used food dyes as marker substances, in which the wind speed was higher than the maximum recommended for spraying. From this, the mean data point is used. The second scenario relates to residents who are exposed to a pesticide in the air for 24 hours per day. Worst-case data are used from Californian monitoring of about 26 active substances. The maximum application rates in the studies tended to be higher than those used in the UK. Air monitoring had been for 72 hours and the highest 24-hour value was used. For example, in the case of chlorpyrifos used on a 60 acre orchard, there had been some spraying on 2 consecutive days and the highest exposure was on the second day. The

[a] http://www.efsa.europa.eu/en/scdocs/scdoc/1351.htm

third scenario is a small child playing on a lawn, with dermal, hand-to-mouth and object-to-mouth exposures. For this scenario, a US Environmental Protection Agency model of the exposures of children from lawn treatments is used.

1.4 All pesticide inhaled is assumed to be retained in the body, none being exhaled. Empirical dermal absorption data are used where available, but otherwise 100% absorption is assumed. The data are used to estimate a systemic dose, which is compared to the Acceptable Operator Exposure Level (AOEL). In practice, for the arable situation, estimates of potential exposure are up to approximately 10% of the AOEL, and often are <1% of the AOEL. For orchard applications, drift is greater and estimates of potential exposure can be up to around one third of the AOEL. Where potential exposure is estimated to exceed the AOEL a pesticide would not be authorised unless further data (e.g. on dermal absorption) allowed a refined exposure assessment.

1.5 The COT heard that a 3½ year research project had been funded to generate better data to underpin risk assessment for bystanders and residents. This was due to report in January 2010. The Committee saw data from biomonitoring studies conducted in different parts of the world and a comparison with predicted exposures based on UK regulatory exposure assessment models. Studies of US farm families included paraoccupational exposures and bystander exposures which were not directly applicable to the UK. However, the data indicated that bystander or resident exposures might be higher than predicted, but are lower than exposures measured in operators, which are lower than exposures predicted in operators. HSE (CRD) and the Health and Safety Laboratory (HSL) were due to initiate a research project in the near future to investigate biomonitoring of rural residents living within 100 m of agricultural land.

1.6 The AOEL is a health-based reference value, analogous to other reference values such as the Acceptable Daily Intake (ADI), but expressed as systemic exposure. The AOEL is usually based on toxicity studies of 90-days duration or less in rats or a one-year dog study. The Committee questioned whether the AOEL was appropriate for use in risk assessment of residents, since exposure might be chronic and low level. This differed from exposure to bystanders which may be acute and perhaps high. It was noted that, while the AOEL was usually based on subchronic toxicity data, anecdotal evidence was of chronic effects such as multiple chemical sensitivity and chronic fatigue syndrome. Moreover, there were no animal models for these effects.

1.7 The COT was provided with data on the ratios of AOELs to ADIs for pesticides after correction for oral absorption. It observed that the ratios were not all in the same direction. In a few cases AOELs were lower than ADIs, or in one instance greater than the Acute Reference Dose (ARfD), after correction for oral absorption. It was noted that it would be unusual for AOELs to be lower than ADIs. In most cases the AOEL was similar to or higher than the ADI after correcting for oral absorption. In order to consider the appropriateness of an AOEL that was higher than the corresponding ADI, more information was needed on the usage pattern of the pesticide. The Committee requested information additional to that provided by CRD on usage pattern (including number of applications and seasonality) for all pesticides where the ratio of the AOEL to ADI was ≥ 5 after adjustment for oral dosing. If the Committee found that the usage patterns for these pesticides did not justify large differences between AOELs and ADIs then it might be appropriate to recommend changes to the process of setting AOELs in some instances. The Committee asked CRD to provide an explanation for the one example (dimoxystrobin) where the ARfD was lower than the AOEL.

1.8 The COT was concerned that the database used to estimate bystander exposure from a close pass of a spray boom was not large and there would have been considerable variation between exposures of individuals. Thus the exposure of a bystander on a single day could be underestimated, which might be of concern for an acutely toxic pesticide. A separate acute reference value (to the standard AOEL) may therefore be required for acute risk assessment of bystander exposure. However, unusually high exposure on a single day was not a concern in relation to the risk assessment for longer term exposures of residents.

1.9 The COT considered information from the Pesticides Incidents Appraisal Panel (PIAP) on “confirmed” cases for 1998-2008, which were defined as cases in which there were clinical symptoms that might be expected from exposure to the cited pesticide formulation, combined with either corroborating medical and (where appropriate) biochemical evidence or evidence of pesticide exposure. PIAP had been instituted to help HSE inspectors in enforcement duties. It uses a standardised approach to assess whether exposure occurred, whether any adverse effects occurred, and whether adverse effects could be related to exposure. The available information tended to be poor, as often either no consent was received from the individual to investigate, or the available medical information was limited. Most incidents were the result of occupational exposure to pesticides. Members observed that two incidents which did not involve occupational exposure involved irritant reactions to exposure. These particular incidents may have been associated with exposure to

dilute mixtures of pesticide formulations, and could possibly have been due to co-formulants rather than active ingredients. Members noted that exposure to sulphuric acid used on potato crops could result in irritant reactions. Notifications of use had now to be posted when using sulphuric acid as a desiccant on potato tops. It was observed that only a limited number of pesticides were implicated in the "confirmed" cases. However, the Health and Safety Executive advised that <5% of possible cases reviewed by PIAP were "confirmed". It was suggested that all "confirmed" and "likely" cases over a year or several years could be examined to gain a better picture of patterns of exposure. It was noted that other sources of information on pesticide incidents were the National Poisons Unit TOXBASE and the Health Episodes Statistics database which recorded hospital admissions in England.

1.10 The COT viewed a DVD submitted by a member of the public presenting evidence of ill health in bystanders and residents. The Committee agreed that these did not provide any evidence of toxic causation. It was pointed out that individuals can have ill health which appears to be linked to exposure, but when the tools are available to investigate further, there is not necessarily any link. Members agreed that some of the exposures reported must have been unpleasant, with, for example, strong smells and/or a greasy film on windows, and that there was no choice about the exposure and often no information on when spraying would take place. The COT agreed that it would be easy for an individual to make an association between their ill health and pesticide exposure on this basis, but this did not prove toxicity.

1.11 The assessment of local effects was considered. There can be local effects on skin, eyes or upper respiratory tract. These arise through irritation or sensitisation. Very rarely, an AOEL is set on the basis of acute inhalation effects using data from toxicity studies with inhalation exposure. More usually, the AOEL is set on the basis of systemic effects only, and there is a separate assessment of irritation and sensitisation. Both active substances and formulated products are tested for their potential to cause irritation and sensitisation. If a product contains a sensitiser at lessthan 5% concentration, then it does not need to be tested for sensitisation or classified as a sensitiser. If a product is classified as a sensitiser or irritant the risk to operators is managed through label warnings, including recommendations for the use of personal protective equipment. When the dilution of pesticide products is considered, even if a product were classified as an irritant or sensitiser, it would not normally meet the criteria to be so classified after dilution. The exception is aerial applications, where the dilution can be up to 20%. However, a product for aerial application would not be approved unless it was not a sensitiser.

1.12 The COT suggested that the scientific literature be examined for information on the effects of dilution of chemicals on irritancy and sensitisation in order to assess whether a hazard was demonstrable when chemicals classified as irritants or sensitisers were diluted 100-fold. If there were no data available, then further research might be needed.

1.13 The Advisory Committee on Pesticides (ACP) had proposed the establishment of a subgroup of COT and ACP members to undertake a detailed review of risk assessment for bystander and residential exposure to pesticides. The Committee agreed that this would be a useful way forward. As part of its work, the subgroup could follow up the COT's requests for further information. The subgroup is expected to start in early 2010. Four COT Members, including a public interest representative, volunteered to join the subgroup.

Cadmium in the 2006 Total Diet Study

1.14 In 2008 the Committee had evaluated the results of analyses for metals and other elements in the Food Standards Agency (FSA) 2006 Total Diet Study and published a statement (COT statement 2008/08). Cadmium was one of the elements surveyed and the Committee had reached the following conclusion: '*The current dietary exposures to cadmium are not of toxicological concern. This conclusion might need to be reviewed after the current risk assessment by the European Food Safety Authority (EFSA) is published.*'

1.15 The EFSA scientific opinion on cadmium in food[b] was adopted in January 2009, establishing a revised Tolerable Weekly Intake (TWI) for cadmium of 2.5 µg/kg bw (equivalent to 0.36 µg/kg bw per day). The opinion noted that the average dietary exposure for adults across Europe is close to or slightly exceeds the revised TWI; and that subgroups of the population may exceed the TWI by 2-fold. EFSA concluded that although adverse effects on kidney function are unlikely to occur at exposures 2-fold greater than the TWI, exposure to cadmium at the population level should be reduced.

1.16 The estimates of dietary exposure to cadmium from the 2006 Total Diet Study for pre-school children aged 1.5-4.5 years (mean and high-level intakes) and for high-level intakes in young people (aged 4-18 years) exceeded the new TWI by up to 2-fold. For other age groups, estimated

[b] http://www.efsa.europa.eu/en/scdocs/scdoc/980.htm

dietary exposures, even for people with high-level dietary intakes, were below the new TWI.

1.17 Members were asked to comment on the revised TWI and to consider whether they wished to revise their previous conclusions. The Committee made the following conclusions:

The approach used by EFSA to derive the TWI was appropriate, although conservative.

Given the conservative manner in which the TWI was derived, and that exceedances from dietary exposure are modest (generally less than 2-fold) and only for a limited part of the lifespan, they do not indicate a major concern. Nevertheless, in view of the uncertainties, it would be prudent to reduce dietary exposures to cadmium at the population level where this is reasonably practical.

Chlorinated paraffins in food

1.18 The COT was asked for advice on possible risks associated with the levels of chlorinated paraffins (CPs) in foodstuffs that had been found in an FSA investigation.

1.19 CPs are a large group of several thousand individual chemicals. They are chlorinated linear hydrocarbons with between 10 and 30 carbon atoms and varying numbers of chlorine atoms, with a maximum of one chlorine atom per carbon atom. Depending on the length of the carbon skeleton, CPs are classified as short (SCCPs: C10-13), medium (MCCPs: C14-17) and long chain (LCCPs: C18-26).

1.20 The industrial applications of CPs vary depending on the chain length, and include use as industrial lubricants in metal manufacturing and as additives in plastics, paints and sealants. In addition, a common current use is as flame retardants. CPs have the potential to contaminate the food chain following their release during product use or through improper disposal. The FSA investigation was carried out as there were no UK data on their occurrence in food and samples were assessed for SCCPs and MCCPs.

1.21 The Committee assessed the available data and established a Tolerable Daily Intake (TDI) of 30 µg/kg b.w. for SCCPs and 4 µg/kg b.w. for MCCPs. Using these TDIs and highly conservative assumptions about dietary exposure, the Committee concluded that the results of the FSA

investigation of occurrence of SCCPs and MCCPs in food do not give rise to concern for human health

1.22 The COT statement can be found at:. http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200905

Developmental neurotoxicity

1.23 The COT report on Variability and Uncertainty in Toxicology (VUT) identified developmental neurotoxicity assessment as an area of recent interest and emphasised the need to keep abreast with methods for assessing developmental neurotoxicity. This recommendation coincided with the anticipated adoption of a new OECD guideline 426 on developmental neurotoxicity, which was adopted in October 2007. The guideline addresses the need to incorporate endpoints of relevance to neurotoxicity in studies of developmental toxicity used for risk assessment. Based on the US EPA developmental neurotoxicity guideline (EPA, 1998) it was drafted to meet a gap in existing OECD guidelines for reproductive and developmental toxicity using a test protocol in laboratory animals.

1.24 A number of chemicals are known to produce developmental neurotoxic effects in humans and other species. Developmental neurotoxicity studies are designed to provide data, including dose-response characterisations, on the potential functional and morphological effects on the developing nervous system of the offspring that may arise from exposure *in utero* and during early life.

1.25 The relevance of extrapolation from animal to human and the issue of whether behavioural tests in rodents are sufficiently sensitive to detect certain more subtle effects was raised in the VUT report and in other papers. The topic has been under consideration by an expert panel assembled by the International Life Sciences Institute (ILSI) whose remit was the “Evaluation and Interpretation of Neurodevelopmental Endpoints for Human Health Risk Assessment”. The ILSI report was comprised of a series of five review papers and a short summary paper all of which were published in Neurotoxicology and Teratology.

1.26 The COT considered that the ILSI papers identified important issues in the interpretation of developmental neurotoxicity studies, and proposed a suitable strategy for assessing such studies. The COT noted that substantial information was required on a study for its thorough evaluation. This level of detail might be available in reports of regulatory

developmental neurotoxicity studies as it could be required by regulatory authorities and in guidelines but was unlikely to be available for published studies due to editorial constraints on space. This would be reflected in the discussion of uncertainties and might influence the weight given to findings.

1.27 Although well established neurotoxicants had not necessarily been tested under the precise conditions used in regulatory studies, it was likely based on a review of available studies that they would produce positive results under such conditions. A number of unpublished case studies on established neurotoxicants had been prepared for the ILSI discussions but were not incorporated in the published paper. The authors were approached through ILSI and agreed that the COT could have access to their unpublished manuscripts. These reviews summarised a great deal of information on the four best characterised agents known to produce developmental effects in humans and allowed conclusions on the predictability of animal developmental neurotoxicity studies for such effects in humans. Essentially the case studies showed that there were developmental effects in animals at about the same exposure level as is damaging in humans.

Glucosamine and hepatotoxicity

1.28 Glucosamine is a popular food supplement taken alone or in combination with chondroitin sulphate usually by sufferers of osteoarthritis. In view of a small number of case reports linking glucosamine and hepatitis, including one that became the subject of a Scottish Fatal Accident Inquiry, the COT was asked to consider whether a causal association was plausible.

1.29 The COT concluded that current evidence does not suggest that glucosamine is likely to be a cause of hepatitis although a causal link cannot be completely excluded. It should be noted, however, that the likelihood of an individual user of glucosamine experiencing adverse effects is, at most, very low.

1.30 The COT statement can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200901

Methylglyoxal

1.31 As part of its annual horizon scanning discussion in February 2009, the Committee was provided with information on occurrence of methylglyoxal (MG) in food, possibly as an intermediate in the formation of acrylamide, and on the association between endogenously formed MG with a number of diseases. The Committee expressed an interest in a more thorough review of methylglyoxal including, if possible, a comparison between dietary exposure to MG and endogenous production. A discussion was held at the June meeting and a statement drafted for the October meeting.

1.32 MG is a reactive dicarbonyl compound that is produced endogenously in the body, primarily through anaerobic glycolysis. MG and other products of glycolysis have been shown to produce adducts in both DNA and proteins. Elevated MG levels and associated MG-protein adducts in the kidney, lens and blood have been associated with complications commonly found in patients with diabetes mellitus. Elevated levels of protein adducts have been associated also with aging, renal failure and Alzheimer's disease and of DNA adducts with cancer.

1.33 As MG is ubiquitous in living cells, it will be found in food products of both animal and plant origin and therefore exogenous exposure occurs through consumption of all foods. Particularly high levels have been reported in manuka honey and some soft drinks. MG can be present as a free molecule in the diet and can be found bound to biological material, such as proteins, as AGEs, which are poorly absorbed.

1.34 The COT concluded that the database on toxicity of MG is poor, and inadequate for characterisation of dose-response relationships. In order to support an evaluation of the risks associated with MG, it was suggested that a study to investigate the kinetics of MG would be the first priority, followed by a 90-day study to assess the toxicity of MG and an *in vivo* genotoxicity study.

1.35 The COT statement can found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200904

Multi-strain assays

1.36 During discussions of the COT Working Group on Variability and Uncertainty in Toxicology about strain differences in xenobiotic metabolism, Dr Michael Festing submitted a number of papers and correspondence.

1.37 Dr Festing's proposal was to use multiple genetically well-characterised inbred strains of laboratory animals in toxicity testing (a multi-strain assay; MSA) in place of an equal number of animals from one or two outbred strains. Dr Festing submitted further correspondence to the COT and the Committee invited him to the February meeting to discuss his views.

1.38 In the light of discussions at this meeting and the meeting in April 2009, members felt that there was value in looking at the theoretical advantages of Dr Festing's proposals, but at that time there was little evidence that utilisation of MSAs would improve on the current risk assessment paradigm. If regulatory frameworks were to change to request MSAs in place of one or more inbred or outbred species then the benefits would need to significantly outweigh the disadvantages of the change. The Committee returned to this topic at their June and September meetings in 2009 to discuss correspondences with Dr Festing. A number of further issues had been identified and it was agreed that no further discussion of this topic was required.

1.39 Minutes of these discussions at the February, April, June and September meetings can be found on the COT's website: http://cot.food.gov.uk/cotmtgs/cotmeets/

National Diet and Nutrition Survey

1.40 The COT was provided with a paper on the National Diet and Nutrition Survey (NDNS) programme and was requested to comment on its utility and importance, particularly with respect to informing UK consumer exposure assessments for chemicals in food. The COT comments were used to inform the review of the FSA's nutrition research and survey portfolio.

1.41 The NDNS programme gathers detailed information on food consumption (by dietary record); nutrient intake (by combining food consumption data with data on the nutrient content of foods); nutritional status (by measurement of blood and urine analytes); physical measurements (for example, height, weight and blood pressure); and socio-economic, demographic and lifestyle characteristics. One of the key benefits of the NDNS programme is the provision of this information in the same individuals; this allows the analysis of links between these parameters.

1.42 In April 2008, a new rolling programme was set up to collect data continuously. The core NDNS rolling programme examines a UK representative cross-sectional sample of 1000 individuals aged 1.5 years

and upwards per year (excluding pregnant and lactating women and people in institutions). The rolling programme provides more frequent dietary data for better tracking of trends over time and allows greater flexibility to respond to changing policy needs, for example, to collect additional data for a specific population group where a need has been identified.

1.43 The NDNS programme provides evidence about the dietary habits and nutritional status of the UK population and is the main source of dietary data used by the FSA for conducting exposure assessments for chemicals in food.

1.44 The Committee unanimously agreed that the NDNS programme is an important resource and supported the move to the rolling programme for continuous rather than periodic data collection. It was noted that the NDNS programme has a wide usage, which supports academic research in addition to informing policy.

Organophosphates and human health: outstanding Government-funded research

1.45 In 1999 the COT published a report entitled “Organophosphates,” which considered whether chronic low level exposure to organophosphates, or acute exposures to levels insufficient to cause overt toxicity, can cause long term adverse health effects. The COT report made recommendations for research in five different areas, expressed in the form of questions to be addressed. Research to address the recommendations was funded jointly by a number of Government Departments. In 2007 the Committee considered a review of the research reports available at that time. At its September 2009 meeting the Committee considered three additional research reports, and the final one was considered in December 2009.

Research project 1: report on SHAPE: Survey of Health and Pesticide Exposure

1.46 This project was a clinical investigation of selected farmers who has reported symptoms of peripheral neuropathy in phase 1 of the SHAPE study. The study design involved unblended examination of patients without a control group and thus could not be used to draw conclusions regarding the association of exposure with findings on clinical investigations, or with signs or symptoms of peripheral neuropathy.

1.47 The Committee received expert advice on the neurophysiological testing. The sample size was considered small and the neurophysiological testing very limited. There were no control subjects or background data on the expected range of values for neurophysiological tests undertaken by the study investigators. Only one upper limb nerve (median in the hand) had been studied and the authors had not controlled for carpal tunnel syndrome. The deep peroneal nerve had been investigated in the lower limb. The extent of electrodiagnostic investigations was considered inadequate to clinically investigate nerve conduction. The researchers had stated the F-response to be a monosynaptic reflex response, which is incorrect; and no data on F-response were presented. The investigators had not attempted to correlate the results of clinical assessments of individuals for signs (e.g. loss or abnormal sensations in extremities) symptoms (e.g. muscle weakness), electrodiagnostic status, and quantitative sensory testing. There was no mention of having controlled for skin temperature. Muscle weakness was poorly defined in the questionnaire, and when assessed clinically only a small number of patients had muscle weakness. It was noted that nerve conduction velocity was more affected in the upper limbs of patients than the lower limbs which would be contrary to expectations from the dying-back neuropathy suggested by the researchers. There was discussion of autonomic dysfunction in patients, but this was not objectively studied.

1.48 The researchers referred to electromyography (EMG) results but no data were presented and there was no quantitative analysis, which would have been informative. The investigation of reflexes was too limited to draw conclusions. It was observed that it was difficult to assess ankle jerks consistently; thus ankle jerks needed to be investigated by a single trained assessor. Quantitative sensory tests for peripheral neuropathy were considered particularly difficult to undertake and had not been adequately performed in this study. Unexposed controls would be needed with assessors blind to exposure status. It is also possible that findings are incidental, if not enough nerves are studied. Testing at least three nerves in the upper limbs and three in the lower limbs would be recommended. Overall, there were many contradictions and the findings neither proved nor disproved clinical neuropathy.

1.49 The situation was different when diagnosing individual patients than in investigation of a group of exposed individuals, but the minimum number of nerves tested would be more than in this study, and on both sides of the body if necessary. Each department should have its own normative data. Each person conducting the testing should have their own normative data. Diagnosis would typically be dependent on findings being below the limit

of the normal range. It was not clear how the normative standards reported by the study investigators had been derived.

1.50 The Committee considered the lack of adequate control data to be a major weakness. There was insufficient information on many aspects of neurophysiological investigations which would have been important for a full assessment of the data, including, for example, on autonomic function and the results of EMG investigations. However, the Committee also considered it important that the researchers should have an opportunity to respond. To summarise, in a selected sample, the researchers had found unusual patterns of neurophysiological responses, but the tests undertaken were technique- and observer- dependent and the Committee could not conclude that genuine abnormalities had been identified.

Research report 2: report on disabling neuropsychiatric disease in famers exposed to organophosphates

1.51 There were major problems with the interpretation of the data from this study, arising from the lack of blinding of exposure and outcome measurements, the low response rate, and limited assessment of confounding. The Committee commented that the study should be considered as a cross sectional investigation, that the methods for investigation of clinical outcomes (in particular peripheral neuropathy and symptoms of Parkinson's disease) were limited, and that the exposures evaluated were to sheep dipping rather than to specific organophosphate pesticides. The low response rate in the phase 2 investigation further limited the value of the study, as had been acknowledged by the study investigators. It was suggested the authors should undertake logistic regression analyses to further investigate the impact of confounding. There was no association with depression and a link with Parkinson's disease appeared unlikely. The findings on peripheral neuropathy suggested an association with sheep dipping, but they were liable to recall bias and no definite conclusions could be reached.

1.52 The Committee considered that the study report had been drafted to a high standard and the investigators had been aware of the inevitable limitations of the study design. The Committee concluded that little reassurance could be drawn from the absence of positive associations for some health outcomes. Nor could conclusions be reached regarding causality from the positive associations that were observed.

Research report 3: Neuropsychological and psychiatric functioning in sheep farmers exposed to organophosphate pesticides

1.53 The interpretation of results was hampered by various aspects of the analyses undertaken, including amalgamation of data on different tasks into a single average score, limited attempt to explore the locus of cognitive functions that might be impaired, and the analysis of continuous performance measures as binary variables (normal/impaired function). There were also some inconsistencies in the findings (e.g. verbal ability was negatively associated with exposure in additional analyses but there were no group differences in the main analysis). Overall, whilst there appeared to be evidence for impairment, the precise nature of this remained to be elucidated, and given the influence of verbal abilities on memory and other cognitive functions, there remained a question of whether associations would remain after appropriate control for this, and whether the impaired motor skills in simple tasks would translate into the observed impairments of speed in cognitively more demanding tasks. These additional analyses could be explored using the available data set.

1.54 Recruitment had been based on self-reported exposure. Neuropsychological testing had been performed by investigators who knew the subjects' occupational status (farmer (exposed) or police officer (control)) but without detailed knowledge of their exposure. Selection was based on reported low level exposure to organophosphates with exclusion of farmers who reported evidence of acute toxicity to organophosphates. It was noted that the response rate had been very low and that recruitment had been partly via campaign groups. Controls were excluded if they had experienced psychiatric problems at any time in the past, but farmers were not excluded if they had suffered psychiatric problems only after they were first exposed to organophosphates (which typically was many years earlier). Some participants had been excluded to improve matching, and it was not clear how these participants were selected, although this was unlikely to make a large difference to the results. The authors had also included comparisons of test data from exposed study subjects with published test norms derived from a cross section of healthy adults in the general population.

1.55 There was a correlation of cognitive function with duration of exposure, but it was not clear if adjustments had been made for age. The Committee was aware that there is a high rate of early retirement due to ill health in police officers.

1.56 It was reported that no association was found between genotype and paraoxonase (PON1) activity measured under non-physiological

conditions. Such assay conditions are not predictive of inter-genotype differences in PON1 activity towards diazinon *in vivo.* No difference was reported in farmers according to work status in either genotype or phenotype. The Committee was unable to reach any conclusions regarding a possible association between PON1 phenotype and neuropsychological outcome on the basis of the information provided.

1.57 The Committee received expert advice on the neuropsychological testing undertaken. The Committee was informed that performance could be impaired by deficits anywhere along a chain of functions that were assessed by a particular test, including, but not limited to, cognition. Therefore the results of tests should be analysed for specific patterns of impairment, not just overall deficits, which had not been done. The statistical approach was considered acceptable in the assessment of clinical status of individuals but less so for group analysis. ANOVA had been used to assess the results of ranges of tests, but the analysis conducted would not tease out the precise nature of any impairment in the exposed group. Thus some of the reported deficits thought to be due to cognitive deficits could be simply due to motor impairment.

1.58 Differences in performance of tasks could be expected between rural farmers and rural police officers. The population norms used were not specified to be from the UK, and results of neuropsychological tests can vary geographically. Test results are also age-dependent, but there appeared to be no separate evaluation of adjustment for age. There would be differences in absolute performance between different geographical population groups but differences in relative performance would not be expected. Further analysis of the datasets would be possible. Adjustment for mood could be included in any further analyses of test data if it were a confounding factor for the specific tasks under analysis. The Committee observed that there were no differences between farmers who had retired through ill health and those currently working, contrary to a prior hypothesis of the researchers.

1.59 In summary, there was some evidence of poorer performance in farmers, but although a large number of tests had been performed, the analysis was not focused, so it was not clear what was causing the poorer performance. Additionally, there was still a need to identify appropriate UK control data, and to adjust for age where it was a potential confounder. It was possible that many of the cognitive differences reported might disappear after adjustment for motor performance. The Committee concluded that no definite conclusions could be drawn from this study report but the data could be subject to further analysis.

1.60 The Committee discussed the extent to which these three research projects addressed the research recommendations made by the COT in 1999. The Committee concluded that the studies reviewed needed to be considered in the context of the review of Government funded research carried out by COT in 2007 and the ongoing review of the peer-reviewed scientific literature on organophosphates. No clear conclusions could be reached from the reports reviewed at this meeting. One Member commented that a particular challenge in the epidemiological investigation of low-level exposure to organophosphates was the difficulty in ascertaining exposure to organophosphates specifically, rather than to pesticides in general, and in excluding confounding effects of other factors associated with farming.

1.61 The Committee discussed the extent to which these three research projects addressed the research recommendations made by the COT in 1999. The Committee concluded that the studies reviewed needed to be considered in the context of the review of Government funded research carried out by COT in 2007 and the ongoing review of the peer-reviewed scientific literature on organophosphates. No clear conclusions could be reached from the reports reviewed at this meeting. A particular challenge in the epidemiological investigation of low-level exposure to organophosphates was observed to be the difficulty in ascertaining exposure to organophosphates specifically, rather than to pesticides in general, and in excluding confounding effects of other factors associated with farming.

Research report 4: Prospective cohort study of sheep dip exposure and 'dipper's' flu'

1.62 In 2007, the COT saw an interim report of this research project. The final report of the project was now available, and the Committee was asked to consider the final report and advise on the significance of the results.

1.63 The study showed that sheep dipping as an activity was associated with subjective reporting of ill health effects. However, the study did not show an association of health effects with objective measures of exposure to organophosphates or pyrethroids. The pattern of health effects did not indicate dipper's flu as it had been previously described. It was surprising that there did not appear to have been an association between pyrethroid dip use and dermal paraesthesiae. The Committee agreed that re-analysis of the data to determine whether dermal paraesthesiae was associated with repeated pyrethroid use or pyrethroid metabolites in urine would be useful to explore a potential exposure-symptom link.

1.64 The Committee expected there to be considerable physical activity involved in sheep dipping which might explain effects such as musculoskeletal pain or fatigue in the following days; there was no control for this.

1.65 Farmers had used organophosphate dips, pyrethroid dips, pour-ons containing pyrethroids or other substances, and/or avermectin injections to treat sheep ectoparasites. Some farmers would have used a combination of products. The results were not broken down by type of application though this would be reflected by the type of active ingredient involved (organophosphates were not injected).

1.66 The COT considered the subject selection, observing that approximately 8700 people were approached to take part, one half did not respond, and ultimately 9.3% of those approached were interviewed. Not all of the interviewed farmers completed symptom diaries and only 5% completed the study. There might be an over-representation of farmers with ill health since they could be more motivated to take part. However, farmers were not included if they were not actively involved in sheep dipping between May 2005 and July 2006, so the study would miss farmers who had retired early due to ill health. Bias may have occurred as farmers who considered they had suffered 'dippers' flu in the past may have been more willing to take part in the study. The prevalence of previous dipper's flu in participants was observed to be more than 20%. Overall it was concluded that there were some difficulties in extrapolating the results to sheep farmers in general, but that the sample was probably a reasonable representation of the community overall.

1.67 Butyrylcholinesterase activity, used to assess exposure to organophosphates, decreased in some farmers following treatment of sheep, and increased in others. Since no farmer had a decrease of more than 20.8%, the Committee considered that the decreases could be consistent with normal variation and it was not possible to conclude that there was evidence of significant exposure to cholinesterase inhibiting agent(s). Changes in butyrylcholinesterase activity (at any level) are not considered to indicate an adverse effect in the absence of an effect on acetylcholinesterase activity measured in erythrocytes.

1.68 Other observations made by the Committee were that:

- Farmers with a certificate of competence for handling pesticides were less likely to report symptoms, which could indicate that other exposures were responsible for reported symptoms.

- The incidence of health effects was highest during the first two days following treatment, but was not associated with indices of organophosphate exposure.
- There was no association between health effects and endotoxin concentration in sheep dip at the end of dipping, but exposure to endotoxins might be more related to the activity of the farmer than the concentration of endotoxins in the dip.
- Only three farmers were reported to have temperatures above 38.2°C after dipping, and this was not related to indices of exposure.
- The presentation of confidence intervals rather than statistical significance would have aided interpretation of results, and there was multiple testing.
- Some of the adjustments made might not be appropriate – for example, having a history of dipper's flu might be an effect modifier rather than a confounder.
- The incidence of dipper's flu in the study varied greatly depending on how many symptoms were included.
- It would be useful to see if there were differences in clinical biochemical parameters between visits one and two.

1.69 The Committee wondered whether exposure to organophosphates from sheep dip use would have decreased since the 1990s and whether there was any evidence that reports of dipper's flu had decreased.

1.70 Approximately 30% of total immunoglobulin E (IgE) blood levels were outside the reference laboratory range on visit two (i.e. following treatment). It was not clear whether there had been any analysis of IgE prior to treatment. More than 30% of farmers reported having various allergies. The Committee wondered whether the time of year of treatment might be important. For example, dipping in the hay fever season might cause the increase in Ig E levels and not chemical exposure.

1.71 Overall, the COT concluded that the study did not provide evidence for acute toxic effects of organophosphates in sheep dippers, though the exposure was low. The negative results could be due to: a) exposure to organophosphates in sheep dippers now being lower than previously; b) limitation of adverse effects to a small number of susceptible individuals, who were not represented in this study; or c) illness described as dipper's flu not being a consequence of exposure to organophosphates. This particular study did not provide information on chronic effects.

1.72 With regard to research recommendation ii) from the Committee's 1999 report "Organophosphates" (how common is 'dipper's flu' and what causes

it?), the Committee agreed that the study provided information on the frequency symptoms of 'dippers flu' after sheep dipping, and indicated that they are not specific effects of organophosphate compounds. With regard to research recommendation iii), the study did not provide evidence of adverse effects due to low level exposure to organophosphate compounds, and did not identify a subset of susceptible individuals.

Pathway Analysis Software for the interpretation of complex datasets

1.73 At its April 2009 meeting whilst discussing the workshop on 21st century toxicology, the Committee noted:

In order to aid the interpretation of toxicological results obtained in vitro and in silico, such results will need to be incorporated into the physiologically-based pharmacokinetic models and pathway analysis strategies that underpin systems biology. It was noted that in vivo research in fields outside toxicology may provide good examples of practical applications. Correspondingly it was felt that a review of pathway analysis strategies could be useful.

1.74 In the past decade there has been an explosion of high-content and high-throughput data associated with a large number of disease states, chemical exposures and biological species. To fully interpret this information it has become necessary to develop a range of software tools that will identify the potentially biologically important patterns within a given set of data, and present it in a context that is both understandable to non specialists and searchable so that the data underlying the constructed networks can be viewed and assessed. To this end a number of analysis tools have been developed. The Committee were provided with an overview of the most commonly used software suites that are available for the interpretation of complex datasets.

1.75 The three major concepts (literature mining, over-representation analysis, and gene ontology) and the commonly used databases that are relied upon for network analysis were highlighted. There are two levels of analysis, namely, pathway identification and pathway visualisation, and the limitations of such analysis software were discussed.

1.76 The Committee agreed that analysis tools are useful for complex datasets, providing a plausible pathway for further identification, rather than an endpoint. The Committee noted that they needed to be aware of such approaches to analysing data because it would be likely that the

Committee would be reviewing increasingly more information from high throughput screening.

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)

1.77 Levels of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) were measured in the 2004 Total Diet Study and the Committee had previously been invited to assess the toxicity of these contaminants. It had published statements in 2006 which recommended TDIs of 3 and 0.3 µg/kg bw per day, respectively. At that time the Committee had stated that the TDIs should be reviewed if new information became available.

1.78 Recent publications by EFSA[c] in 2008 and the Office of Water of the US Environmental Protection Agency[d] in 2009 had proposed lower health-based guidance levels for PFOA and PFOS than those recommended by the COT. The US EPA had subsequently proposed limits for these substances in drinking water which were far lower than those used in the UK.

1.79 Members were asked to review their previous advice in the light of the new evaluations by the EFSA and the US EPA. The difference in the assessments was not in the toxicological endpoints used to derive the TDIs, but in the uncertainty factors applied and the reasoning behind them. The EFSA had used an additional factor of 2 to compensate for uncertainties relating to the internal dose kinetics, whereas the US EPA had developed data-derived extrapolation factors for toxicokinetics, concluding that measures of internal exposure should be used for interspecies extrapolation.

1.80 Regarding PFOA, Members were able to follow the reasoning of the EFSA approach, which they considered justifiable. The COT concluded that the US EPA approach was unsatisfactory because it made too many assumptions that were not supported by data and the uncertainty factor of 81 for interspecies toxicokinetics, as opposed to 4 and 8 applied by COT and EFSA respectively, was excessive. The Committee concluded that some additional allowance for interspecies toxicokinetic differences (such as that used by the EFSA) was appropriate. The COT therefore adopted the TDI derived by the EFSA for PFOA (1.5 µg/kg bw per day).

[c] http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902012410.htm.
[d] http://www.epa.gov/waterscience/criteria/drinking/pha-PFOA_PFOS.pdf.

1.81 Regarding PFOS, Members noted that similar concerns regarding the US EPA methodology applied to PFOS. They agreed there was no need to account for uncertainty due to the short duration of the critical study in primates because an extensive database in rodents supported the primate NOAEL. They concluded that the larger uncertainty factor used by the EFSA and the US EPA to allow for differences in interspecies toxicokinetics was not necessary. Members therefore re-confirmed their previous evaluation of PFOS and the TDI of 0.3 µg/kg bw per day.

1.82 An updated statement on the TDI for PFOA can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200902

Polychlorinated naphthalenes in Food

1.83 The Committee was asked for advice on possible risks associated with the levels of polychlorinated naphthalenes (PCNs) in foodstuffs that had been found in an FSA investigation.

1.84 PCNs are a group of 75 congeners, with structures similar to those of polychlorinated dibenzo-p-dioxins and -furans (PCDDs and PCDFs). The PCN congeners contain between one and eight chlorine atoms bound to the naphthalene structure.

1.85 PCNs were formerly manufactured extensively, and they possess high chemical and thermal stability, good weather resistance, good electrical insulating properties and low flammability properties. Their usage is now banned in most countries, including the UK. PCNs can also be produced as combustion products during waste incineration and may also be released when products containing PCNs are disposed of to landfill.

1.86 PCNs have been detected in fish and human milk in other countries. The FSA investigation was carried out as there were currently no UK data on PCNs in food.

1.87 The COT concluded that because some PCNs exhibit dioxin-like activity, protection of public health requires a cumulative approach to risk assessment for this aspect of their toxicity. The currently available data were inadequate to establish TEFs for PCNs, but in the absence of other data, relative potencies compared to TCDD from in vitro studies could be used as a highly conservative approach to indicate if dioxin-like activity of PCNs in food presents a risk to the consumer. It was considered unlikely

that all the toxic effects of PCNs occur through interactions similar to those of dioxins, but the available studies on PCNs were not considered sufficient to permit a full hazard characterisation. Although the data were insufficient for a robust risk assessment, the results of the FSA investigation did not suggest specific toxicological concerns.

1.88 The COT statement can be found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200905

Toxicological aspects of the SACN report on Iron

Introduction

1.89 In their 1998 report, *Nutritional Aspects of the Development of Cancer*, the Committee on Medical Aspects of Food Policy (COMA) highlighted the possible links between red and processed meat and colorectal cancer and recommended that "*higher consumers should consider a reduction*" in consumption. However, it was also noted that as this could compromise iron status, the possible adverse implications of this advice should be the subject of review. To assess this, the Scientific Advisory Committee on Nutrition (SACN), the expert committee succeeding COMA, established a working group to consider iron and health. In their review, the SACN Working Group considered both the beneficial and adverse effects of increased and decreased iron intakes.

1.90 The draft report of the SACN working group was published for consultation in June 2009 and the COT was asked to comment on the sections of the report that considered the possible adverse effects of excess iron and, in particular, the potential adverse effects on iron supplementation on growth in iron-replete children and on the incidence and morbidity of infectious disease.

Negative effects on the growth of iron replete infants

1.91 Several studies are available that suggest iron supplementation could reduce weight and length gain in iron-replete infants (Idjradinata *et al*, 1994; Dewey *et al*, 2002: Majumdar *et al*, 2003; Lind *et al*, 2008) compared to placebo, although this effects was not reported in a small study by Ziegler *et al* (2009). The COT agreed with the draft SACN conclusion that *"Limited evidence suggests that iron supplementation may have detrimental effects on the physical growth of iron replete infants and children*" but noted that it was uncertain whether the effect would occur in older children, since the children in the studies were aged between 4 and

24 months. It was also recognised that the doses of iron used in the supplementation studies were significantly higher than both iron intakes from food and the Reference Nutrient Intake for iron. It was agreed that any advice would need careful targeting, so that children who needed iron supplementation for medical reasons, would not be deterred from taking them.

Effect of iron supplementation on infectious disease incidence and morbidity

1.92 The COT considered the section of the draft report discussing the effects of excess iron on the incidence and morbidity of infectious disease and the draft conclusion that "*On balance, there is no evidence to suggest that improving iron status in the UK would have any impact on infectious disease incidence or morbidity. Some evidence suggests that iron supplementation to improve iron status may have adverse effects in some subgroups of the population, e.g. those with HIV and children at risk of diarrhoea*". The COT agreed with this conclusion and added that there were a number of studies suggesting that occupational inhalation of metal fumes was associated with an increase in respiratory disease such as lobar pneumonia which might be of relevance to this section of the report. The Committee noted that the effect of iron on emerging diseases such as H1N1 influenza should also be considered.

Other aspects of high iron intake considered in the draft report

1.93 Members had no comments on other effects associated with iron excess and did not wish to consider any topic in more detail. It was noted that the COC would be providing comments with respect to the associations between iron and red meat intake and carcinogenicity.

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Vitamin E in pregnancy

Introduction

1.94 Vitamin E is a generic description of a group of eight lipid soluble chemicals which prevent lipid oxidation and maintain membrane integrity throughout the body. As a result of vitamin E's anti-oxidant function, it has been investigated for potential beneficial effects in women at risk of pre-eclampsia.

1.95 In a large randomised placebo-controlled trial by Poston *et al.* (2006) women were given 1000 mg vitamin C and 400 IU vitamin E or placebo. More low birth weight babies were born to women in the treatment group (28%) compared to the controls (24%). The mean birth weights of the babies in the treatment and placebo groups were 2901 and 2967 g respectively. Additionally, in a small prospective observational study by Boskovic *et al* (2005) it was suggested that birth weights were significantly reduced (3173 $\pm$ 467 g) in the babies of women who had taken more that 400 IU vitamin E per day during pregnancy, compared to the babies of women in the control group (3417 $\pm$ 56 g). The authors themselves noted that the finding could be due to chance.

1.96 As part of their horizon scanning exercise, the COT considered whether the papers raised concerns about the potential effects of vitamin E in pregnancy, and whether there was sufficient information available to make a full review of vitamin E in pregnancy worthwhile. The Committee initially considered the study by Poston *et al* (2006) noting that, although this was a large and randomised trial, the different characteristics of the two groups, as described in the paper, indicated that the association could be due to chance. They concluded that the finding was of interest but did not indicate significant concern. Members then considered that the investigation by Boskovic *et al* (2005) noting that this was a small study

with a strong potential for selection bias and the results could be due to chance. It was considered that there was no likely or plausible mechanism for the reported effect at the doses of vitamin E present in supplements. There were few animal studies investigating the effects of vitamin E alone but, where these were available, there was no indication of any adverse effects. It was noted that both the UK Expert Group on Vitamins and Minerals and the EU Scientific Committee on Food had undertaken full reviews of vitamin E to establish safe upper levels and had not identified any concerns.

Additional information

1.97 Although COT members considered that the two studies did not indicate significant concern they requested additional information on a number of areas: whether there were any intervention studies currently in progress; the status of any relevant Cochrane reviews; details of the relevant animal data as considered by EVM and SCF; and, effects associated with vitamin C. This was provided at a subsequent meeting.

1.98 There were three relevant Cochrane systematic reviews: vitamin E supplementation in pregnancy (Rumbold and Crowther, 2005a), anti-oxidants for preventing pre-eclampsia (Rumbold and Crowther, 2008) and vitamin C supplementation in pregnancy (Rumbold and Crowther, 2005b). No evidence of any effects on birth weights was noted in the reviews but the number of studies considered was very small. In addition to the Poston *et al* (2006) study, two additional studies were considered in the Cochrane reviews, these reported that anti-oxidant treatment (1g vitamin C and 400 IU E) was associated with a non-significant decrease (Beazley *et al*, 2005) and a non-significant increase (Rumbold *et al,* 2006) in birth weights respectively. As most of the studies were examining the effects of anti-oxidants on pre-eclampsia, the anti-oxidant treatment was given late in pregnancy, usually in the second trimester, making it difficult to draw conclusions.

1.99 It was noted that there were several large intervention studies of the effects of anti-oxidants in pregnancy currently in progress, but it was unclear when any publications were expected.

1.100 The COT agreed that the available animal data, while limited, did not suggest any concerns with regard to vitamin E since doses up to 1500 mg/kg bw had not resulted in any adverse effects. There were also no data suggesting that vitamin C was associated with adverse reproductive effects.

Conclusion

1.101 Overall, COT members agreed that a full review of vitamin E in pregnancy was not necessary at the current time, but that it should remain under review.

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Committee procedures

Horizon Scanning

1.102 At the February 2009 meeting, members were provided with information on planned and possible discussion items for the year, and invited to comment on emerging issues that might also need to be addressed.

1.103 A Member alerted the Committee to the use of over-the-counter antacids by pregnant mothers and evidence of increased asthma in their children. This was agreed by another Member who noted that there were some animal data confirming this association.

1.104 Members also discussed the balance of expertise on the Committee and agreed that ‘dietary exposure assessment’ and ‘systems biology’ should be added to the list of specialist expertise required by the Committee.

Working Groups and Workshops

Lowermoor Subgroup

1.105 Members were previously informed that the deaths of two individuals who had lived in the area which received contaminated water following the 1988 Lowermoor Water Pollution Incident had been referred to the West Somerset coroner. The two individuals both had a neurodegenerative disease and had been reported to have higher than usual levels of aluminium in the brain. Information on brain neuropathology and aluminium concentrations was available for one of the individuals but not the other.

1.106 The COT was informed that Department of Health lawyers had advised that publication of the Subgroup's report before the Coroner's proceedings were completed could be seen as an attempt to bias the jury and this had led to a delay in publication. The inquest had been postponed to November 2010 and therefore the final Subgroup report will not be published until 2011.

Workshop on 21st Century Toxicology

1.107 In February 2009 the Committee held a one-day workshop on 21st Century toxicology where invited experts gave presentations on recent advances in toxicology. Insights into uses for toxicogenomics, computational toxicology, metabonomics and batteries of high-throughput screens were described with an emphasis on moving towards obtaining greater mechanistic understanding.

1.108 Such understanding informs risk assessment and can provide a basis for developing predictive toxicology. Members participated in discussions along with other delegates at the meeting and subsequently while producing a statement containing the speakers' abstracts and summarised discussions.

1.109 The COT statement can found at: http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2009/cot200903

Ongoing work

Chemical exposure resulting from landfill sites

1.110 In 2001, the Committee published a statement on a major study of health outcomes in populations living around landfill site. The Committee was largely reassured by the findings but considered that the small raised risk for all congenital anomalies for people living around special waste landfill sites merited further investigation. At the time, the Committee was informed that a programme of research and reviews was underway on congenital anomalies and landfill sites. This included a project to measure emissions of chemicals, common air pollutants and biohazards from landfill sites, and further epidemiological studies by the Small Area Health Statistics Unit (SAHSU).

1.111 The Committee reviewed the results of these studies from 2007 to 2009. A statement is under preparation and will be published in 2010.

Idiopathic Environmental Intolerance: Evidence for a toxicological mechanism

1.112 In their conclusions on the Royal Commission on Environmental Pollution (RCEP) report on crop spraying and health of residents and bystanders, the Committee had recommended that a further review of Idiopathic Environmental Intolerance (IEI, also described as Multiple Chemical Sensitivity) be undertaken.

1.113 The COT have considered a draft discussion paper on the evidence for toxicological mechanisms for IEI. The COT requested further consideration of psychological aspects of IEI in consultation with experts in psychology. Further discussions will take place during 2010 after which a statement will be drafted.

Para-occupational exposure to pesticides and health outcomes

1.114 In September 2009 the COT considered a review of para-occupational exposure to pesticides and health effects in people in a para-occupational setting. An example of para-occupational exposure to pesticide is someone who co-habits with a farm employee, who has the potential to experience greater exposures to pesticides than a neighbour who does not. The COT will complete its evaluation after the COC has provided its opinion on the studies relating to cancer.

Waste and Resources Action Programme (WRAP)

1.115 Waste And Resources Action Programme (WRAP) Confidence in Compost Programme's had produced three peer-reviewed risk assessments looking at biological and chemical risks associated with the use of composts from different source segregated feedstocks across a range of agricultural sectors. The FSA intends to seek advice on the microbiological aspects from the Advisory Committee on the Microbiological Safety of Food (ACMSF) and on chemical aspects from COT early in 2010. The COT discussed an initial paper on the background to the work, its context and the methodology used for the assessment of risks.

2009 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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Declaration of COT members' interests during the period of this report
(an up-to-date version can be found on the COT website)

MEMBER	Personal Interest		Non Personal Interest	
	COMPANY	**INTEREST**	**COMPANY**	**INTEREST**
Professor D Coggon	Halifax Standard Life	Shareholder	Colt Foundation British Occupational Health Research Foundation Faculty of Occupational Medicine Public Health Commission	Trustee Trustee President and Trustee Member
Dr D Bell	Alliance & Leicester BAA BG Centrica HBOS Plc International Power National Grid RT Group Rolls Royce Scottish Power Thus Transco United Utilities University of Nottingham	Shareholder Employee	Food Standards Agency Central Science Laboratory Dow Aptuit Inc EFSA CEF Panel British Toxicology Society	Research Contract Part funded PhD studentship Research Grant Consultancy Member (with renumeration) Member of executive committee

Professor A Boobis OBE	Banco Santander SA Barclays BG Group BT Group Centrica Plc HBOS Iberdrola SA National Grid Scottish Power Thus Astellas Pharma Sumitomo Chemical (UK) Plc Proctor & Gamble Howrey LLP	Shareholder Consultancy	GlaxoSmithKline Food Standards Agency Department of Health Commission of the EU (FP6) ESRC ILSI HESI Elsevier JMPR JECFA (vet drugs) EFSA PPR Panel (Panel on Plant Protection Products and their Residues) ECETOC Task Force on Guidance for Classification of Carcinogens under GHS EFSA Scientific Committee Working Group on Risk-Benefit Assessment EFSA Scientific Committee Working Group on the Benchmark Dose	Support by Industry Research Contract PhD Studentship Unpaid chair of Board of Trustees Editor-in-Chief; Food and Chemical Toxicology Member
Dr R Dearman	Syngenta CTL AstraZeneca Research Institute for Fragrance Materials, (RIFM) European Chemical Plasticizers Industry (ECPI)	Shareholder Consultancy Consultancy	Unilever Syngenta European Chemical Plasticizers Industry (ECPI) American Chemical Council (ECPI) BASF RIFM	Research Grant Research Grant Research Grant Research Grant Research Grant Research Grant
Professor C de Vries	NONE	NONE	Schering AG Yamanouchi	Research Grant

Dr C Elcombe	CXR Biosciences Ltd	Salaried Director Shareholder	Various Pharmaceutical and chemical companies	Contract Research at CXR
Dr J Foster	AstraZeneca	Shareholder	NONE	NONE
Dr A Hansell	Dept of Epidemiology & Public Health Imperial College London (includes Small Area Health Statistics Unit) Greenpeace Halifax	Employee Supporter (non-active) Shareholder	GlaxoSmithKline AstraZeneca	Research Grant Research Grant
Professor D Harrison	The Forensic Institute, University of Edinburgh Lothian NHS Response Genetics University of Florida University of Canberra	Shareholder Consultant (no fee payable) Consultant Consultant	EMMS Nazareth Melville Trust Medical Research Scotland Alma Diagnostics Yorkshire Cancer Research DoH GTAC HPA Committee on Carcingenicity CRUK Science Strategy Advisory Group Biomedical & Therapeutics Res Comm. (Scotland)	Trustee Trustee Trustee Research Collaboration Scientific advisory committee Vice chair Member Member Member
Dr J Hinson (to 31st March 2009)	GlaxoSmithKline	Shareholder	Society for Endocrinology Journal of Endocrinology Current Opinions in Endocrinology and Diabetes	Council member and Education Advisor Member of the editorial board

Dr P Jackson (to 11th February 2009)	Carillion Computacenter Ecofin Friends Provident Hochschild Mining Plc Informa Legal General Mapeley Melrose Senior St Ives St James Place Capital TT Electronics Venture Production	Shareholder	Bayer	Departmental Research Funding
Professor J Konje				
Professor B Lake (from 1st April 2009)	LFI/BIBRA	Consultancy	British Toxicology Society Society of Toxicology	Member Member
Dr G McNeill	Smith & Nephew Diageo Café Direct BHP Billiton	Shareholder	World Cancer Research Fund	Grant panel member
Professor I Morris	Takada Pharmaceuticals Society for Endocrinology Society for Medicines Research Society for study of fertility British Society for Toxicology	Consultancy Membership		Son is a student fellow of British Heart Foundation
Dr N Plant	NONE	NONE	Xenobiotica British Toxicology Society Pfizer GlaxoSmithKline AstraZeneca	Associate Editor Member of Education sub-committee Research Funding

Dr D Ray	University of Nottingham ZLB Behring (Switzerland) Astellas pharmaceuticals CEFIC ESAP	Employee Consultancy Consultancy Independent advisor		
Dr D Tuthill	Cardiff & Vale NHS Trust SMA Nutricia Milupa	Salary Consultancy	Royal College of Paediatrics and Child Health Welsh Paediatric Society British Society of Paediatric Gastroenterology, Hepatology and Nutrition Paediatric Research Society British Association of Parenteral and Enteral Nutrition Nutrition Society British Society of Clinical Allergy and Immunology	Fellowship
Miss A Ward	NONE	NONE	Farm Animal Welfare Council	Member
Mrs A Williams	NONE	NONE	NONE	NONE

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 independent authoritative advice on potential mutagenic hazards and risks is required. Frequently recommendations for further studies are made.

During 2009, the Committee provided advice on a wide range of topics including genotoxicity of fumagillin, parachloroaniline and tobacco products. The COM finalised its statement on the mutagenicity of acrylamide.

The Committee undertook a review of thresholds for *in vivo* mutagens and reviewed recent data on the utility of the GADD45a GFP genotoxicity assay and the mouse lymphoma assay. A review of recent publications on the use of toxicogenomics in genotoxicology was undertaken.

We have also begun the process of reorganising the presentation of COM advice on the internet to produce guidance documents which can be updated when required in addition to formal statements on the mutagenicity of chemicals. This will be an important area of work for 2010.

Professor P B Farmer Chair
MA DPhil CChem FRSC

COM evaluations

Acrylamide

Background

2.1 Acrylamide is a small, simple molecule (Figure 1). It is an α,β-unsaturated carbonyl with electrophilic reactivity. This means it can react with nucleophilic groups (amines, carboxylates, sulphydryls etc) on biological molecules, such as proteins or DNA. *In vivo*, acrylamide may be metabolised to the reactive epoxide glycidamide, which is thought to have a role in acrylamide related toxicity.

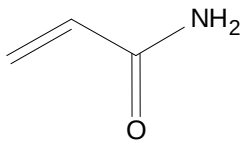

Figure 1: Acrylamide

2.2 In January 2007, the Health and Safefty Executive (HSE) requested that the Committee on Mutagenicity (COM) provide an opinion on the evidence regarding germ cell mutagenicity of acrylamide and the evidence regarding a threshold for germ cell mutagenicity with this chemical. The Committee was provided with a copy of the EU Risk Assessment Report and a submission from the Polyelectrolyte Producers Group (PPG), discussing the evidence regarding germ cell mutagenicity of acrylamide and the evidence for a threshold for germ cell mutagenicity with this chemical. A response was published in February 2007 (COM/07/S2) http://www.iacom.org.uk/statements/Acrylamide.htm. The COM was made aware of a response from the Polyelectrolyte Producers Group (PPG) to the chair (dated 8 May 2007) at the COM meeting of the 17 May 2007 http://www.iacom.org.uk/papers/documents/mut0716.pdf and agreed to a further evaluation of the genotoxicity data on acrylamide at the request of HSE. In view of the widespread dietary exposure to acrylamide, the Food Standards Agency requested that such a review should consider all available genotoxicity data on acrylamide.

2.3 The COM agreed that the EU risk assessment review completed by HSE (EU Risk Assessment report 2002) could be used as a basis for the review, and for this to be extended with a systematic review of the scientific literature available subsequent to 1995.

2.4 The Secretariat drafted an overview of the EU Risk Assessment of acrylamide and outlined a strategy for the review. The search strategy was devised in

order to identify all relevant studies that had not been cited in the EU Risk Assessment Report, and the last update to the search was performed on the 23rd September 2008. Details of this search strategy can be found in Annex A to the COM statement which is reproduced at the end of this annual report. Members reviewed the findings of the EU Risk Assessment Report and were content with the search strategy used for the COM review. Members were presented with a systematic review of data relating to the genotoxicity of acrylamide and glycidamide published after 1995, and other pre 1995 references that had not been included in the EU risk assessment report. This paper also provided an initial discussion of the acrylamide genotoxicity data, and this was extended to include the metabolite glycidamide.

2.5 The PPG were invited to give presentations at the October 2007 and February 2008 meetings and have submitted data and supporting references for Members to consider at several points during the review (as noted in relevant minutes and discussion papers). The PPG met with the Secretariat prior to each meeting in order to explain the Committee's procedures and to provide advice on the structure and content of the submissions, highlighting areas where more detail would be valuable to the Committee's deliberations. The PPG submitted comments on the second draft Working Paper and a relevant abstract from a recent scientific meeting (McDaniel *et al.,* 2008 Poster presentation at the 39th Annual Environmental Mutagen Society Meeting 2008, October 18-22). Both were tabled at the October 2008 meeting.

2.6 In January 2009, PPG submitted comments of the fourth draft working paper. They noted the absence of discussion of the *in vivo* potency of acrylamide, the relative contribution of putative mutagenic pathways, and the contribution of DNA repair. They also commented on the COM interpretation of the dose-response for micronuclei induction and the biological plausibility of applying linear or threshold models to the data; and suggested that the genotoxic risk be put in the context of human exposure with mention of a practical threshold in the conclusions. The COM noted PPG's proposals for a number of changes to the working paper and agreed to include a number of these proposals with some amendments.

COM conclusions

2.7 The EU risk assessment report concluded that acrylamide is an *in vitro* mutagen, and *in vivo* somatic cell and germ cell mutagen. The predominant effect was clastogenicity with some evidence for aneugenicity. The published evidence available since 1995 extends the effects of acrylamide to include identifiable glycidamide DNA adducts and gene mutations, detectable in cultured mammalian cells and somatic cells *in vivo,* and with mutation spectra which are consistent with those adducts. An element of the mutagenic effect

of acrylamide, therefore, appears to be due to the formation of DNA adducts following metabolism to glycidamide.

(a) Assessment of the genotoxic potential of acrylamide is complicated by multiple potential mechanisms, which include extensive protein binding / enzyme inhibition, oxidative stress and DNA adduct formation. It is plausible that each of these mechanisms may contribute to the genotoxicity of acrylamide. These mechanisms are not mutually exclusive.

(b) Acrylamide is an *in vivo* mutagen. In experiments reviewed in this statement, genotoxic effects are generally only seen at relatively high acute doses (ca 50 mg/kg bw i.p. in mice). However genotoxic effects are also reported at much lower dose levels in repeat dose studies (ca 4 mg/kg bw, i.p.for 28 days in mice).

(c) The default assumption is that there is no level of exposure to this genotoxic carcinogen that is without some risk. In order to move away from this assumption, it will be necessary to identify evidence of a threshold with supporting mechanistic data for all of the potential genotoxic mechanisms of acrylamide in somatic cells and germ cells. Based on the currently available evidence, it should be considered that there is no level of exposure to acrylamide that is without some risk, although we acknowledge that the genotoxic effects of exposure to very low levels of acrylamide are likely to be pragmatically indistinguishable from background.

2.8 The COM agreed a statement can be found at: http://www.iacom.org.uk/statements/documents/COM09S1Acrylamide.pdf

Fumagillin

Background

2.9 Fumagillin dicyclohexylamine (fumagillin DCHA) is an antibiotic veterinary medicine authorised for use in honey bees for the prevention of infections caused by the *Nosema apis* parasite present in the gut of infected bees (Figure 2). Fumagillin DCHA is fed to the colony in winter over a period of several weeks in a medicated syrup as a supplementary food source to eradicate the parasites. The commercial formulation of fumagillin DCHA is a stabilised water-soluble preparation, Fumidil-B (CEVA Animal Health). Fumidil-B contains the excipient polysorbate 80, sodium phosphate (anhydrous) and sodium acid phosphate (anhydrous).

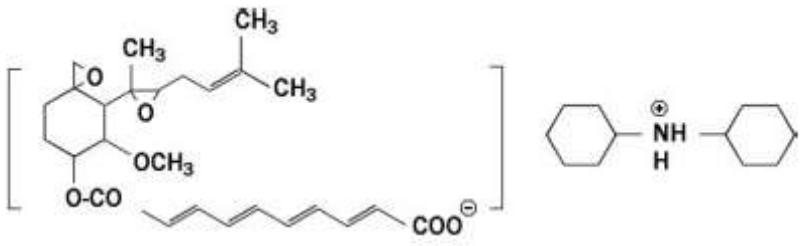

Figure 2. Structure of Fumagillin DCHA Salt

2.10 Fumagillin DCHA at the time of the COM evaluation during 2009 did not have a maximum residue level (MRL) status because the Committee on Veterinary Medicinal Products (CVMP) were unable to make a recommendation when the substance was evaluated in 1999. The main reasons given were that no ADI could be established because no overall NOEL was identified for repeated dose toxicity, reproductive toxicity or teratogenicity/fetotoxicity and no conclusions could be reached on the genotoxicity or carcinogenic potential of fumagillin. The veterinary medicine Marketing Authorisation Holder (MAH), CEVA Animal Health, indicated that they might make another MRL application to address the absence of the MRL. The MAH sought scientific advice from the CVMP and, in October 2006, the MAH stated that a 90-day repeated dose toxicity study was ongoing and that five mutagenicity tests had been performed. Reproductive toxicity studies have not been conducted. The COM was made aware of reports of genotoxic effects of fumagillin DCHA in cytogenetic tests both *in vitro* and *in vivo* published by the Stanimirovic group (see reference list at the end of the COM statement on Fumagillin at the end of this annual report). These reports were reviewed by VMD who recommended that an independent opinion should be sought on interpretation of the results, to establish if there is a potential risk to consumer safety. Subsequently, the MAH provided VMD with reports of six additional genotoxicity studies conducted between 2004 and 2007, together with an expert report on the genotoxic potential of fumagillin and a critique of the genotoxicity studies submitted by the MAH.

2.11 The COM was asked by the VMD for an opinion on the genotoxicity of fumagillin DCHA and in particular the interpretation of the published studies undertaken by the Stanimirovic group. The COM has not been asked in this review to advise on consumer risk assessment of consumption of fumagillin, fumagillin DCHA, or its breakdown products as potential contaminates of honey.

COM conclusions

2.12 The COM agreed that the Stanimirovic data were limited and no definite conclusions could be reached. There were several possible explanations for

the differences between the results obtained for *in vivo* genotoxicity studies undertaken the Stanimirovic group and the MAH. These included possible differences in absorption, metabolism of the administered test material, differences in stability of the test materials including storage, and different impurity profiles between test materials used by the research groups. The COM agreed that the genotoxicity data on fumagillin acid and dicyclohexylamine tested separately did not provide sufficient information to draw conclusions on the role of these substances in the potential mutagenicity of fumagillin DCHA. The COM agreed that a repeat of the Stanimirovic study in mice (using the same test protocol) with test material sourced by the MAH should be undertaken with appropriate measures of systemic absorption. The COM considered that a second *in vivo* tissue evaluation should be undertaken and suggested a site of contact comet formation in the gastrointestinal tract (with an appropriate positive control substance). Negative data from appropriately conducted tests (according to the Stanimirovic protocol) using two tissues in mice would be sufficient to refute Stanimirovic data. Equivocal or positive data from such tests would confirm that fumagillin DCHA should be considered an *in vivo* mutagen. The Committee also commented if any genotoxicity was observed with fumagillin DCHA, more genotoxicity data (*in vitro* chromosomal aberration test in human lymphocytes) should be provided on dicyclohexylamine to evaluate its potential role. (Any study should also include fumagillin DCHA for quantitative comparison). The COM considered that the differences in statistical reporting in the Stanimirovic group publications as highlighted by the MAH were not necessarily founded. Members agreed that further additional data on the influence of light/dark conditions on the genotoxicity of fumagillin DCHA were not necessary. Members agreed that the data on potential fungicidal mode of action submitted were not relevant to the potential genotoxicity mode of action of fumagillin DCHA.

2.13 The COM recommended the following testing strategy for fumagillin DCHA.

(a) A further *in-vivo* mutagenicity study using the same protocol used by Stanimirovic et al. (*Mutat Res* (2007) 628, 1-10.) to include sampling of bone marrow for MN and chromosomal aberrations.

(b) A site of contact comet assay using gastrointestinal (stomach) tissue. (The comet assay should also include an appropriate positive control substance).

(c) If any genotoxicity is observed with fumagillin DCHA, more genotoxicity data (*in vitro* chromosomal aberration test in human lymphocytes) should be provided on dicyclohexylamine to evaluate its potential role. (Any study should also include fumagillin DCHA for quantitative comparison).

2.14 The COM agreed a statement can be found at: http://www.iacom.org.uk/statements/documents/COM09S2FumagillinforVMD2.pdf

Parachloroaniline

Background

2.15 Parachloroaniline ((4- chloroaniline, 4-CA). see figure 3 below) is a potential human metabolite of the pesticide diflubenzuron. There is experimental evidence for urinary excretion of 4-CA in swine exposed to diflubenzuron, and for its presence as a metabolite in goats (liver) and in hens (liver and kidney). The Advisory Committee on Pesticides (ACP) asked the COM for a view on the available genotoxicity data on para-chloroaniline

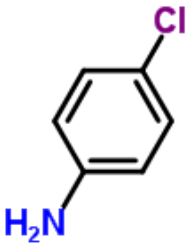

Figure 3 Parachloroaniline.

2.16 The Committee was aware that NTP (U.S. National Toxicology Program) bioassays for potential carcinogenicity have been undertaken in rats and mice. There was clear evidence of carcinogenicity in male rats (splenic sarcoma and osteosarcoma associated with fibrosis of the spleen, and phaeochromocytoma of the adrenal gland). There was equivocal evidence for tumours of the spleen in female rats. There was some evidence for liver tumours in male mice and no evidence for carcinogenicity in female mice. It is notable that increased haemangiosarcomas were seen in both rats and mice (in spleen and/or liver).

COM conclusions

2.17 The COM reached a number of conclusions;

(a) The COM concluded that 4-CA was an *in vitro* mutagen.
(b) No definite conclusions on the *in vivo* mutagenicity could be drawn on the information reviewed.
(c) A further *in vivo* genotoxicity testing strategy was agreed. This comprised two studies. Study ii) should be undertaken if the results of Study i) were negative or equivocal.

Study i) a repeat MN test in mice conducted to internationally acceptable standards to include sampling of the bone marrow and peripheral blood for reticulocytes

Study ii) The second study should be a rat liver UDS assay with a concurrent rat comet assay to investigate DNA damage in the spleen, liver and other tissue (not considered to be a rat tumour target organ).

2.18 The COM agreed a statement which can be found at: http://www.iacom.org.uk/statements/documents/ParachloroanilineforcomintersitetDec09.pdf

Tobacco products

2.19 The Department of Health (DH) had specifically requested an update of the 2004 joint COM/COC/COT statement. Dossiers on the toxicological testing of tobacco product ingredients in their burnt and unburnt forms are submitted to DH. As there are no internationally agreed approaches to the hazard assessment of these products, scientific advice was sought from the COM on the suitability of mutagenicity tests for the evaluation of these products. Another reason for the DH request was that there are a number of new products purporting to reduce harm to users (i.e. by reducing exposure to harmful chemicals), for which the Department had no means of evaluating toxicity. New tobacco products that potentially reduce exposure to harmful chemicals, such as electrically heated tobacco products, are known as PREPS. There was a contention that existing tests do not give sufficient information to draw meaningful conclusions.

2.20 The Committee considered a draft discussion paper on the genotoxicity of tobacco products. This was provided in conjunction with a short discussion paper on the regulatory aspects relating to the toxicity testing of tobacco products and a scoping paper on the toxicology of tobacco products. The documents provided to COM followed-up the 2004 joint COM/COC/COT statement on the toxicological testing of tobacco products. Members were also provided with a copy of a letter to the Secretariat from British American Tobacco (BAT), outlining their approach to the toxicology of tobacco products and an additional paper on whole smoke exposure of human pulmonary carcinoma cells. Members also had access to a submission from Philip Morris. Additionally, members were provided with an email from an independent expert on smoking behaviour on compensatory smoking. The overall objective was to produce an update statement from COM/COC/COT.

2.21 As an initial comment, members agreed with the statements abstracted from WHO Technical Series Report 945 that the rate limiting steps in the

mechanistic pathways leading to tobacco product induced disease were not understood and hence this limited the value which could be attributed to the available data on biomarkers. The available data on biomarkers of mutagenicity would inform on overall exposure to mutagens. Members commented that the available test strategies for evaluation of mutagenicity of tobacco products had been largely dependent on the practicality of deriving cigarette smoke condensate (CSC) or total particulate matter (TPM) which could be easily obtained, stored frozen and transported between laboratories and the observation that there was a correlation between potency in skin painting bioassays of tumourigenicity in mice and potency in *Salmonella typhimurium* mutagenicity tests.

2.22 COM members encouraged the development of whole smoke exposure procedures which were likely to provide more relevant data on mutagenic activity of tobacco smoke, but noted none of the test systems had been adequately validated and there was no agreement on what reference material would be used for comparative purposes.

2.23 The COM made a number of comments on the draft discussion paper on the genotoxicity of tobacco products.

Validity of genotoxicity tests

2.24 Members reaffirmed that any ranking of mutagenicity of tobacco products could not be extrapolated to *in vivo* exposure to chemicals in tobacco smoke. Thus tobacco smoke was a multi-site carcinogen in humans and it was not possible to evaluate which exposures were relevant for each of the fifteen different target organ cancers induced by tobacco smoke. Members commented that data on appropriate reference materials were needed for comparative data on whole smoke methods currently under development, and that the smoking regimes used did not necessarily reflect human exposure to tobacco smoke. It was also noted that mutagenic effects *in vivo* would also be influenced by target organ inflammation.

2.25 Members noted that potency rankings were also dependent on the smoking regime used. Members commented that there were advantages to reporting mutagenicity data on a per cigarette basis and on a per mg nicotine basis. The former gave an easy measure on mutagenic potency per unit consumed whereas reporting data in terms of mutagenicity/mg nicotine more closely reflected the behaviour of smokers who adjusted cigarette consumption to maintain nicotine exposure. The COM agreed that there was a need for international harmonisation to reach a consensus on mutagenicity test procedures, use of reference materials, and cigarette smoke generation regimes.

Potential effects of ingredients, additives and flavours

2.26 Members felt that the mutagenicity evaluation of ingredients, additives and flavours by adding test materials to tobacco products pyrolysing and then testing CSC in *in vitro* mutagenicity tests with *Salmonella typhimurium* would not provide any useful information on the mutagenic properties of the pyrolysed ingredients, additives and flavours.

Biomarkers of effect

2.27 Members agreed that biomonitoring of urinary mutagenicity using *Salmonella typhimurium* TA98 and TA 100 in the presence of exogenous metabolic activation using rat liver S-9 from Aroclor 1254 treated rats might inform on potential risks of bladder carcinogenesis but not for other tobacco related cancer target organs. Thus urinary mutagenicity was essentially a biomarker of exposure to absorbed mutagens that were sensitive to the mutagenicity testing regime used. Members noted the standard deviation for urinary mutagenicity in the paper submitted (Mendes P et al *Regulatory Toxicology and Pharmacology*, 51, 295-305, 2008) suggested there were large inter individual differences in absorbed mutagens. There was discussion relating to the possibility of developing biomarkers for potential inflammation induced by tobacco smoke.

Available information on PREPS

2.28 The available data on mutagenicity suggested significant reductions in both *in vitro* mutagenic activity in *Salmonella typhimurium* TA98 and TA 100 in the presence of exogenous metabolic activation using rat liver S-9 from Aroclor 1254 treated rats and urinary mutagenicity in biomonitoring studies using a number of acceptable study designs. These data indicated that mutagenicity was not reduced to background levels. The data were consistent with a substantial reduction in exposure to mutagenic effects of aromatic amines in tobacco smoke. Overall the COM agreed the data supported the approaches used to reduce exposure to mutagens, notwithstanding the primary advice not to smoke tobacco products, but cautioned that the association between chemical mixtures present in tobacco smoke and disease outcomes was very complex and no conclusions regarding risk of mutagenicity could be reached from the available data.

Horizon Scanning

2.29 The horizon scanning exercise provides information which can be used by Government Departments/Regulatory Agencies to identify important areas for future work. Regarding progress on topics raised in the 2008 horizon scanning exercise, members were informed that a large amount of committee time had been spent undertaking reviews of aclonifen, fumagillin and tobacco products. Progress had been made on thresholds (and a draft guidance document on the risk assessment of *in vivo* mutagens), toxicogenomics and a draft outline proposal for a testing strategy. No progress had been made on mutational finger prints or mitochondrial mutagenicity.

2.30 The committee agreed that the main priority for COM work in 2010 would be to consider a revision of the mutagenicity testing strategy. Members agreed that a review of the mutagenicity of nanomaterials would be important and that the consideration of mutational spectra to investigate the role of chemicals in mutagenicity and carcinogenesis could be useful. Regarding mutagenicity testing, the COM made some suggestions, which included consideration of the PIG A assay, the potential integration of genotoxicity tests into standard toxicity studies; measures for cytotoxicity in genotoxicity tests; top doses; reliability of cell types; and the use of oncogene/tumour suppressor gene arrays. Members also suggested epigenetics as a potentially important topic.

2.31 The Committee agreed that the highest priority should be to review COM guidance on testing strategy and undertake a specific review of nanomaterial genotoxicity testing. One member noted that his group had recently published a review of nanomaterial genotoxicity and this would be a useful starting point for any review.

Test Strategies and Evaluation

Mouse Lymphoma (MUT/09/10)

2.32 The committee was provided with a paper (Wang J et al., Toxicological Sciences 2009, 109 (1), 96-105) which reported data on detailed genetic alterations in L5178Y $TK^{+/-}$ mutants with either small or large colony growth characteristics from studies investigating the mutagenicity of 3'- azido-3-deoxythymidine (AZT), mitomycin C (clastogens) and taxol (aneugen). Colonies that exhibited significant loss of heterozygosity in chromosome 11 were selected for further investigation. The increased mutation frequency in studies ensured that a high proportion of the mutants selected were due to chemical treatment. TK gene dosage, G-banding analysis for chromosomal changes, and FISH for detection of chromosome 11 numerical changes were

undertaken. The results showed complex genetic changes with all three test substances, with evidence for deletion, recombination and aneuploidy. The absence of a functional P53 gene in L5178Y $TK^{+/-}$ cells was in part responsible for survival of cells with larger scale DNA damage. The authors suggested that these new data provide evidence for the utility of the mouse lymphoma assay (MLA) in a mechanistically based genotoxicity hazard identification battery. The COM strategy suggests that the MLA is suitable for regulatory use for the detection of gene mutations and provides complimentary rather than equivalent data to metaphase analysis.

2.33 The COM was aware that it recommended the MLA in its guidance on a strategy for mutagenicity testing (or an alternative of equivalent statistical power) as the third *in vitro* test in stage 1. More recently the COM has seen data to suggest that the MLA can detect clastogens and in some instances aneugens (the latter only at high doses resulting in cytotoxicity). The committee was asked its views on the proposed use of the MLA as part of a mechanistically based genotoxicity hazard identification battery.

2.34 Members agreed that this was an interesting paper. However, it was felt that the method outlined in the paper is dependent on a selective growth mechanism and thus will only detect the loss of chromosome 11 TK^{+}. This meant that only a limited analysis could be conducted and that non-disjunction could not be detected. The test might be useful as an indicator of aneuploidy, but would not permit exact measurement. It was noted that chromosomal aberration studies had indicated that cells with structural chromosomal aberrations and aneuploidy do not survive cell division when changes represented a balanced event and genetic gain is better tolerated than loss and thus would not go on to form a colony. Colonies that were found would represent potentially toxicological relevant events. Most colonies analysed had acquired a duplicate chromosome 11. This may indicate that cells with a loss of chromosome 11 do not survive. Members also noted the importance of the lack of p53 gene in L5178Y $TK^{+/-}$ cells leading to genomic instability. The COM agreed that small and large colonies related to different mutagenic events, but that this was not demonstrated by the data presented. Members also felt that it was probably better to use the micronucleus test to analyse for aneuploidy. Overall, the committee agreed that MLA was a useful assay when used as part as of a battery of tests for mutagenicity, but could not be used in isolation of other tests.

GADD 45a GFP assay

2.35 The committee had been introduced to the TK6 GADD 45a assay in 2007 when Professor Walmsley (Gentronix Ltd) had given a comprehensive talk on this newly developed high-throughput *in vitro* genotoxicity assay. The assay

utilises GADD45a, a gene considered to play a role in DNA repair, cell cycle control and apoptosis in response to genotoxicity. Induction of GADD45a has been identified in early gene expression in microarray experiments in response to a wide range of genotoxins (e.g. direct DNA damaging, topoisomerase inhibitors, nucleotide synthesis inhibitors, aneugens and generators of reactive oxygen species) in various cell types. The increase in GADD45a gene expression suggested that it could be used as a marker for genotoxic stress. In the test system GADD45a is fused to a green fluorescent protein (GFP) gene. The plasmid construct is transfected into P53 proficient human lymphoblastoid cell line (TK6) and the assay is conducted in microplates. After incubation with test compounds GFP reporter fluorescence and cell culture absorbance are measured.

2.36 Since the original presentation, a number of significant studies have been conducted to further validate the assay and introduce modifications. Most importantly, a protocol using metabolic activation and a higher throughput schedule had been outlined. A written overview detailing these developments by Professor Walmsley was submitted to the COM. A number of peer reviewed published papers were also made available to members covering areas such as: inter-laboratory validation; metabolic activation; further general validation; a trial of ECVAM recommended chemicals as part of a project to reduce the number of false positives; and a higher throughput protocol. Generally, the assay appeared to perform robustly and had been shown to have high specificity (correct identification of negatives) and sensitivity (correct identification of positives. However, one study by Olaharski A *et al* (Mutation Research, 672, 10-16, 2009) suggested a lower sensitivity.

2.37 The COM agreed that there was a lot of new data conducted to acceptable standards that provided evidence of a high degree of sensitivity and specificity. Regarding the inter-laboratory trial by Billinton N *et al*., (Mutation Research, 653, 23-33, 2008), members noted that this study had included a number of genotoxic and non-genotoxic compounds, but none of the genotoxic chemicals required metabolic activation. The GADD45a assay had been adapted to use S9 exogenous metabolic activation by Jagger C *et al*., (Mutagenesis, 24, 35-50, 2009) but it was felt that this aspect of the assay was less well validated. Overall, members felt that the assay was as good as any other *in vitro* genotoxicity test without metabolic activation. However, they wished to see more data with metabolic activation. Members felt that the evaluation of the results for the Roche proprietary compounds was important to deriving the overall estimate of sensitivity in this study. In answer to a question from the chair, Professor Walmsley reported that Gentronix did not have access to the identity of the Roche proprietary compounds. The secretariat was asked to obtain any information Roche were willing to provide on an in-confidence basis for COM members only.

2.38 The COM agreed that the GADD45a-GFP assay might be useful as a pre-screening tool similar to DEREK, but that it could not be used in a regulatory genotoxicity testing strategy at present. More data on the use of the GADD45a assay with metabolic activation and further analysis of the low sensitivity reported by the study by Olaharski *et al*., 2009 would be required before the committee could produce a statement on the use of this assay.

Ongoing Reviews

Thresholds for *in vivo* mutagens

2.39 The Committee considered a draft discussion paper on studies investigating thresholds in mutagenicity published since the COM 2001 statement. Members also heard a presentation from Dr Gareth Jenkins (University of Swansea) at the February 2009 meeting which included an outline of the various definitions used to describe thresholds for genotoxic effects. Dr Jenkins concluded that some genotoxins have demonstrated a threshold for mutagenicity both *in vitro* and *in vivo*. However, it is not possible to generalise to other chemicals that have not been tested to the same extent. There is a need to consider chemicals on a case-by-case basis and to have confidence in the mechanism for a threshold and the dataset. To date the evidence was most convincing for ethyl methanesulphonate (EMS).

2.40 The COM considered pre-publication studies undertaken by Roche to investigate the threshold for genotoxicity of EMS. In brief, during 2007, several thousand HIV patients had ingested Viracept (Nelfinavir mesylate) tablets as an HIV protease inhibitor, which contained relatively high levels of the impurity EMS. The available *in vitro* mutagenicity and toxicity data for EMS did not allow a full risk assessment of this incident to be undertaken. This led the manufacturer Roche, to undertake *in vivo* mutagenicity studies in mice (i.e.bone marrow (BM) micronucleus (MN), *lac*Z gene mutation in BM, liver and small intestine). Roche employed a novel statistical analysis of the data andundertook investigations to allow a risk assessment based on toxicokinetic data. Overall, the COM agreed that threshold had been demonstrated for EMS mutagenicity and that there was an adequate MOE between the NOEL for mutagenicity and the likely maximum exposures in patients who ingested the EMS contaminated Viracept tablets. Members briefly discussed the hypothetical argument of the one-hit hypothesis of mutagenicity and noted this still applied even though there was a great deal of redundancy in DNA.

2.41 The COM considered a draft guidance documents at the June 2009 and October 2009 meetings. It was agreed that the draft Guidance document on

the risk assessment of *in vivo* mutagens could be split into two sections i.e. a section on thresholds for mutagenicity and a section on the risk assessment of *in vivo* mutagens. This would be consistent with the proposal to produce guidance documents which could be rapidly updated when required.

Toxicogenomics

2.42 The COT/COC/COM intend to update their joint statement on toxicogenomics published in 2004. To contribute to this process a literature search had been conducted and studies most relevant to the COM was considered at the October 2008 and February 2009 meetings. This included a number of studies that for the first time had made comparisons between transcriptomics and proteomics for the same mutagen using identical culture conditions except that transcriptomics was measured 4h post exposure and proteomics 12h post exposure. Members noted that although there was some comparability between the two toxicogenomic approaches for both MNNG and BPDE regarding overall functions affected by treatment, there was very little comparability at the individual gene level. Overall, members considered that there was no evidence from these studies for a good correlation between transcriptomics and proteomic approaches. It was also noted that changes seen at the mRNA level did not necessarily mean there would be a change at the protein level and vice versa. An International Life Sciences Institute/Health and Environmental Sciences Institute (ILSI/HESI) trial of inter-laboratory variation in transcriptomic studies for genotoxicity has been published and should be considered during 2010.

Development of guidance documents on COM internet site

2.43 The structure of the proposed Guidance section of the COM website. Is under consideration and will be presented to the COM for comment in 2010. It is intended that the Guidance notes should be divided into areas that could be updated more quickly. It was suggested that the draft Guidance document on the risk assessment of *in vivo* mutagens could be split into two sections i.e. a section on thresholds for mutagenicity and a section on the risk assessment of *in vivo* mutagens.

2009 Membership of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

CHAIR

Professor Peter B Farmer MA DPhil CChem FRSC
Professor of Biochemistry, Cancer Studies and Molecular Medicine,
Cancer Biomarkers and Prevention Group, Biocentre, University of Leicester

MEMBERS

Dr Carolyn Allen BSc MSc PhD
Non-specialist Member

Dr Brian Burlinson CBiol MIBiol PhD
Director of Cellular and Molecular Toxicology, Huntingdon Life Sciences

Dr Gillian Clare BSc PhD
Cytogeneticist, Covance

Dr Julie Clements BSc PhD (upto 31 March 2009)
Head of Genetic and Molecular Toxicology, Covance

Dr Barry M Elliott BSc MSc PhD
Senior Toxicologist, Syngenta Central Toxicology Laboratory

Dr David Gatehouse BSc PhD CIBiol FIBiol FRCPath
Consultant in Genetic Toxicology, Covance

Mrs Rosie Glazebrook MA
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Professor Nigel J Gooderham BSc PhD CChem FRSC FBTS (upto 31 March 2009)
Professor of Molecular Toxicology, Biomolecular Medicine, Imperial College London

Dr Gareth Jenkins BSc, MSc, PhD (from 1 April 2009)
Reader, Institute of Life Science, Swansea School of Medicine
Honorary Non-clinical Senior Lecturer, Swansea NHS Trust

Professor David Kirkland BSc (Hons), PhD (from 1 April 2009)
Principal, Kirkland Consulting (from 1 July 2009), until 1 July 2009, Vice President of Scientific and Regulatory Consulting, Covance Laboratories Europe

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Reader in Medical Statistics, Postgraduate Medical School, University of Surrey

Dr Anthony Lynch BSc (Joint Honours) PhD (from 1 April 2009)
Manager Investigative Studies & New Screening Technologies, Genetic Toxicology, GlaxoSmithKline

Dr Ian Mitchell BA PhD (upto 31 March 2009)
Consultant in Genetic and Molecular Toxicology, Kelvin Associates and Chilfrome Enterprises Ltd

Dr Elizabeth M Parry BSc DPhil
Part-time Senior Research Fellow, School of Medicine, University of Wales

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

SECRETARIAT

Mr J Battershill BSc MSc	Joint Scientific Secretary – Health Protection Agency
Dr D Benford BSc PhD FBTS	Joint Scientific Secretary – Food Standards Agency
Dr L Hetherington BSc PhD	Scientific – Health Protection Agency
Mr S Robjohns BSc MSc	Scientific – Health Protection Agency
Ms S Kennedy	Administrative Secretary – Health Protection Agency

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)	Santander Bradford & Bingley Foreign & Colonial Friends Provident Health Effects Institute Torotrak ILSI HESI	Shareholder Shareholder Shareholder Shareholder Research Committee Member Shareholder Committee Member	American Chemistry Council	Research support and conference attendance expenses.
Dr C Allen	NONE	NONE	NONE	NONE
Dr B Burlinson	Huntingdon Life Sciences	Salary Employee Share Option Holder	NONE	NONE
Dr G Clare	Covance Allied Domecq AstraZeneca Diageo HBOS Marks & Spencer	Consultant Shareholder Shareholder Shareholder Shareholder Shareholder	NONE	NONE
Dr J Clements (to 31 March 2009)	Covance	Salary Share Option Shareholder	NONE	NONE
Dr B M Elliott	Syngenta AstraZeneca	Salary Share Option Holder Shareholder	NONE	NONE
Dr D Gatehouse	Covance GlaxoSmithKline	Salary Independent Consultant Shareholder Pension Share Option Holder Shareholder	NONE	NONE

Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Professor N J Gooderham (to 31 March 2009)	Banco Santander CENES Silence Therapeutics Hargreaves Lansdown Proctor & Gamble	Shareholder Shareholder Shareholder Shareholder Consultant	FSA GlaxoSmith Kline FEMA (USA)	Research contract CASE studentship Research support
Dr G Jenkins (from 1 April 2009)	NONE	NONE	Hoffman-LaRoche Hoffman-LaRoche Unilever CEFIC/ECE TOC	Research Grant 2008 – 2010 Consultancy 2008 Research Grant 2008 - 2010 Honorarium 2008
Dr D Kirkland (from 1 April 2009)	Covance Covance Kirkland Consulting	Salary & Consultant (until June 2009) Stock Options Principal	NONE	NONE
Dr D P Lovell	National Grid Transco Pfizer	Shareholder Shareholder Share Options Pension	AstraZeneca National Grid Transco	Spouse Shareholder Spouse Shareholder
Dr A Lynch (from 1 April 2009)	GlaxoSmithKline	Salary Shareholder	NONE	NONE
Dr I Mitchell (to 31 March 2009)	Kelvin Associates IM Enterprises Chilfrome Enterprises GlaxoSmithKline	Associate Consultant Director/Creditor Director Pensioner Option and Shareholder	NONE	NONE

	Allergy Therapeutics BG Cadbury Schweppes GEC GSK ICH Mitchell & Butler Pfizer Real Good Food Renishaw Royal Dutch Shell RTZ Unilever Vedanta BP Centrica Green King Scottish & Southern	Consultant Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder PEP Holder PEP Holder PEP Holder PEP Holder		
Dr E M Parry	Invesco Fleming Legal & General Quintiles	PEP Holder PEP Holder PEP Holder Consultancy	NONE	NONE
Prof D H Phillips	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid ECETOC Servier Butler Jeffries (solicitors)	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Honorarium Honorarium Honorarium	NONE	NONE

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

Preface

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) evaluates chemicals for their carcinogenic potential in humans at the request of UK Government Departments and Agencies. The membership of the Committee, agendas and minutes of meetings, and statements are all published on the internet (http://www.iacoc.org.uk/).

During 2009, the Committee considered a number of interesting and challenging topics. These included the provision of advice to the Department of Health on current tests used to evaluate the carcinogenicity of tobacco products and being used to support claims made by manufacturers of new products, a review of recently published studies of cancer incidence around municipal solid waste incinerators; and further work on our ongoing risk assessment of the effects of combined exposures to chemical carcinogens. Also, we were asked by the Food Standard Agency's Scientific Advisory Committee on Nutrition for our views on the evidence for the relationship between red and processed meat consumption and the risk of colorectal cancer. It is fortunate that the Committee possesses the wide range of expertise required to advise on such a variety of topics.

Ms Denise Howel, Dr Ruth Roberts and Dr David Shuker retired from the committee in 2009. I would like to thank them on behalf of the committee and secretariat for their valuable contributions over the years and to wish them well in the future. We welcomed a number of new members, with expertise in toxicology, pathology and medical statistics, with whom I look forward to working.

I would like to thank the members and secretariat of the Committee for the work they have undertaken during the past year. We look forward to new challenges in 2010

Professor David H Phillips
BA PhD DSc FRCPath

COC evaluations

Carcinogenicity testing of tobacco products

3.1 The Department of Health asked for an update of the 2004 COC/COM/COT statement on the toxicity of tobacco products because of the increasing literature in this area and a growing concern about the strategies used for the carcinogenicity testing of tobacco products. There is no internationally agreed approach to the hazard assessment of these products and so the Department required scientific advice on the suitability of the tests used to evaluate the carcinogenicity of tobacco products and on the suitability of the toxicological data used to support the claims made by manufacturers of new products which purport to reduce harm to users.

3.2 The Committee was asked for advice in the following areas:

I. Whether the approaches currently used to evaluate the carcinogenic potency of tobacco and its products are suitable, and the inhalation and dermal carcinogenicity of tobacco smoke.

3.3 The Committee advised that some of the animal models used to assess the carcinogenic potency of tobacco had been discredited. Lung sectioning is not straightforward and delivery of whole smoke to the lungs is technically challenging because of difficulties in managing inhaled particle size. Skin may not be representative of other organs. Overall, these studies might help to identify and characterise some aspects of the hazard posed by these products, but it is not possible to use them as a basis for comparative risk assessment.

II. The validity of claims of reduced exposure, harm or risk posed by existing and novel tobacco products.

3.4 This discussion included modified products, potentially reduced exposure products (PREPs), novel nicotine delivery systems (such as e-cigarettes) and smokeless tobacco products. Members disagreed with the notion that the studies reviewed demonstrated a reduction in carcinogenic potential associated with a reduction in exposure to harmful substances. These studies did not support the hypothesis that these products are associated with a lower risk of overall carcinogenicity than conventional cigarettes, although there may be limited evidence for specific tumour types.

3.5 There was some uncertainty as to whether e-cigarettes only deliver nicotine in a vapour, or whether users of these products are exposed to other chemicals. If these products only contain nicotine, they would not be expected to contribute to exposure to tobacco derived carcinogens.

3.6 The Committee noted that, in developing approaches to assess the carcinogenic potential associated with the use of novel and existing products,

there may be a temptation to develop tests that are sensitive, but not necessarily predictive of the real risk. Using such tests would result in spurious claims. It may also be inappropriate to perform direct comparisons of products without taking into account changes in smoking behaviour that might be expected to occur once the use of the new product has become established. It was noted that, in a number of intervention studies where electrically heated cigarettes were used for up to 12 months, product use increased throughout the study with no apparent plateau.

3.7 Members agreed with the view of the World Health Organisation (WHO) i.e. that these products are not legitimate cessation aids for smokers trying to quit because they have not been adequately tested, nor to be proven nicotine replacement therapy (NRT) products. At present, there is no evidence to confirm safety or efficacy and there are no peer-reviewed studies on these products. However, it is possible that they could be smoking cessation aids, albeit with appropriate clinical studies and toxicity analyses.

III. Suitability of the approaches used to assess the contribution of individual or mixed ingredients or additives to the overall toxicity of tobacco products.

3.8 The Committee considered that the available studies used to assess the contribution of individual or mixed ingredients or additives to the overall toxicity of tobacco products are inadequate to assess the risks posed by conventional cigarettes, so it is not possible to assess the modulation of that risk resulting from inclusion of additives. The relationship between effect (an increase in biomarker) and exposure is also poorly understood. Furthermore, it is possible that additives might alter smoker behaviour, such as to increase product use; this increased exposure would be likely to result in an increased risk.

IV. Whether there are validated biomarkers of effect for tobacco or its products

3.9 The Committee considered that the development of biomarkers of harm for tobacco products, particularly in relation to cancer, was a laudable but an unrealistic goal. The carcinogenic mechanisms underlying tobacco carcinogenesis are very complex, and are likely to be different in the various target organs and tissues, so it will be very difficult to identify a suitable comprehensive biomarker of effect. The ‘omics technologies might provide some alternatives but these would tend to be biomarkers of exposure, rather than effect. Metabonomics might be able to identify biomarkers of early effects in adequately designed prospective studies amongst smokers, although the Committee was sceptical about the likelihood of finding a suitable biomarker.

V. The proposed use of Cancer Risk Indices for the prioritisation of carcinogens in cigarette smoke.

3.10 The Cancer Risk Index (CRI) approach to tobacco carcinogenesis ranks constituents of tobacco smoke according to their toxicological hazard and concentration. It is proposed as a prioritisation method. Members questioned the aims of the CRI approach and how a prioritisation of carcinogens in tobacco smoke would be used. Since the available studies are inadequate to assess the risks posed by conventional cigarettes, it is not possible to assess the risks following removal of a specific carcinogenic element of the product. It would be very difficult to infer reduced harm on the basis of studies examining a limited number of endpoints.

3.11 Overall, the Committee concluded that, although it would be desirable to identify and remove carcinogenic components from tobacco products, it is not clear whether this would result in any reduction in harm. Concern was also expressed that the highly uncertain potential reduction in harm could be used to market these products to smokers who may have otherwise successfully given up smoking.

Non-Hodgkin's lymphoma

3.12 Malignant tumours of the lymphoid system, lymphoma, are divided into two major groups: Hodgkin's disease and non-Hodgkin's lymphoma (NHL). NHL is not a single disease but a mixture of disease entities. There are several schemes that have been used to characterise the disease. The majority of NHLs are of B lymphocyte origin, arising in lymph nodes. Treatment and prognosis depend on subtype.

3.13 NHL is the seventh most common cancer in men and the sixth most common cancer in women in the UK and statistics indicate that the incidence has increased since the 1970s. The COC has reviewed the scientific literature to assess whether there is any convincing evidence that environmental chemicals are responsible for the reported increase in the incidence of non-Hodgkin's lymphoma.

3.14 There are a number of suspected, non-chemical risk factors for NHL. The strongest and most well-established factors are characterised by dysregulation or suppression of immune cell (T-cell). These include specific infections such as HIV/AIDS, immune deficiency and persistent immune suppression following organ transplantation. However, risk factors for which there is strong evidence of an association are considered to account for only a small percentage of total NHL cases.

3.15 The Committee reviewed 57 studies of the association between NHL and exposure to environmental chemicals, including pesticides, organic solvents,

industrial chemicals, and chemicals associated with lifestyle. The following conclusions were reached:

I. There is limited evidence of an increased risk of NHL following nonoccupational exposure to polychlorinated biphenyls (PCBs). It would be valuable for the data on PCBs to be considered in more detail, preferably in the form of a meta-analysis or pooled analysis. However, any positive association with PCBs would not explain the trends in incidence of this cancer, given that PCB levels in the environment have decreased over the last few decades.

II. The available evidence on exposure to 1,3-butadiene and NHL does not provide convincing evidence of an association.

III. There is no clear evidence of an association between benzene exposure and NHL in the general population. One study has shown an increased risk of NHL from benzene in those with a family history of malignant haematologic neoplasms.

IV. After reviewing the available data, we conclude that there is no convincing evidence from epidemiological studies that environmental chemicals are responsible for the reported increase in NHL incidence which has occurred over the past 3 to 4 decades. As noted above, there is limited evidence of an association between NHL and non-occupational exposure to PCBs.

3.16 A statement can be found at: http://www.iacoc.org.uk/statements/documents/NonHodgkinslymphomaJan2009.pdf

Folic acid

3.17 From 2005 to 2007, the COC provided advice to the Scientific Advisory Committee on Nutrition (SACN) and the FSA on whether dietary folic acid intake is associated with increased cancer risk. The Committee concluded that, on balance, it was content with the recommendation by the SACN, and subsequent proposals by the FSA Board, to recommend to UK health ministers that there should be mandatory fortification of a food with folic acid, with controls on voluntary fortification and guidance on use of supplements, monitoring of the folic acid intakes and status of the UK population and postulated risks – including cancer incidence – and a review of the data on the benefits and possible risks 5 years after introduction of mandatory fortification. Members asked to be informed of the outcome of the 5 year review.

3.18 Subsequently, Members were informed that the Chief Medical Officer had decided to convene a special subgroup of the Scientific Advisory Committee on Nutrition (SACN) to examine further two papers on the potential adverse effects of folic acid on the risk of colorectal cancer and that the Chairman and

one member had been invited to participate in this working group. The group was presented with pre-publication data from a consortium of researchers conducting clinical trials on B-vitamins. In 2009, at the request of the COC Chairman, Dr Robert Clarke, the consortium co-ordinator, presented these pre-publication results to the Committee. The item was taken as reserved business and the details of the discussion will be published when the results of all the B vitamin trials are published, which is expected to be by the end of 2010.

Persistent environmental chemicals in human milk

3.19 The incidence of testicular cancer has been increasing gradually in many countries since the 1960s and the reasons for the increase are largely unknown. A review by the COC in 2006 identified no clear chemical aetiology. The incidence varies widely around the world and varies with ethnicity. In 2009, the COC reviewed a paper[1] which noted that there is a three to fourfold higher incidence of testicular cancer in Denmark than in Finland and postulated that endocrine disrupting chemicals may be responsible for the increase in testicular cancer and that exposure to these chemicals may be higher in Denmark than in Finland. The paper described an ecological study which compared levels of endocrine disrupting chemicals in human milk samples taken from Danish and Finnish women who had been part of an earlier cohort study on cryptorchidism, although only milk from women who delivered a healthy, non-cryptorchid boys was included in the study. The authors reported that the levels of chemicals were generally higher in the Danish samples, where the concentration range of persistent organic pollutants was also much broader and included some quite high values. The authors concluded that the study revealed conspicuous differences between the levels of chemicals in Danish and Finnish human milk samples and that specific chemical signatures were found in the two countries. The COC was asked whether it agreed with this conclusion and for comments on the study.

3.20 The Committee commented that, since it was an ecological study, it was not possible to determine whether any association was causal and other systematic differences between the populations might explain the effects seen in testicular cancer rates. A number of reservations were expressed about the reporting of the analytical methods, the sample collection and processing, and the statistical analyses used. The Committee noted that it would be reasonable to expect that 6 out of 121 chemicals might be different between two national populations and that, in view of the classes of persistent organic pollutants that had been identified, it was reasonable to assume that there would be some correlation amongst many of the chemicals.

[1] K. Krysiak-Baltyn, J. Toppiari, N.E. Skakkebaek, T.S. Jensen, H.E. Virtanen, K.-W. Schramm, H. Shen, T. Vartiainen, H. Kiviranta, O. Taboureau, S. Brunak and K.M. Main (2009). Country-specific chemical signatures of persistent environmental compounds in breast milk. Published in: International Journal of Andrology, Volume 32, pages 1-9.

3.21 The COC concluded that, from the data provided, it might be possible to say that the chemical signature may be different when comparing the two sampled groups; however, it is not possible to infer that this signature is representative of the Danish and Finnish populations and, therefore, any associations should be regarded with caution.

Municipal waste incinerators

3.22 In light of recent public interest and new European Union (EU) legislation on emissions from plants which incinerate or co-incinerate waste. The COC updated its advice on cancer incidence near municipal solid waste incinerators (MSWIs). The COC last discussed this topic in the late 1990s following the publication of a study by the Small Area Health Statistics Unit on cancer incidence near incinerators in Great Britain and concluded. "*The Committee was reassured that any potential risk of cancer due to residency (for periods in excess of 10 years) near to municipal solid waste incinerators was exceedingly low and probably not measurable by the most modern epidemiological techniques. The Committee agreed that, at the present time, there was no need for any further epidemiological investigations of cancer incidence near municipal solid waste incinerators"2.*

3.23 As of November 2008, there were 18 MSWIs in operation in England and Wales, one in operation on the Isle of Man and two in operation in Scotland. All of these MSWI are Energy from Waste (EfW) incinerators, generating energy such as heat and electricity as by-products. The by-products of the incinerator process may contain potentially toxic pollutants and emissions, which will contribute to background pollution levels. The Committee was informed that, since 1996, there have been significant cuts in emissions from incinerators in order to meet strict limits set by EU legislation. The EU Waste Incineration Directive (2000/76/EC, often termed "WID"), which applies to the incineration and co-incineration of both hazardous and non-hazardous waste, will further reduce the potential to pollute. The WID regulations introduced strict regulatory controls and minimum technical standards throughout the European Community for waste incinerators and co-incinerators which incinerate and co-incinerate waste. As a result, currently operating MSWIs are permitted to emit far lower levels of pollutants than were permitted in the past.

3.24 Six further relevant epidemiological papers had been published since the 2000 statement, three of which investigated cancer incidence around a single incinerator in France. Positive associations were reported between exposure

[2] Cancer incidence near municipal solid waste incinerators in Great Britain. COC statement COC/00/S1 - March 2000.
http://www.iacoc.org.uk/statements/Municipalsolidwasteincineratorscoc00s1march2000.htm

to pollutants from MSWI (principally, PCDDs and PCDFs) and non-Hodgkin's lymphoma (NHL), soft tissue sarcomas (STS), and childhood cancers. No association or a negative association was reported between emissions of PCDDs and PCDFs and invasive breast cancer. The Committee noted that all the epidemiology studies were carried out on incinerators in operation prior to the imposition of the current strict controls on emissions.

3.25 After reviewing the studies, the Committee decided that it was unable to draw conclusions from one of the studies and that only limited conclusions could be drawn from two further studies because they included emission sources other than MSWIs and failed to adjust for confounding factors. Three of the further studies were carried out around the same incinerator in France which was reported to emit far higher concentrations of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans than currently permitted. Although these studies indicated some evidence of a positive association between two of the less common cancers i.e NHL and soft-tissue sarcoma and residence near to incinerators in the past, the Committee considered that the results could not be extrapolated to current incinerators, which emit lower amounts of pollutants. Moreover, they are inconsistent with the results of the larger study on cancer incidence around municipal incinerators carried out by the Small Area Health Statistics Unit. It concluded, therefore, that there was no need to change the advice given in the previous statement but that the situation should be kept under review.

3.26 A statement can be found at: http://www.iacoc.org.uk/statements/documents/COC09S2UpdatestatementonCancerIncidenceandMSWIsMarch09.pdf .

OECD Guidance Document for the performance of chronic toxicity and carcinogenicity studies

3.27 The Organisation for Economic Cooperation and Development (OECD) is currently developing a guidance document for the performance of chronic toxicity and carcinogenicity studies, to support the relevant Test Guidelines. In 2008, Members had recommended that the UK should propose leading on the chapter on histopathology and this offer was accepted by the OECD. The scope of the chapter was later expanded to include all investigations. In 2009, the Committee commented on a draft outline for this chapter, which had been developed from existing OECD Guidance, using Society of Toxicologic Pathology Guidance documents, standard texts and published literature. It was agreed that the new Guidance Document should be drafted as a stand alone document that replaces the previous OECD guidance. A number of comments were made on the document and Members offered to provide recent publications which would be more appropriate references for some

parts of the document. It was also recommended that a section on ophthalmoscopy be included in the chapter.

Scientific Advisory Committee on Nutrition Report on Iron and Health

3.28 During 2009, the Scientific Advisory Committee on Nutrition (SACN) sought advice from the COC on the evidence for the relationship between red and processed meat consumption and the risk of colorectal cancer (CRC), as part of the consultation on its draft Report on Iron and Health. This report summarised the available epidemiological and mechanistic evidence on this topic.

3.29 The Chairman of SACN Working Group on Iron provided a brief background of the draft report and informed the Committee that there were a number of uncertainties in the data. With reference to cancer, the draft SACN report concluded that red and processed meat is "*probably*" associated with colorectal cancer (CRC). The SACN advice was more moderate than that of the World Cancer Research Fund (WCRF) report on diet and cancer, which had concluded that red and processed meat is a "convincing" cause of CRC.

3.30 Members discussed the available studies and concluded that, although the majority of the studies indicate red and processed meat intake is associated with increased risk of CRC, the evidence is not unequivocal. It was noted that meat consumption varies with socioeconomic status and that eating meat is associated with many other lifestyle factors. Therefore, all studies will be subject to considerable confounding which is unlikely to be completely removed during epidemiological analysis, although residual confounding is unlikely to entirely explain the observed increased risk reported in most studies. Genetic predisposition is unlikely to be a potential confounder, except in particular circumstances. However, it is possible that dietary preferences might be influenced by *perceived* familial susceptibility to disease. Members advised that any recommendations should take account of the biological and epidemiological limitations of the evidence base.

3.31 The various potential biological mechanisms for the association between red and processed meat and CRC risk was considered. It was noted that the hypothesis that the mechanism may be heterocyclic amines (HCA) produced during the cooking of meat had weakened. Recent studies had failed to show an association between well-cooked meat and cancer and the Margin of Exposure between carcinogenic dose of HCAs in experimental studies and human exposure is large. Members noted that there was not strong evidence linking CRC risk with N-nitroso compounds, which are found in processed meats, and it was noted that endogenous formation can exceed exogenous exposure. Members also considered oxidative stress associated with the iron contained in meat, although it was noted that the majority of dietary iron

comes from vegetables, supplements and fortified foods. Overall, although each mechanism was considered plausible, none was supported by robust evidence.

3.32 The Committee made a number of comments on the wording of the SACN draft conclusion but supported the view that there is an association between the consumption of red and processed meat and CRC, although it is not known whether the relationship is causal. It was suggested that the conclusion should be re-worded to make this clearer and that this should also feature prominently in risk communication. Members also concluded that, even with the residual uncertainties, any risk appeared to be small.

3.33 WHO/IPCS Harmonization Project: Framework Document on Risk Assessment of the combined exposures to multiple chemicals

3.34 At the July meeting, the Committee's views were invited on a document produced by the World Health Organisation (WHO) International Programme on Chemical Safety (IPCS) entitled 'Risk assessment of the combined exposures to multiple chemicals'. Comments had been invited from groups and individuals with an interest in the area.

3.35 It was noted that the methodology described was only applicable to chemicals acting by a common mode of action. Members considered it useful that the document developed two parallel tiered approaches for exposure and hazard assessment but commented that discussion and development of hazard index/quotient would have been helpful. It was noted that the approach was intended to aid the assessment of a low level of exposure to a mixture, not a high level of exposure. The worked examples were considered to greatly enhance the document.

3.36 A number of further comments were made and the Secretariat undertook to pass the Committee's comments back to the IPCS.

Horizon scanning

3.37 The COC undertakes "horizon scanning" exercises at regular intervals to identify new and emerging issues which have the potential to impact on public health. A number of topics were identified by the secretariat for consideration by the Committee at the 2009 exercise, including those outstanding from the 2008 exercise. From these and Committee members' own proposals, the COC decided that the following items should be taken forward:

- An update review of the literature on interaction between genotype and chemicals in the environment on the induction of cancer
- A joint meeting with the COM on thresholds of genotoxicity
- Endogenous DNA adducts
- The carcinogenicity of carbon nanotubules

- Mononuclear cell leukaemia in the Fischer 344 rat
- The cancer risk of exposure to environmental tobacco smoke in childhood
- The use of Zebrafish in mechanistic studies

3.38 In addition, the Committee asked to discuss the output of a workshop held by the International Life Sciences Institute Health and Environmental Sciences Institute on Intermittent/Short-Term Exposure to Carcinogens to be held in December 2009.

Ongoing topics

Carcinogenicity of mixtures

3.39 The COC continued to discuss the assessment of chemical mixtures with regard to carcinogens and their modes of action. A statement is expected in 2010.

RNA related effects as a mechanism of carcinogenicity

3.40 Ribonucleic acid (RNA), which is made up of nucleic acids, has a variety of functions in a cell and is found in many organisms. RNA and deoxyribonucleic acid (DNA) differ functionally. DNA primarily serves as the storage material for genetic information. RNAs are versatile molecules capable of an array of functions. In recent years many new small functional RNAs have been found. RNA is usually thought of as messenger RNA that serves as a template for translation of genes into proteins. In contrast, functional and non-coding RNA molecules are transcribed from a DNA sequence, but not translated into proteins. The encoding DNA sequence is often referred to as an RNA gene. Functional

3.41 RNA genes in the human genome include transfer RNA (tRNA), ribosomal RNA (rRNA) and various other small non-coding RNAs. Several hundred genes in our genome encode small functional RNA molecules collectively called microRNAs (miRNAs).

3.42 At the 2008 horizon scanning exercise, it was suggested that it would be appropriate to review emerging research data in the scientific literature on RNA related effects as a mechanism of carcinogenicity. The Committee was provided with a review of the role played by mechanisms involving RNA in cancer development. It was decided that the review should be updated to include, if possible, a review of any emerging papers on environmental chemicals interacting with RNA processes. The topic will be discussed further at a future meeting.

The potential carcinogenic risk of Insulin-like growth factor-1 (IGF-1) in the diet

3.43 The COC was asked to advise on concerns raised by a member of the public in relation to a book ("Your Life In Your Hands" by Professor Jane Plant) which suggested that consumption of IGF-1 in dairy produce could lead to an increased risk of developing certain cancers. The Committee considered that the evidence presented in the book was incomplete, and of inconsistent quality, so any conclusions drawn from the book must be regarded as provisional and would need to be confirmed following a fuller systematic review of the scientific literature before they could be acted upon. This is currently ongoing and will be discussed by the Committee in due course.

2009 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

CHAIR

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

MEMBERS

Dr Carolyn Allen BSc MSc PhD
Non-specialist Member

Professor Alan Boobis OBE BSc PhD CBiol FIBiol
Section of Experimental Medicine and Toxicology, Division of Medicine, Imperial College London

Dr Philip Carthew BSc MSc PhD FRCPath
Senior Pathologist, SEAC Toxicology Unit, Unilever

Professor Peter B Farmer MA DPhil CChem FRSC
Professor of Biochemistry, Cancer Studies and Molecular Medicine, Cancer Biomarkers and Prevention Group, Biocentre, University of Leicester

Mrs Rosie Glazebrook MA
Non-specialist Member

Dr Peter Greaves MBChB FRCPath (from 1 April 2009)
Consultant Pathologist and Honorary Senior Lecturer, Department of Cancer Studies & Molecular Medicine, University of Leicester

Professor David Harrison BSc MB ChB MD FRCPath FRCP(Edin) FRCS(Edin) (upto 31 March 2009)
Professor and Head of Department of Pathology, Director, University of Edinburgh Cancer Research Centre

Ms Denise M Howel BSc MSc CStat FIS (to 31 March 2009)
Senior Lecturer in Epidemiological Statistics, Institute of Health and Society, Newcastle University

Dr David P Lovell PhD BSc (Hons) FSS FIBiol CStat CBiol (from 1 April 2009)
Reader in Medical Statistics, Postgraduate Medical School University of Surrey

Dr Brian G Miller BSc PhD CStat
Director of Research Operations, Institute of Occupational Medicine

Dr Christopher Powell BSc PhD DipRC Path FRC Path FBTS (from 1 April 2009)
European Registered Toxicologist, Director Non –clinical Development Europe GlaxoSmithKline

Professor Ruth A Roberts BSc PhD ATS FBTS (to 31 March 2009)
Director of Toxicology, Safety Assessment UK, AstraZeneca

Professor David E G Shuker BSc ARCS PhD DIC CChem FRSC (to 31 March 2009)
Professor of Organic Chemistry, The Open University

Dr Paolo Vineis MD PhD
Professor of Environmental Epidemiology, Department of Epidemiology and Public Health, Imperial College London

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

Dr Lindsay Wright PhD (from 1 April 2009)
Team Leader in General Toxicology Sciences, Therapy Area Toxicologist for Infection Therapy Area, Project Team Representative, Astra Zeneca

SECRETARIAT

Ms F Pollitt MA DipRCPath	Joint Scientific Secretary – Health Protection Agency
Dr D Benford BSc PhD FBTS	Joint Scientific Secretary – Food Standards Agency
Mr J Battershill BSc MSc	Scientific – Health Protection Agency
Dr L Hetherington BSc PhD	Scientific – Health Protection Agency
Ms S Kennedy	Administrative Secretary– Health Protection Agency

Declaration of COC members interests during the period of this report

Member	Personal Interest		Non-personal Interest	
	Company	Interest	Company	Interest
Professor D H Phillips (Chairman)	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid Servier Buller Jeffries (Solicitors)	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Honorarium Honorarium	NONE	NONE
Dr C Allen	NONE	NONE	NONE	NONE
Prof A Boobis OBE	Bank Santander Barclays Bank BG Group BT Group Centrica HBOS Iberdrola SA Transco Scottish Power Sumitomo Chemical (UK) PLC Endura Fine Chemicals	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy	GlaxoSmithKline ESRC FSA Department of Health ILSI HESI Elsevier JMPR JECFA (vet drugs) EFSA PPR Panel EFSA CONTAM Panel EFSA Scientific Committee Working Group on Risk-Benefit Assessment EFSA Scientific Committee Working Group on the Benchmark Dose ECETOC Task	Support by Industry PhD Studentship Research Contract Unpaid member of Board of Trustees Editor-in-Chief Food & Chemical Toxicology Member

			Force on Guidance for Classification of Carcinogens under GHS ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues.	
Dr P Carthew	Unilever Gwathmey, USA	Salary Consultant	NONE	NONE
Prof P B Farmer	Santander Bradford & Bingley Foreign & Colonial Friends Provident Torotrak EFSA ILSI HESI	Shareholder Shareholder Shareholder Shareholder Shareholder Committee Member Committee Member	American Chemistry Council CEFIC	Research support and Conference attendance expenses. Research Support
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr P Greaves (from 1 April 2009)	Shire Pharmaceutical Development UKAstellas Pharma Europe WIL-Biotechnics LLD, USA BASF, Ludwigshafen, Germany Novo Nordisk, Malov, Denmark Teva Pharmaceuticals, Israel Lundbeck, Copenhagen, Denmark	Consultant	NONE	NONE

	Renovo Ltd, Manchester UK INEOA Healthcare, Warrington, UK Synosia Therapeutics, San Francisco, US			
Professor D Harrison (to 31 March 2009)	The Forensic Institute, University of Edinburgh Lothian NHS Response Genetics University of Florida University of Canberra	Shareholder Consultant (no fee payable) Consultant Consultant	PI Medical Research (Scotland) Chair EMMS Nazareth Member Scientific Advisory Committee, Yorkshire Cancer Research	Non specific research funding from Cancer Research UK. Breakthrough CSO & other grant agencies. Trusteee Trustee (Healthcare Charity) Trustee
Ms D Howel (to 31 March 2009)	NONE	NONE	NONE	NONE
Dr D Lovell (from 1 April 2009)	National Grid plc Pfizer	Shareholder Shareholder	AstraZeneca National Grid plc	Spouse shareholder
Dr B G Miller	Iberdrola SA	Shareholder	NONE	NONE
Dr C Powell (from 1 April 2009)	GlaxoSmithKline	Shareholder and salary	NONE	NONE
Professor R A Roberts (to 31 March 2009)	AstraZeneca HBOS P & O	Salary Shareholder Shareholder	NONE	NONE

Professor D E G Shuker (to 31 March 2009)	NONE	NONE	NONE	NONE
Dr P Vineis	NONE	NONE	NONE	NONE
Dr N Wallis	Pfizer	Salary Shareholder	NONE	NONE
Dr L Wright (from 1 April 2009)	AstraZeneca	Salary and shareholder	NONE	NONE

Annex 1 – Terms of Reference

To advise at the request of:

Food Standards Agency
Health Protection Agency
Department of Health
Department for Business, Enterprise & Regulatory Reform
Department of Transport, Local Government and the Regions
Department of Trade and Industry
Health and Safety Executive
Chemical Regulations Directorate
Veterinary Medicines Directorate
Medicines and Healthcare Products Regulatory Agency
Home Office
Scottish Executive
National Assembly for Wales
Northern Ireland Assembly
Other Government Departments and Agencies

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 or 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.

Annex 2 – Code of Coduct for members of advisory committees

Public service values

Members of the COC/COM/COT (hereafter referred to as "the Committee") must at all times:

- observe the highest standards of **impartiality**, **integrity** and **objectivity** in relation to the advice they provide and to the management of their Committee;
- be **accountable**, through the Chair of the Food Standards Agency and the Chief Medical Officer, to Ministers, Parliament and the public for its activities and for the standard of advice it provides;
- in accordance with Government policy on **openness**, fully comply with the Freedom of Information Act 2000[1]

The Ministers of the sponsoring departments are answerable to Parliament for the policies and performance of the Committee, including the policy framework within which it operates.

Standards in Public Life

Members are expected to:

- comply with this Code, and ensure they understand their duties, rights and responsibilities, and that they are familiar with the function and role of their Committee and any relevant statements of Government policy. If necessary members should consider undertaking relevant training to assist them in carrying out their role;
- not misuse information gained in the course of their public service for personal gain or for political purpose, nor seek to use the opportunity of public service to promote their private interests or those of connected persons, firms, businesses or other organisations; and
- not hold any paid or high profile unpaid posts in a political party, and not engage in specific political activities on matters directly affecting the work of the Committee. When engaging in other political activities, Committee members should be conscious of their public role and exercise proper discretion. These restrictions do not apply to MPs (in those cases where MPs are eligible to be appointed), to local councillors, or to Peers in relation to their conduct in the House of Lords.

[1] Any member of the public seeking guidance on how to submit a freedom of information request please see the Directgov website:
http://www.direct.gov.uk/en/Governmentcitizensandrights/Yourrightsandresponsibilities/DG_4003239

- follow the Seven Principles of Public Life set out by the Committee on Standards in Public Life[2];

Selflessness

Holders of public office should take decisions solely in terms of the public interest. They should not do so in order to gain financial or other material benefits for themselves, their family, or their friends.

Integrity

Holders of public office should not place themselves under any financial or other obligation to outside individuals or organisations that might influence them in the performance of their official duties.

Objectivity

In carrying out public business, including making public appointments, awarding contracts, or recommending individuals for rewards and benefits, holders of public office should make choices on merit.

Accountability

Holders of public office are accountable for their decisions and actions to the public and must submit themselves to whatever scrutiny is appropriate to their office.

Openness

Holders of public office should be as open as possible about all the decisions and actions that they take. They should give reasons for their decisions and restrict information only when the wider public interest clearly demands.

Honesty

Holders of public office have a duty to declare any private interests relating to their public duties and to take steps to resolve any conflicts arising in a way that protects the public interests.

Leadership

Holders of public office should promote and support these principles by leadership and example.

These principles apply to all aspects of public life. The Committee has set them out here for the benefit of all who serve the public in any way.

[2] http://www.public-standards.gov.uk/

Role of Members

Members have collective responsibility for the operation of their Committee. Members are appointed as individuals to fulfil the role of their respective Committees, not as representatives of their particular profession, employer or interest group and have a duty to act in the public interest. Members are appointed on a personal basis, even when they are members of stakeholder groups and organisations. If a member declares an organisation's view rather than a personal view they should make it clear at the time of declaring that view.

Members must:

- engage fully in collective consideration of the issues, taking account of the full range of relevant factors, including any guidance issued by the Food Standards Agency, Health Protection Agency and the Department of Health
- undertake on appointment to comply with the Code of Practice for Scientific Advisory Committees[3]
- not divulge any commercially sensitive information, pre-publication or unpublished research data provided to the Committee
- agree an annual report
- ensure that an appropriate response is provided to complaints and other correspondence, if necessary with reference to the sponsor department; and;
- ensure that the Committee(s) does not exceed its powers or functions.

A member's role on the Committee should not be limited by the expertise or viewpoint she or he was asked to bring to it. Any statement/report belongs to the whole Committee. Members should regard themselves free to question and comment on the information provided or the views expressed by any of the other members, even though the views or information provided do not relate to their own area of expertise.

If members believe the committee's method of working is not rigorous or thorough enough, they have the right to ask that any remaining concerns they have be put on the record.

Individual members should inform the Chair (or the Secretariat on his or her behalf) if they are invited to speak in public in their capacity as a Committee member.

Communications between members and the Food Standards Agency (FSA) Board, CMO and/or Ministers will generally be through the Chair except where the Chair has agreed that an individual member should act on its behalf. Nevertheless, any member has the right of access to the FSA Board and/or the CMO on any matter that he or she believes raises important issues relating to his or her duties as a Committee member. In such cases the agreement of the rest of the Committee should normally be sought.

[3]Currently located at: http://www.bis.gov.uk/assets/biscore/goscience/c/cop-scientific-advisory-committees.pdf

Committee appointments can be terminated early by either party, by giving 3 months notice, in writing. Should the Committee be disbanded before the end of the period of appointment, appointments will terminate on dissolution.

In the event that a member is found guilty of grave misconduct their appointment will be terminated immediately, in the case of the COT by the Chair of the FSA. The Department of Health has delegated the powers for appointments to the COC and COM to the NHS Appointments Commission and it will terminate appointments in consultation with the HPA/DH.

Role of the Chair

The Chair has particular responsibility for providing effective leadership on the issues above. In addition, the Chair is responsible for:

- ensuring that the Committee meets at appropriate intervals,
- ensuring that the minutes of meetings accurately reflect proceedings and any reports to the FSA Board and/or Ministers accurately record the decisions taken
- ensuring that where appropriate, the views of individual members have been recorded;
- representing the views of the Committee to the general public;
- ensuring that new members are briefed on appointment (and their training needs considered), and providing an assessment of their performance, on an annual basis or when members are considered for re-appointment to the Committee or for appointment to the board of some other public body.
- providing urgent advice to the FSA and HPA on issues within the remit of the Committee, in liaison with the Secretariat,

Role of the Deputy Chair

The Deputy Chair will assume the role of the Chair as described above if the Chair is not available.

Role of the Secretariat

The primary function of the Secretariat is to facilitate the business of the Committee. This includes supporting the Committee by arranging its meetings, assembling and analysing information, and recording conclusions. An important task is ensuring that proceedings of the Committee are properly documented and recorded. Minutes of all

Committee meetings will be taken. These will accurately reflect the proceedings and discussions that take place and will be recorded on a non-attributable basis except where the views of one or more individual members need recording (for example, when declaring an interest).
The Secretariat is also a source of advice and guidance to members on procedures and processes.

The Secretariat is drawn from staff of the Food Standards Agency and the Health Protection Agency. However, it is the responsibility of the Secretariat to be an impartial and disinterested reporter and at all times to respect the Committee's independent role. The Secretariat is required to guard against introducing bias during the preparation of papers, during meetings, or in the reporting of the Committee's deliberations. Current contact details for each of the Secretariats are shown on the back page of this report.

Role of the Assessor

Meetings of the Committee (and working groups) may be attended by Assessors. The Assessors are nominated by, and drawn from, the Agencies and Departments that sponsor the Committee, receive its advice, or have other relevant policy interests.

Assessors are not members of the Committee and do not participate in Committee business in the manner of members.

The role of an Assessor is to keep their parent Department or Agency informed about the Committee's work and act as a conduit for the exchange of information. They do this by:

- advising the Committee on relevant policy developments and the implications of Committee proposals;
- informing the Committee work through the provision of information
- being informed by the Committee on matters of mutual interest
- sharing with the Secretariat the responsibility of ensuring that information is not needlessly withheld from the Committee. Assessors should make the Committee aware of the existence of any information that has been withheld from the Committee on the basis that it is exempt from disclosure under Freedom of Information legislation unless that legislation provides a basis for not doing so.
- ensuring that their parent Department or Agency is promptly informed of any matters which may require a response from Government.

Role of other Officials, Invited Experts and Contractors

Officials from Government Departments (not departmental assessors), Regulatory Agencies and Devolved Administrations may be called upon to advise the Committee on relevant developments in order to help the Committee formulate its advice.

Invited experts and contractors may also bring particular technical expertise, which may be requested by the Committee on some occasions.

In the event of an official, invited expert or contractor not being able to attend written submissions may be sent via the Secretariat.

Role of Observers

Members of the public and other interested parties may attend meetings as observers. However, they should not attempt to participate in Committee discussions.

If an interested party wishes to provide information relevant to a topic for consideration by the Committee, they should be submitted in writing to the Secretariat at **least** seven(7) working days before the meeting. The Secretariat will discuss with the Chair the most appropriate way to present the information to the committee and the Chair's decision will be final.

Observers who have submitted information in advance of the meeting **may** be invited to provide further explanation or to make brief comments at the discretion of the Chair.

Observers and/or organisations must not interfere in the work of the Secretariat or input from invited experts, contractors, officials from Government Departments and Agencies in any way which, in the view of the Chair, constitutes harassment and/or might hinder the work of the Committee. Observers and/or organisations must allow other observers and other interested parties to attend items free from interference before, during and after a meeting.

Observers and/or organisations are required to respect the work of the Committee. The Committee's discussions represent the development of its view and any comments made in developing the agreed Committee view should not be attributed to individuals. Where a subject will be considered over several meetings, observers are asked to maintain the confidentiality of the discussion until an agreed Committee opinion is finalised. The Committee's conclusions are not finalised until completion of any necessary consultation and publication of a statement or report.

Under no circumstances will Observers be permitted to record Committee proceedings, on the basis that this might inhibit free discussion. The published minutes of the meeting would provide a record of the proceedings.

Failure to observe this code of conduct may lead to exclusion of individual observers and/or organisations from meetings of the Committee.

All observers and/or organisations are requested to read follow the Committees Openness policy (Annex 3)

Definitions

In this Code, 'the industry' means:

- Companies, partnerships or individuals who are involved with the production, manufacture, sale or supply of products subject to the following legislation;

  General Food Regulations 2004

  The Food Safety Act 1990 (Amendment) Regulations 2004

  The Medicines Acts 1968 and 1971, 1981, 1986 & 2003

  The Food and Environmental Protection Act 1985

  The Consumer Protection Act 1987

  The Cosmetic (Safety) (Amendment) Regulations 2008

  Registration, Evaluation, Authorisation and Restriction of Chemicals (EC1970/2006)

- Trade associations representing companies involved with such products;

- 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.

- 'the Secretariat' means the Secretariat of the COC, COM and COT;

- 'the Agency' means either the Food Standards Agency or the Health Protection Agency; and

- references to "member(s)" includes the Chair.

Declaration of Members' Interests

Different types of Interest

The following is intended as a guide to the kinds of interests which should be declared. Where members are uncertain as to whether an interest should be declared, they should seek guidance from the Secretariat or, where it may concern a particular product which is to be considered at a meeting, from the Chair at that meeting.

If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them.

However, neither the members nor the Secretariat are under any obligation to search out links of which they might *reasonably* not be aware. This Code suggests that interests of close family members are declared, members have in the past limited such declarations to personal partners, parents, children (minor and adult), brothers, sisters and the personal partners of any of these with the emphasis on disclosure only where the interest may, or may be perceived (by a reasonable member of the public) to influence a members' judgement.

The Secretariat is required to publish an up-to-date register of members' interests and these can be found on the relevant Committees website.

Personal Interests

A personal interest involves the member personally. The main examples are:

- **Consultancies and/or direct employment:** any consultancy, directorship, position in or work for industry which attracts regular or occasional payments in cash or kind;

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

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

- **Membership or Affiliation:** any membership role or affiliation that you or a close family member has to clubs or organisations with an interest or involvement in the work of the Agency.

Non-Personal Interests

A non-personal interest involves payment which benefits the organisation in which the member works, but is not received by the member personally. The main examples are:

- **Fellowships:** the holding of a fellowship endowed by industry;

- **Support by Industry:** any payment, other support or sponsorship which does not convey any pecuniary or material benefit to a member personally, but which does benefit their position or organisation, e.g.

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

  ii) a grant or fellowship or other payment to sponsor a post or a member of staff or a post graduate research programme for which the 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 responsible.

Members are under no obligation to seek out knowledge of work done for, or on behalf of, the industry or other relevant bodies by departments in which they work, if they would not normally expect to be informed.

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

At meetings members are required to declare relevant interests and to state whether they are personal or non-personal interests and whether they are specific or non-specific to the matter, product or substance under consideration.

Specific Interests

A member must declare a *personal specific* interest if they have at any time worked on a matter, product or substance under consideration and have personally received payment for that work, in any form.

A member must declare a *non-personal specific* interest if they are aware that the organisation in which they work has at any time worked on the matter, product or substance under consideration but they have not personally received payment for that work, in any form.

Non-specific Interests

A member must declare a *personal non-specific* interest if they have a **current** personal interest in a company concerned with a matter, product or substance under consideration, which does not relate specifically to the matter, product or substance under discussion.

A member must declare a *non-personal non-specific* interest if they are aware that the organisation in which they work is **currently** receiving payment from the company

concerned which does not relate specifically to the matter, product or substance under discussion.

If a member is aware that a substance, product or matter under consideration is or may become a competitor of a substance, product or matter manufactured, sold or supplied by a company in which the member has a *current personal* interest, they should declare their interest in the company marketing the rival product, substance or matter.

Handling conflicts of interests

The purpose of these provisions is to avoid any danger of Committee members being influenced, or appearing to be influenced, by their private interests in the exercise of their public duties. All members should declare any personal or business interest which may, or may be *perceived* (by a reasonable member of the public) to, influence their judgement. A guide to the types of interest that should be declared is mentioned above.

(i) Declaration of Interests to the Secretariat

Members are required to inform the Agency in writing prior to appoint of their *current personal and non-personal* interests, including the principal position(s) held. Members are not required to disclose the amount of any salary, fee, shareholding, grant etc. An interest is current if the member has an on-going financial involvement e.g. if he or she holds shares in industry, has a consultancy contract, or if they or the organisation for which they are responsible is in the process of carrying out work for the industry.

Following appointment members are asked to inform the Secretariat at the time of any change in their *personal* interests. However, the Secretariat will contact each member on an annual basis to update their declaration of interests. Changes in *non-personal* interests can be reported annually, and those involving less than £1000 from a particular company in the previous year need not be declared.

The register of interests is kept up-to-date and open to the public via the website.

(ii) Declaration of Interest at Meetings

Members of the Committee are required to verbally declare any direct interests relating to salaried employment or consultancies, or those of close family [4] members in matters under discussion at each meeting, and if items are taken by correspondence between meetings. The declaration should note whether the interest is *personal or non-personal*, whether it is *specific* to the item under discussion, or *non-specific* and whether it is current or lapsed. Having fully explained the nature of their interest the Chair will, decide whether and to what extent the member should participate in the discussion and determination of the issue and it should be recorded in the minutes of the meeting.

[4] Guidance suggests close family members include personal partners, parents, children (minor and adult), brothers, sisters and the personal partners of any of these.

Withdrawal from meetings

If a declaration of interest has been made and the Committee decides that the member should not participate in the discussion and should withdraw from the meeting (even if held in public) and it should be recorded in the minutes of the meeting.

The Chair may first allow them to make a statement on the item under discussion.

Personal liability of Committee members

The Department of Health has a formal statement of indemnity for its advisory committee members, which includes the COC and COM, its guidance is taken from the Cabinet Office "Model Code of Practice for Board Members of Advisory Non-Departmental Public Bodies" and states that *"Legal proceedings by a third party against individual board members of advisory bodies are very exceptional. A board member may be personally liable if he or she makes a fraudulent or negligent statement which result in a loss to a third party; or may commit a breach of confidence under common law or criminal offence under insider dealing legislation, if he or she misuses information gained through their position. However, the Government has indicated that individual board members who have acted honestly, reasonably, in good faith and without negligence will not have to meet out of their own personal resources any personal civil liability which is incurred in execution or purported execution of their board functions. Board members who need further advice should consult the sponsor department."*[5] except where the person has acted recklessly.

The FSA has also drawn up a formal statement of indemnity for its advisory committee members.

INDEMNITY BY THE FOOD STANDARDS AGENCY TO MEMBERS OF THE COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

1. Subject as provided in paragraph 3 of this document, the Food Standards Agency hereby undertakes with the Members[6] of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment ("the Members") to indemnify them against all liability in respect of any action or claim which may be brought, or threatened to be brought, against them either individually or collectively by reason of or in connection with the performance of their duties as Members, including all costs, charges and expenses which the Members may properly and reasonably suffer or incur in disputing any such action or claim.

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[5] Paragraph 40 Code of Practice for Scientific Advisory Committees http://www.bis.gov.uk/assets/biscore/goscience/c/cop-scientific-advisory-committees.pdf

[6] Members of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment also includes members of Working Groups and other *Ad Hoc* expert groups of that Committee.

2. The Members shall as soon as practicable notify the Food Standards Agency if any action or claim is brought or threatened to be brought against them in respect of which indemnity may be sought pursuant to paragraph 1, and if an action or claim is brought, the Food Standards Agency shall be entitled to assume the defence. The Agency shall notify the Members as soon as practicable if it intends to assume the defence and the Members shall then provide to the Agency such information and assistance as it shall reasonably request, subject to all out of pocket expenses properly and reasonably incurred by them being reasonably reimbursed. The Food Standards Agency shall, to the extent reasonable and practicable, consult with and keep the Members informed as and when reasonably requested by the Members in respect of any action or claim. If the Food Standards Agency does not assume the defence of such action or claim, the Members shall keep the Agency fully informed on its progress and any consequent legal proceedings and consult with the Agency as and when required concerning the action or claim.

3. The indemnity contained in paragraph 1 shall not extend to any losses, claims, damages, costs, charges, expenses and any other liabilities:

(a) in respect of which the Members are indemnified by or through any defence organisation or insurers or;

(b) which may result from bad faith (including dishonesty), wilful default or recklessness on the part of the Members; or

(c) which may result from any of the following circumstances:

(i) any settlement made or compromise effected on behalf of the Members of any action or claim brought, or threatened to be brought, against the Members; or

(ii) any admission by the Members of any liability or responsibility in respect of any action or claim brought, or threatened to be brought, against them; or

Members taking action that they we were aware, or ought reasonably to have been aware, might prejudice the successful defence of any action or claim, once the Members had become aware that such an action or claim had been brought or was likely

Annex 3 – Openness

Introduction

1. The Committee on Toxicity (COT) and its sister committees the Committee on Mutagenicity (COM) and Committee on Carcinogenicity (COC) are non-statutory independent scientific advisory committees which advise the Chair of the Food Standards Agency and the Chief Medical Officers (for England, Scotland, Wales and Northern Ireland) and, through them, the Government on a wide range of matters concerning chemicals in food, consumer products and the environment.

2. The Government is committed to make the operation of scientific advisory committees such as the COT/COM/COC hereafter referred to as "the Committee" more open and to increase accountability. The Committee is aware that the disclosure of information that is of a confidential nature and is communicated in circumstances importing an obligation of confidence is subject to the common law of confidentiality. There are some circumstances making disclosure of confidential information lawful for example, where the individual to whom the information relates has consented; where disclosure is in the public interest; and where there is a legal duty to do so. However, guidance is set out in the Freedom of Information Act 2000[7] which gives any person legal rights of access to information which is held by a public authority.

3. The Committee has agreed to hold open meetings as standard practice. Interest groups, consumer organisations etc can attend (subject to the appropriate procedures for handling commercially sensitive information and research not in the public domain, paragraphs 9-15 refer).

4. The Committee appoints lay/public interest member(s) to help to increase public scrutiny of Committee business.

5. The Committee has agreed to the publication of agendas, draft and finalised minutes, discussion papers and statements on the internet.

6. Statements will summarise all the relevant data, such as information regarding potential hazards/risks for human health in respect of the use of products and chemicals, and any recommendations for further research.

7. The Committee will be asked for an opinion based on the data available at the time of consideration. It is recognised that, for many chemicals, the toxicological information is incomplete and that recommendations for further research to address these gaps may form part of the Committee's advice

8. The release of documents (papers, minutes and statements) where the Committee has agreed an opinion on the available unpublished data but where further additional information is required in order to finalise the Committee's conclusions, needs to be considered on a case-by case basis. The relevant considerations include

[7] http://www.direct.gov.uk/en/Governmentcitizensandrights/Yourrightsandresponsibilities/DG_4003239

the likelihood that such additional data would alter the Committee's conclusion, any representations made by a company about, for example, commercial harm that early disclosure could cause and also the public interest in disclosure.

Procedures for handling commercially sensitive information and research data not in the public domain

Background

9. The Committee operates on a presumption of openness. However, it is recognised that the nature of the work will at times provide the Committee access to information that is not in the public domain. Decisions on confidentiality will be exercised consistently with consideration to the Freedom of Information Act 2000 and Environmental Information Regulations 2004.

10. Where there is a need to discuss matters that cannot be put in the public domain the Committee may hold a discussion in "Reserved Business". These items will be generally discussed either at the beginning or the end of an open meeting. It is expected that such cases will be infrequent and only in clearly justified circumstances. For the most part this comprises information which is commercially sensitive such as product formulations/specifications, methods of manufacture, and reports of toxicological investigations and company evaluations and safety assessment. It would also include pre-publication or unpublished research data.

11. "Reserved Business" items will be clearly indicated as such. The Committee will advise its reasons for withholding any information, and, if possible, an indication of when and where the information withheld may be published. Information subject to such restriction, including reserved sections of the minutes will be placed in the public domain as soon as practicable should the restrictions cease to apply at a later date.

12. Normal procedure is to publish a summary of the Committee's advice on their respective websites, in the Annual Report and where necessary to ask companies to release full copies of submitted reports for retention by the British Library at the completion of a review. Given the clear Ministerial commitment to the publication of detailed information regarding the activities of advisory committees, and in particular following the assessment of products which are already available to the general public, the Committee will publish statements via the Internet soon after they have been finalised.

13. Except in cases where there is legislation under which information has been submitted and which deals with disclosure and non-disclosure, the general principle of the common law duty of confidentiality will apply. This means that any information which is commercially sensitive, pre-publication or unpublished research data and has been obtained in circumstances importing a duty of confidence may not be disclosed unless consent has been given or there is an overriding public interest in disclosure (such as the prevention of harm to others).

14. The following procedure will be adopted which allows commercially sensitive information to be identified, assessed and appropriate statements to be drafted and

published on the basis of a prior mutual understanding with the companies. There is scope for companies to make representations also after submission of the information and prior to publication regarding the commercial sensitivity of data supplied and to comment on the text of statements which are to be published. However, companies would not have a right of veto in respect of such statements.

Procedures prior to committee consideration

Initial discussions

15. Upon referral to Committee the Secretariat will liaise with the relevant company supplying the product in the UK to:

i) clearly state the policy of Committee openness (summarised above)

ii) identify and request the information needed by the Committee (e.g. test reports, publications etc).

Commercially sensitive information

iii) The company will be asked to clearly identify any commercially sensitive information and the reason for confidentiality.

Pre-publication and unpublished research data

iv) The Committee and Secretariat will respect the confidentiality of authors of (unpublished or pre-publication) research data.

Handling confidential data

v) The procedures by which the Committee will handle commercially sensitive information, pre-publication or unpublished research data and the public availability of papers, minutes, conclusions and statements where reference is made to such data will be discussed with the company or author prior to submission of papers to the Committee and is outlined in paragraphs 9-15 above. Companies will be informed that confidential annexes to Committee papers (e.g. where detailed information supplied in confidence such as individual patient information and full study reports of toxicological studies) will not be disclosed but that other information will be disclosed unless agreed otherwise with an individual company.

vi) The following is a suggested list of information which **may** be disclosed in Committee documents (papers, minutes and statements). The list is not exhaustive and is presented as a guide:
   a) name of product (or substance/chemical under consideration),
   b) information on physico-chemical properties,
   c) methods of rendering harmless,
   d) a summary of the results and evaluation of the results of tests to establish harmlessness to humans,

e) methods of analysis,
f) first aid and medical treatment to be given in the case of injury to persons,
g) surveillance data (e.g. monitoring for levels in food, air, or water).

Procedures during and after Committee consideration

vii) The timing of release of Committee documents (papers, minutes and statements) where the item of business involved the consideration of confidential data would be subject to the general provisions outlined in paragraphs 9-15 above. Documents would not be released until the Committee statement is available.

viii) The most important outcome of the Committee consideration is likely to be the agreed statement. Companies will be given an opportunity to comment on the statement prior to publication and to make representations (for example, as to commercial sensitivities in the statement). The Chair would be asked to consider any comments provided, but companies would not be able to veto the publication of a statement or any part of it. Companies will continue to be asked to release full copies of submitted reports for retention by the British Library at the completion of a review.

Dissenting views

16. The Committee should not seek consensus at the risk of failing to recognise different views on a subject. Any significant diversity of opinion among the members of the Committee that cannot be resolved should be accurately reflected in the minutes or report. Committee decisions should always include an explanation of where differences of opinion have arisen during discussions, specifically where there are unresolved issues and why conclusions have been reached. If however member(s) feel they cannot support the Committee conclusions they may declare a 'minority report' identifying which member(s) are making the minority report and setting out their position.

COC/COM/COT papers

17. Committee papers are available on the respective website. Papers will not include commercially sensitive documents, pre-publication, unpublished or material in the public domain. Where possible a cover page with weblinks (current at the time) will be provided.

Remuneration and Committee finance

18. The COT has no independent budget or expenditure. In the financial year 2009/10 the FSA allowed £80,000.00, excluding Secretariat resources for the operation of the COT.

19. Committee members may claim a fee for Committee meetings:

COC and COM Committee Chair £198 per day
COC and COM Committee Member £153 per day
COT Committee Chair £196.38 per day
COT Committee Member £153.64 per day

From1 October 2009:
COT Committee Chair £205 per day
COT Committee Member £160 per day

Where COT members are unable to attend a meeting but contribute in writing, a £50.00 reading fee is paid.

Review of fee rates

20. Fees in respect of the COT are set by the FSA and for COC and COM by the Department of Health. The FSA will review and revise COT rates every 2 years with the intention that rates should rise in line with the recommendations of the Senior Salaries Review Board with regard to pay in the Senior Civil Service. The FSA will also take into account comparisons with rates paid in similar advisory bodies in the UK. The next revision in rates will take effect from 1 October 2011.

Travel and other expenses

21. Committee members are entitled to reimbursement of reasonable travel and subsistence expenses necessarily incurred on official committee business. Members must seek value for money and are encouraged to use the most cost effective and environmentally sustainable options for travel and accommodation.

Working Groups

22. The Committee may establish Working Groups to consider particular topics in depth or to make brief assessments of particular issues and advise the main Committee on the possible need for further action. Such Groups contain a number of Committee members (supplemented, as necessary, by external expertise in the particular subject being considered). A Committee Chair will play a leading role in deciding which Committee members should be invited to join such groups, which may meet on a number of occasions in a particular year. Committee members may claim an allowance for participating on a Working Group.

Terms and conditions of appointment

23. Appointments of members may be staggered so that only a proportion retire or are re-appointed each year, to help ensure continuity. (Note: The COC/COM/COT Chairs are *ex officio* members of General Advisory Committee on Science (GACS) for the term of their appointment as the COC/COM/COT Chair. COC and COM Chairs are *ex officio* members of each other's Committees.)

24. COC and COM members are usually expected to attend 3 meetings a year. COT members are expected to attend 7 meetings a year. Members should allow appropriate preparation time. Meetings will usually be in London but may also be held in other parts of the UK.

25. The COC/COM/COT Chair must also be available for a number of other activities including: attending, with the FSA Chief Scientist, the FSA Board's annual discussion of the Agency's science; engaging with the media on any high-profile relating to the Committee's work, and discussion with the Agency Chief Scientist and GACS Secretariat in planning and developing the Committee's work (including discussing and agreeing with the Agency's Chief Scientist a framework for providing assurance on the work of the Scientific Advisory Committees in providing advice to the Agency). It is expected that these additional activities might require 5-10 days input per year.

Feedback on performance

26. The COT Chair and members are asked to provide brief feedback on their experience on the committee each year to help the Agency ensure that the Committee operates effectively and identify any areas for improvement.

27. Committee members are normally appointed for a term of 3 years (a maximum 10 years/3 terms per member). The COT uses a feedback self assessment form as one of the tools used to determine whether or not a committee member should be re-appointed at the end of their (3 year) term.

Annex 4 – Good Practice Agreement for Scientific Advisory Committees

Introduction

1. *Guidelines 2000: Scientific Advice and Policy Making*[1] set out the basic principles which government departments should follow in assembling and using scientific advice, thus:
   - think ahead, identifying the issues where scientific advice is needed at an early stage;
   - get a wide range of advice from the best sources, particularly where there is scientific uncertainty; and
   - publish the scientific advice they receive and all the relevant papers.

2. The *Code of Practice for Scientific Advisory Committees*[2] (revised in December 2007) provided more detailed guidance specifically focused on the operation of scientific advisory committees (SACs). The Agency subsequently commissioned a *Report on the Review of Scientific Committees*[3] to ensure that the operation of its various advisory committees was consistent with the remit and values of the Agency, as well as the Code of Practice.

3. The Food Standards Agency's Board has adopted a **Science Checklist** to make explicit the points to be considered in the preparation of papers dealing with science-based issues which are either assembled by the Executive or which draw on advice from the Scientific Advisory Committees.

4. Scientists who serve on a scientific advisory committee which advises the Agency are expected to comply with the **Universal Ethical Code** for Scientist, launched by the Government's Chief Scientific Adviser in March 2007.

5. The Board welcomed a proposal from the Chairs of the independent SACs to draw up Good Practice Guidelines based on, and complementing, the Science Checklist.

6. These Guidelines have been developed by nine advisory committees:

Advisory Committee on Animal Feedingstuffs[4]
Advisory Committee on Microbiological Safety of Foods
Advisory Committee on Novel Foods and Processes
Advisory Committee on Research (disbanded in 2007)
Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment[5]
Committee on Mutagenicity of Chemicals in Food, Consumer

[1] Guidelines on Scientific Analysis in Policy Making, OST, October 2005. Guidelines 2000: Scientific advice and policy-making. OST July 2000
[2] Code of Practice for Scientific Advisory Committees, OST December 2001
[3] Report on the Review of Scientific Committees, FSA, March 2002
[4] Joint FSA/Defra Secretariat, FSA lead
[5] Joint FSA/HPA Secretariat, HPA lead

Products and the Environment[6]
Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment[7]
Scientific Advisory Committee on Nutrition[8]
Spongiform Encephalopathy Advisory Committee[9]

7. These committees share important characteristics. They:
   - are independent;
   - work in an open and transparent way; and
   - are concerned with risk assessment not risk management.

8. The Guidelines relate primarily to the risk assessment process since this is the committees' purpose. However, the Agency may wish on occasion to ask the independent scientific advisory committees whether a particular risk management option is consistent with their risk assessment.

9. Twenty seven principles of good practice have been developed. However, the different committees have different duties and discharge those duties in different ways. Therefore, not all of the principles set out below will be applicable to all of the committees, all of the time.

10. This list of principles will be reconsidered by each committee annually as part of the preparation of its Annual report, and will be attached as an Annex to it.

Principles

Defining the issue

1. The FSA will ensure that the issue to be addressed is clearly defined and takes account of stakeholder expectations. The committee Chair will refer back to the Agency if discussion suggests that a re-definition is necessary.

Seeking input

2. The Secretariat will ensure that stakeholders are consulted at appropriate points in the committee's considerations and, wherever possible, SAC discussions should be held in public.

3. The scope of literature searches made on behalf of the committee will be clearly set out.

4. Steps will be taken to ensure that all available and relevant scientific evidence is rigorously considered by the committee, including consulting external/additional scientific experts who may know of relevant unpublished or pre-publication data.

[6] Joint FSA/HPA Secretariat, HPA lead
[7] Joint FSA/HPA, FSA lead
[8] Joint FSA/DH Secretariat
[9] Joint Defra/FSA/DH Secretariat

5. Data from stakeholders will be considered and weighted according to quality by the committee.

6. Consideration by the secretariat and the Chair will be given to whether expertise in other disciplines will be needed.

7. Consideration will be given by the Secretariat or by the committee to whether other scientific advisory committees need to be consulted.

Validation

8. Study design, methods of measurement and the way that analysis of data has been carried out will be assessed by the committee.

9. If qualitative data have been used, they will be assessed by the committee in accordance with the principles of good practice, e.g. set out in guidance from the Government's Chief Social Researcher[10].

10. Formal statistical analyses will be included wherever possible. To support this, each committee will have access to advice on quantitative analysis and modelling as needed.

11. When considering what evidence needs to be collected for assessment, the following points will be considered:
    - the potential for the need for different data for different parts of the UK or
    - the relevance to the UK situation for any data originating outside the UK; and
    - whether stakeholders can provide unpublished data.

12. The list of references will make it clear which references have either not been subject to peer review or where evaluation by the committee itself has conducted the peer review.

Uncertainty

13. When reporting outcomes, committees will make explicit the level and type of uncertainty (both limitations on the quality of the available data and lack of knowledge) associated with their advice.

14. Any assumptions made by the committee will be clearly spelled out, and, in reviews, previous assumptions will be challenged.

15. Data gaps will be identified and their impact on uncertainty assessed by the committee.

[10] There is of guidance issued under the auspices of the Government's Social Research Unit and the Chief Social Researcher's Office (Quality in Qualitative Evaluation: A Framework for assessing research evidence. August 2003. www.strategy.gov.uk/downloads/su/qual/downloads/qqe-rep.pdf and The Magenta Book. www.gsr.gov.uk/professional_guidance/magenta_book/guidance.asp).

16. An indication will be given by the committee about whether the database is changing or static.

Drawing conclusions

17. The committee will be broad-minded, acknowledging where conflicting views exist and considering whether alternative hypotheses fit the same evidence.

18. Where both risks and benefits have been considered, the committee will address each with the same rigour.

19. Committee decisions will include an explanation of where differences of opinion have arisen during discussions, specifically where there are unresolved issues and why conclusions have been reached.

20. The committee's interpretation of results, recommended actions or advice will be consistent with the quantitative and/or qualitative evidence and the degree of uncertainty associated with it.

21. Committees will make recommendations about general issues that may have relevance for other committees.

Communicating committees' conclusions

22. Conclusions will be expressed by the committee in clear, simple terms and use the minimum caveats consistent with accuracy.

23. It will be made clear by the committee where assessments have been based on the work of other bodies and where the committee has started afresh, and there will be a clear statement of how the current conclusions compare with previous assessments.

24. The conclusions will be supported by a statement about their robustness and the extent to which judgement has had to be used.

25. As standard practice, the committee secretariat will publish a full set of references (including the data used as the basis for risk assessment and other committee opinions) at as early a stage as possible to support openness and transparency of decision-making. Where this is not possible, reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

26. The amount of material withheld by the committee or FSA as being confidential will be kept to a minimum. Where it is not possible to release material, the reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

27. Where proposals or papers being considered by the Board rest on scientific evidence, the Chair of the relevant scientific advisory committee (or a

nominated expert member) will be invited to the table at Open Board meetings to provide this assurance and to answer Members' questions on the science. To maintain appropriate separation of risk assessment and risk management processes, the role of the Chairs will be limited to providing an independent view on how their committee's advice has been reflected in the relevant policy proposals. The Chairs may also, where appropriate, be invited to provide factual briefing to Board members about particular issues within their committees' remits, in advance of discussion at open Board meetings.

Universal Ethical Code for Scientists

The Universal Ethical Code for Scientists, developed by the Government Chief Scientific Adviser, is a public statement of the values and responsibilities of scientists. The term 'scientists' means anyone whose work uses scientific methods, including social, natural, medical and veterinary sciences, engineering and mathematics.

Rigour, respect and responsibility: A universal ethical code for scientists

Rigour, honesty and integrity

- Act with skill and care in all scientific work. Maintain up to date skills and assist their development in others.
- Take steps to prevent corrupt practices and professional misconduct. Declare conflicts of interest.
- Be alert to the ways in which research derives from and affects the work of other people, and respect the rights and reputations of others.

Respect for life, the law and the public good

- Ensure that your work is lawful and justified.
- Minimise and justify any adverse effect your work may have on people, animals and the natural environment.

Responsible communication: listening and informing

- Seek to discuss the issues that science raises for society. Listen to the aspirations and concerns of others.
- Do not knowingly mislead, or allow others to be misled, about scientific matters. Present and review scientific evidence, theory or interpretation honestly and accurately.

You can read the full version of the Code at:
http://www.food.gov.uk/science/researchpolicy/commswork/ethcode

Annex 5 – Glossary of Terms

a priori: The formulation of a hypothesis before undertaking an investigation or experiment.

Absorption (biological): Process of active or passive transport of a substance into an organism, in humans this is usually through the lungs, gastrointestinal tract or skin

Acceptable Daily Intake (ADI): Estimate of the amount of a substance in food or drink, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime by humans without appreciable health risk.

Acceptable Risk: Probability of suffering disease or injury which is considered to be sufficiently small to be "negligible"

Acute: Short term, in relation to exposure or effect.

Acute reference dose (ARfD): Estimate of the amount of a substance in food or drink, expressed on a body weight basis, that can be ingested in a period of 24 hours or less without appreciable health risk.

Acute toxicity: Adverse effects that occur over a short period of time (up to 14 days) immediately following exposure.

Adduct: A chemical grouping which is covalently bound (see covalent binding) to a large molecule such as DNA (qv) or protein.

Adenoma: A benign neoplasm arising from a gland forming epithelial tissue such as colon, stomach or respiratory tract.

Adverse effect: Change in morphology, physiology, biochemistry, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences.

Aetiology: study of causation or origination

Ah receptor: The Ah (Aromatic hydrocarbon) receptor protein regulates some specific gene expressions associated with toxicity. The identity of the natural endogenous chemicals which bind to the Ah receptor is unknown. Binding to the Ah receptor is an integral part of the toxicological mechanism of a range of chemicals, such as chlorinated dibenzodioxins and polychlorinated biphenyls.

Alkylating agents: Chemicals which leave an alkyl group covalently bound to biologically important molecules such as proteins and nucleic acids (see adduct). Many alkylating agents are mutagenic, carcinogenic and immunosuppressive.

Allele: Alternative form of a gene.
Allergen: Substance capable of stimulating an allergic reaction.

Allergy: The adverse health effects that may result from the stimulation of a specific immune response.

Allergic reaction: an adverse reaction elicited by exposure to a previously sensitised individual to the relevant antigen.

Ames test: *In vitro* (qv) assay for bacterial gene mutations (qv) using strains of *Salmonella typhimurium* developed by Ames and his colleagues.

Androgen: The generic term for any natural or synthetic compound that can interact with and activate the androgen receptor. In mammals, androgens (for example, androstenedione and testosterone) are synthesised by the adrenal glands and the testes and promote development and maintenance of male secondary sexual characteristics.

Aneugenic: Inducing aneuploidy (qv).

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

Apoptosis: A form of active cell death resulting in fragmentation of the cell into membrane-bound fragments (apoptotic bodies). These are usually rapidly removed *in vivo* by engulfment by phagocytic cells. Apoptosis can occur normally during development, but is often triggered by toxic stimuli.

Base pair (bp): Two complementary nucleotide (qv) bases joined together by chemical bonds.

Benchmark dose (BMD) modelling: An approach to dose-response assessment that aims to be more quantitative than the NOAEL process. This approach constructs mathematical models to fit all data points in the dose-response study and uses the best fitting model to interpolate an estimate of the dose that corresponds to a particular level of response (a benchmark response), often 10%. A measure of uncertainty is also calculated, and the lower confidence limit on the benchmark dose is called the BMDL. The BMDL accounts for the uncertainty in the estimate of the dose-response that is due to characteristics of the experimental design such as sample size. The BMDL can be used as the point of departure for derivation of a health-based guidance value or a margin of exposure.

Bias: In the context of epidemiological studies, an interference which at any stage of an investigation tends to produce results that depart systematically from the true values (to be distinguished from random error). The term does not necessarily carry an imputation of prejudice or any other subjective factor such as the experimenter's desire for a particular outcome.

Bioavailability: A term referring to the proportion of a substance which reaches the systemic circulation unchanged after a particular route of administration.

Bioinformatics: The science of informatics as applied to biological research. Informatics is the management and analysis of data using advanced computing techniques. Bioinformatics is particularly important as an adjunct to genomics research, because of the large amount of complex data this research generates.

Biomarker: Observable change (not necessarily pathological) in an organism, related to a specific exposure or effect.

Body burden: Total amount of a chemical present in an organism at a given time.

Bradford Hill Criteria: Sir Austin Bradford-Hill established criteria that may be used to assist in the interpretation of associations reported from epidemiological studies:-

- Strength – The stronger the association the more likely it is causal. The COC has previously noted that the relative risks of <3 need careful assessment for effects of bias or confounding.
- Consistency – The association has been consistently identified by studies using different approaches and is also seen in different populations with exposure to the chemical under consideration.
- Specificity – Limitation of the association to specific exposure groups or to specific types of disease increases likelihood that the association is causal.
- Temporality – The association must demonstrate that exposure leads to disease. The relationship of time since first exposure, duration of exposure and time since last exposure are all important in assessing causality.
- Biological gradient – If an association reveals a biological gradient or dose-response curve, then this evidence is of particular importance in assessing causality.
- Plausibility – Is there appropriate data to suggest a mechanism by which exposure could lead to concern? However, even if an observed association may be new to science or medicine it should not be dismissed.
- Coherence – Cause and effect interpretation of data should not seriously conflict with generally known facts.
- Experiment – Can the association be demonstrated? Evidence from experimental animals may assist in some cases. Evidence that removal of the exposure leads to a decrease in risk may be relevant.
- Analogy – Have other closely related chemicals been associated with the disease?

Bronchial: Relating to the air passages conducting air from the trachea (windpipe) to the lungs.

C. elegans: *Caenorhabditis elegans*, a nematode or roundworm, the first animal to have its genome completely sequenced and all the genes fully characterised.

Cancer: Synonym for a malignant neoplasm – that is, a tumour (qv) that grows progressively, invades local tissues and spreads to distant sites (see also tumour and metastasis).

Candidate gene: A gene that has been implicated in causing or contributing to the development of a particular disease.

Carcinogenesis: The origin, causation and development of tumours (qv). The term applies to benign as well as malignant neoplasms and not just to carcinomas (qv).

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

Carcinogen: 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 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 active 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 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').

Case-control study: (Synonyms - case comparison study, case referent study, retrospective study) A comparison is made of the proportion of cases who have been exposed to a particular hazard (e.g. a carcinogen) with the proportion of controls who have been exposed to the hazard.

Cell 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. 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 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.

Chromosomal aberrations: Collective term of particular types of chromosome damage induced after exposure to exogenous chemical or physical agents which damage the DNA. (see clastogen).

Chromosome: In simple prokaryotic organisms, such as bacteria and most viruses, the chromosome consists of a single circular molecule of DNA containing the entire genetic material of the cell. In eukaryotic cells, the chromosomes are thread-like structures, composed mainly of DNA and protein, which are present within the nuclei of every cell. They occur in pairs, the numbers varying from one to more than 100 per nucleus in different species. Normal somatic cells in humans have 23 pairs of chromosomes, each consisting of linear sequences of DNA which are known as genes (qv).

Chronic effect: Consequence which develops slowly and has a long-lasting course (often but not always irreversible).

Chronic exposure: Continued exposures occurring over an extended period of time, or a significant fraction of the life-time of a human or test animal.

Clastogen: An agent that produces chromosome breaks and other structural aberrations such as translocations. Clastogens may be viruses or physical agents as well as chemicals. Clastogenic events play an important part in the development of some tumours.

Clearance: Volume of blood or plasma, or mass of an organ, effectively cleared of a substance by elimination (metabolism and excretion) in a given time interval. Total clearance is the sum or the clearances for each eliminating organ or tissue.

Clone: A term which is applied to genes, cells, or entire organisms which are derived from - and are genetically identical to - a single common ancestor gene, cell, or organism, respectively. Cloning of genes and cells to create many copies in the laboratory is a common procedure essential for biomedical research.

Coding regions: those parts of the DNA that contain the information needed to form proteins. Other parts of the DNA may have non-coding functions (e.g. start-stop, pointing or timer functions) or as yet unresolved functions or maybe even ‘noise’.

Codon: a set of three nucleotide bases in a DNA or RNA sequence, which together code for a unique amino acid.

Cohort: A defined population that continues to exist through time.

Cohort study: (Synonyms - follow-up, longitudinal study) The study of a group of people defined at a particular point in time (the cohort), who have particular characteristics in common, such as a particular exposure. They are then observed over a period of time for the occurrence of disease. The rate at which the disease develops in the cohort is compared with the rate in a comparison population, in which the characteristics (e.g. exposure) are absent.

Complementary DNA (cDNA): cDNA is DNA that is synthesised in the laboratory from mRNA by reverse transcription. A cDNA is so-called because its sequence is the complement of the original mRNA sequence.

Confounding variable: (synonym - confounder) An extraneous variable that satisfies BOTH of 2 conditions: (1) it is a risk factor for the disease under study (2) it is associated with the study exposure but is not a consequence of exposure. For example cigarette smoking is a confounding variable with respect to an association between alcohol consumption and heart disease. Failure to adjust for a confounding variable results in distortion of the apparent magnitude of the effect of the exposure under study. (In the example, smoking is a risk factor for heart disease and is associated with alcohol consumption but is not a consequence of alcohol consumption.)

Congeners: Related compounds varying in chemical structure but with similar biological properties.

Covalent binding: Chemical bonding formed by the sharing of an electron pair between two atoms. Molecules are combinations of atoms bound together by covalent bonds.

Cytochrome P450 (CYP): An extensive family of haem-containing proteins involved in enzymic oxidation of a wide range of endogenous and xenobiotic (qv) substances and their conversion to forms that may be more easily excreted. In some cases the metabolites produced may be reactive and may have increased toxicity. In other cases the substances may be natural precursors of hormones (e.g. steroids).

Cytogenetic: Concerning chromosomes, their origin, structure and function.

Deletion: A chromosomal aberration in which a proportion of the chromosome is lost. Deletions may range in size from a single nucleotide (qv) to an entire chromosome. Such deletions may be harmless, may result in disease, or may in rare cases be beneficial.

DNA (Deoxyribonucleic 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 (qv).

DNA probe: A piece of single-stranded DNA, typically labelled so that it can be detected (for example, a radioactive or fluorescent label can be used), which can single out and bind with (and only with) another specific piece of DNA. DNA probes can be used to determine which sequences are present in a given length of DNA or which genes are present in a sample of DNA.

DNA repair genes: Genes which code for proteins that correct damage in DNA sequences. When these genes are altered, mutations may be able to accumulate in the genome, ultimately resulting in disease.

Dominant lethal assay: See Dominant Lethal mutation.

Dominant lethal mutation: A dominant mutation that causes death of an early embryo.

Dose: Total amount of a substance administered to, taken or absorbed by an organism.

Endocrine modulator (synonym – endocrine disruptor): A chemical, which can be naturally occurring or man-made, that causes adverse health effects in an organism, as a result of changes in hormonal function.

Endonuclease: An enzyme that cleaves its nucleic acid substrate at internal sites in the nucleotide sequence.

Enterohepatic circulation: Cyclical process involving intestinal re-absorption of a substance that has been excreted through bile followed by transfer back to the liver, making it available for biliary excretion again.

Epidemiology: Study of factors determining the causes, frequency, distribution, and control of diseases in a human population.

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

Erythema: Reddening of the skin due to congestion of blood or increased blood flow in the skin.

Erythrocyte: Red blood cell.

Estrogen: Sex hormone or other substance capable of developing and maintaining female characteristics of the body.

Exogenous: Arising outside the body.

Exposure Assessment: Process of measuring or estimating concentration or intensity, duration and frequency of exposure to an agent present in the environment.

Fibrosarcoma: A malignant tumour arising from connective tissue (see 'tumour').

Fluorescence In-Situ Hybridisation: A technique which allows individual chromosomes and their centromeres to be visualised in cells.

Fetotoxic: Causing toxic, potentially lethal effects to the developing fetus.

Forestomach: (See glandular stomach).

Full gene sequence: the complete order of bases in a gene. This order determines which protein a gene will produce.

Gavage: Administration of a liquid via a stomach tube, commonly used as a dosing method in toxicity studies.

Gene: The functional unit of inheritance: a specific sequence of nucleotides along the DNA molecule, forming part of a chromosome (qv).

Gene expression: The process by which the information in a gene is used to create proteins or polypeptides.

Gene families: Groups of closely related genes that make similar products.

Gene product: The protein or polypeptide coded for by a gene.

Genetic engineering: Altering the genetic material of cells or organisms in order to make them capable of making new substances or performing new functions.

Genetic polymorphism: a difference in DNA sequence among individuals, groups, or populations (e.g. a genetic polymorphism might give rise to blue eyes versus brown eyes, or straight hair versus curly hair). Genetic polymorphisms may be the result of chance processes, or may have been induced by external agents (such as viruses or radiation). Changes in DNA sequence which have been confirmed to be caused by external agents are generally called “mutations” rather than “polymorphisms”.

Genetic predisposition: susceptibility to a disease which is related to a polymorphism, which may or may not result in actual development of the disease.

Genetically modified organism (GMO): An organism which has had genetic material inserted into, or removed from, its cells.

Genome: All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs.

Genomic DNA: The basic chromosome set consisting of a species-specific number of linkage groups and the genes contained therein.

Genomics: The study of genes and their function.

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

Genotype: The particular genetic pattern seen in the DNA of an individual. “Genotype” is usually used to refer to the particular pair of alleles that an individual possesses at a certain location in the genome. Compare this with phenotype.

Glandular stomach: The stomach in rodents consists of two separate regions - the forestomach and the glandular stomach. Only the glandular stomach is directly comparable to the human stomach.

Half-life: Time in which the concentration of a substance will be reduced by half, assuming a first order elimination process.
Hazard: Set of inherent properties of a substance, mixture of substances or a process involving substances that make it capable of causing adverse effects to organisms or the environment.

Hepatic: Pertaining to the liver.

Hepatocyte: The principal cell type in the liver, possessing many metabolising enzymes (see 'metabolic activation').

Hepatotoxic: Causing toxicity to the liver.

Horizon Scanning: The systematic examination of potential threats, opportunities and likely future developments, which are at the margins of current thinking and planning. Horizon scanning may explore novel and unexpected issues, as well as persistent problems and trends. Overall, horizon scanning is intended to improve the robustness of policies and the evidence base

Human Genome Project: An international research effort aimed at discovering the full sequence of bases in the human genome, led in the UK by the Wellcome Trust and Medical Research Council.

Hyperplasia: An increase in the size of an organ or tissue due to an increase in the number of cells.

Hypertrophy: An increase in the size of an organ or tissue due to an increase in the volume of individual cells within it.

Idiosyncrasy: Specific (and usually unexplained) reaction of an individual to e.g. a chemical exposure to which most other individuals do not react at all. General allergic reactions do not fall into this category.

***In situ* hybridisation (ISH)**: Use of a DNA or RNA probe to detect the presence of the complementary DNA sequence in cloned bacterial or cultured eukaryotic cells.

***In vitro**:* A Latin term used to describe effects in biological material outside the living animal (literally “in glass”).

***In vivo**:* A Latin term used to describe effects in living animals (literally “in life”).

Incidence: Number of new cases of illness occurring during a given period in a specific population.

Inducing agent: A chemical which, when administered to an animal, causes an increase in the expression of a particular enzyme. For example, chlorinated dibenzodioxins are inducing agents which act via the Ah-receptor (qv) to induce cytochrome P450 (qv) CYP1A1.

Intraperitoneal: Within the abdominal cavity.

Isomer: Isomers are two or more chemical compounds with the same molecular formula but having different properties owing to a different arrangement of atoms within the molecule. The ß-isomer of alitame is formed when the compound degrades and the atoms within the molecule are rearranged.

kilobase (kb): A length of DNA equal to 1000 nucleotides.

Knockout animals: Genetically engineered animals in which one or more genes, usually present and active in the normal animal, are absent or inactive.

LD50: The dose of a toxic compound that causes death in 50% of a group of experimental animals to which it is administered. It can be used to assess the acute toxicity of a compound, but is being superseded by more refined methods.

Leukaemia: A group of neoplastic disorders (see tumour) affecting blood-forming elements in the bone marrow, characterised by uncontrolled proliferation and disordered differentiation or maturation. Examples include the lymphocytic leukaemia's which develop from lymphoid cells and the myeloid leukaemia's which are derived from myeloid cells (producing red blood cells, mainly in bone marrow).

Ligand: A molecule which binds to a receptor.

Lipids: Fats, substances containing a fatty acid and soluble in alcohols or ether, but insoluble in water.

Lipophilic: 'Lipid liking' - a substance which has a tendency to partition into fatty materials.

Lymphocyte: A type of white blood cell that plays central roles in adaptive immune responses.

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').

Malignancy: See 'tumour'.

Margin of exposure (MOE) approach: A methodology that allows the comparison of the risks posed by different genotoxic and carcinogenic substances. The MOE approach uses a reference point, often taken from an animal study and corresponding to a dose that causes a low but measurable response in animals. This reference point is then compared with various dietary intake estimates in humans, taking into account differences in consumption patterns.

Messenger RNA (mRNA): The DNA of a gene is transcribed (see transcription) into mRNA molecules, which then serve as a template for the synthesis of proteins.

Meta-analysis: In the context of epidemiology, a statistical analysis of the results from independent studies, which aims to produce a single estimate of an effect.

Metabolic activation: Metabolism of a compound leading to an increase in its activity, whether beneficial (e.g. activation of a pro-drug) or deleterious (e.g. activation to a toxic metabolite).

Metabolic activation system: A cell-free preparation (e.g. from the livers of rats pre-treated with an inducing agent (qv)) added to *in vitro* tests to mimic the metabolic activation typical of mammals.

Metabolism: Chemical modification of a compound by enzymes within the body, for example by reactions such as hydroxylation (see cytochrome P450), epoxidation or conjugation. Metabolism may result in activation, inactivation, accumulation or excretion of the compound.

Metabolite: Product formed by metabolism of a compound.

Metabonomics: Techniques available to identify the presence and concentrations of metabolites in a biological sample.

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 chromosomal aberrations (qv) - known as metaphase analysis.

Metastasis: The process whereby malignant cells become detached from the primary tumour mass, disseminate (mainly in the blood stream or in lymph vessels) and 'seed out' in distant sites where they form secondary or metastatic tumours. Such tumours tend to develop at specific sites and their anatomical distribution is often characteristic; it is non-random.

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. Centromere positive micronuclei contain DNA and/or protein material derived from the centromere. The presence of centromere positive micronuclei following exposure to chemicals can be used to evaluate the aneugenic (qv) potential of chemicals.

Micronucleus test: See Micronuclei.

Mitogen: A stimulus which provokes cell division in somatic cells.

Mitosis: The type of cell division which occurs in somatic cells when they proliferate. Each daughter cell has the same complement of chromosomes as the parent cell.

Mouse lymphoma assay: An *in vitro* assay for gene mutation 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 mutations within the gene and small, which represent 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.

Mouse spot test: An *in vivo* test for mutation, in which pregnant mice are dosed with the test compound and mutations are detected by changes (spots) in coat colour of the offspring. Mutations in the melanocytes (skin pigment cells) of the developing fetus are measured.

Mucosal: Regarding the mucosa or mucous membranes, consisting of epithelium (qv) containing glands secreting mucus, with underlying layers of connective tissue and muscle.

Murine: Often taken to mean “of the mouse”, but strictly speaking means of the Family Muridae which includes rats and squirrels.

Mutagen: is a physical or chemical agent that changes the genetic information (usually DNA) of an organism

Mutation: A permanent change in the amount or structure of the genetic material in an organism or cell, which can result in a change in phenotypic characteristics. The alteration 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 descendent daughter cells.

Mycotoxin: Toxic compound produced by a fungus.

Neoplasm: See 'tumour'.

Neoplastic: Abnormal cells, the growth of which is more rapid that that of other cells.

Nephrotoxicity: Toxicity to the kidney.

Neurobehavioural: Of behaviour determined by the nervous system.

Neurotoxicity: Toxicity to the nervous system.

No observed adverse effect level (NOAEL): The highest administered dose at which no adverse (qv) effect has been observed.

Non-genotoxic: See 'carcinogens'.

Non-Hodgkin lymphomas: (NHLs) are a diverse group of hematologic cancers which encompass any lymphoma other than Hodgkin’s Lymphoma

Nucleic acid: One of the family of molecules which includes the DNA and RNA molecules. Nucleic acids were so named because they were originally discovered within the nucleus of cells, but they have since been found to exist outside the nucleus as well.

Nucleotide: the "building block" of nucleic acids, such as the DNA molecule. A nucleotide consists of one of four bases - adenine, guanine, cytosine, or thymine - attached to a phosphate-sugar group. In DNA the sugar group is deoxyribose, while in RNA (a DNA-related molecule which helps to translate genetic information into proteins), the sugar group is ribose, and the base uracil substitutes for thymine. Each group of three nucleotides in a gene is known as a codon. A nucleic acid is a long chain of nucleotides joined together, and therefore is sometimes referred to as a "polynucleotide."

Null allele: inactive form of a gene.

Odds ratio (OR): The odds of disease in an exposed group divided by the odds of disease in an unexposed group.

OECD: Organisation for Economic Cooperation and Development

Oedema: Excessive accumulation of fluid in body tissues.

Oestrogen: (See estrogen)

Oligonucleotide: A molecule made up of a small number of nucleotides, typically fewer than 25.

Oncogene: A gene which is associated with the development of cancer (see proto-oncogene).

Organochlorine: A group of chemical compounds, containing multiple chlorine atoms, that are usually of concern as environmental pollutants. Some organochlorines have been manufactured as pesticides or coolants and others arise as contaminants of manufacturing processes or incineration.

Pharmacokinetics: Description of the fate of drugs in the body, including a mathematical account of their absorption, distribution, metabolism and excretion (see toxicokinetics).

Pharmacogenomics: The science of understanding the correlation between an individual patient's genetic make-up (genotype) and their response to drug treatment. Some drugs work well in some patient populations and not as well in others. Studying the genetic basis of patient response to therapeutics allows drug developers to design therapeutic treatments more effectively.

Phenotype: The observable physical, biochemical and physiological characteristics of a cell, tissue, organ or individual, as determined by its genotype and the environment in which it develops.

Phytoestrogen: Any plant substance or metabolite that induces biological responses in vertebrates and can mimic or modulate the actions of endogenous estrogens usually by binding to estrogen receptors.

Plasmid: A structure composed of DNA that is separate from the cell's genome (qv). In bacteria, plasmids confer a variety of traits and can be exchanged between

individuals- even those of different species. Plasmids can be manipulated in the laboratory to deliver specific genetic sequences into a cell.

Plasticiser: A substance which increases the flexibility of certain plastics.

Polymer: A very large molecule comprising a chain of many similar or identical molecular sub units (monomers) joined together (polymerised). An example is the polymer glycogen, formed from linked molecules of the monomer glucose.

Polymerase chain reaction (PCR): A method for creating millions of copies of a particular segment of DNA. PCR can be used to amplify the amount of a particular DNA sequence until there are enough copies available to be detected.

Polymorphism: (see genetic polymorphism)

^{32}P postlabelling: A sensitive experimental method designed to measure low levels of DNA adducts induced by chemical treatment.

Prevalence: The number of cases of a disease that are present in a population at a given time.

Primer: Short pre-existing polynucleotide chain to which new deoxyribonucleotides can be added by DNA polymerase.

Proteomics: The determination of the function of all of the proteins encoded by the organism's entire genome.

Proto-oncogene: One of a group of normal genes which are concerned with the control of cellular proliferation and differentiation. They can be activated in various ways to forms (oncogenes) which are closely associated with one or more steps in carcinogenesis. Activating agents include chemicals and viruses. The process of proto-oncogene activation is thought to play an important part at several stages in the development of tumours.

Receptor: A small, discrete protein in the cell membrane or within the cell with which specific molecules interact to initiate a change in the working of a cell.

Recombinant DNA: DNA molecules that have been created by combining DNA more than one source.

Reference nutrient intake (RNI): An amount of the nutrient that is enough, or more than enough, for most (usually at least 97%) of people in a group. If the average intake of a group is at the RNI, then the risk of deficiency in the group is very small.

Regulatory gene: A gene which controls the protein-synthesising activity of other genes.

Relative risk: A measure of the association between exposure and outcome. The rate of disease in the exposed population divided by the rate of disease among the unexposed population in a cohort study or a population-based case control study. A

relative risk of 2 means that the exposed group has twice the disease risk compared to the unexposed group.

Renal: Relating to the kidney.

Reporter gene: A gene that encodes an easily assayed product that is coupled to the upstream sequence of another gene and transfected (qv) into cells. The reporter gene can then be used to see which factors activate response elements in the upstream region of the gene of interest.

Risk: Possibility that a harmful event (death, injury or loss) arising from exposure to a chemical or physical agent may occur under specific conditions.

Risk Assessment: process of evaluating a potential hazard, likelihood of suffering, or any adverse effects from certain human activities

Risk Management: process designed to identify, contain, reduce, or eliminate the potential for harm to the human population; usually concerned with the delivery system and site rather than performance.

RNA (ribonucleic acid): a molecule similar to DNA (qv), which helps in the process of decoding the genetic information carried by DNA.

SAHSU: Small Area Health Statistics Unit

Safety: Practical certainty that injury will not result from a hazard under defined conditions.

SCF: The European Commission's Scientific Committee on Food (formerly the Scientific Committee for Food).

Single nucleotide polymorphism (SNP): DNA sequence variations that occur when a single nucleotide in the genome sequence is altered. For example, a SNP might change the DNA sequence A**A**GGCTAA to A**T**GGCTAA. By convention, SNPs occur in at least 1% of the population.

Sister chromatid exchange (SCE): Exchange of genetic material between two sub-units of a replicated chromosome.

Stakeholder: A person or organisation representing the interests and opinions of a group with an interest in the outcome of (for example) a review or policy decision.

Suppressor gene: A gene which helps to reverse the effects of damage to an individual's genetic material, typically effects which might lead to uncontrolled cell growth (as would occur in cancer). A suppressor gene may, for example, code for a protein which checks genes for misspellings, and/or which triggers a cell's self-destruction if too much DNA damage has occurred.

Surfactant: Also called: surface-active agent. A substance, such as a detergent, that can reduce the surface tension of a liquid and thus allow it to foam or penetrate solids; a wetting agent.

Systematic review: A review that has been prepared using a documented systematic approach to minimising biases and random errors.

TDI: See 'Tolerable Daily Intake'.

Teratogen: A substance which, when administered to a pregnant woman or animal, can cause congenital malformations (structural defects) in the baby or offspring.

Testicular Dysgenesis Syndrome (TDS): The hypothesis that maldevelopment (dysgenesis) of the fetal testis results in hormonal or other malfunctions of the testicular somatic cells which in turn predispose a male to the disorders that comprise the TDS, i.e. congenital malformations (cryptorchidism and hypospadias) in babies and testis cancer and low sperm counts in young men.

Threshold: Dose or exposure concentration below which an effect is not expected.

Tolerable Daily Intake (TDI): An estimate of the amount of contaminant, expressed on a body weight basis (e.g. mg/kg bodyweight), that can be ingested daily over a lifetime without appreciable health risk.

Toxic Equivalency 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. TEF systems have been published for the chlorinated dibenzodioxins, dibenzofurans and dioxin-like polychlorinated biphenyls, and for polycyclic aromatic hydrocarbons.

Total Toxic Equivalent (TEQ): Is a method of comparing the total relative toxicological potency within a sample. It is calculated as the sum of the products of the concentration of each congener multiplied by the toxic equivalency factor (TEF).

Toxicodynamics: The process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Toxicogenic: producing or capable of producing a toxin.

Toxicogenomics: A new scientific subdiscipline that combines the emerging technologies of genomics and bioinformatics to identify and characterise mechanisms of action of known and suspected toxicants. Currently, the premier toxicogenomic tools are the DNA microarray and the DNA chip, which are used for the simultaneous monitoring of expression levels of hundreds to thousands of genes.

Toxicokinetics: The description of the fate of chemicals in the body, including a mathematical account of their absorption, distribution, metabolism and excretion. (see pharmacokinetics)

Transcription: the process during which the information in a length of DNA (qv) is used to construct an mRNA (qv) molecule.

Transcriptomics: Techniques available to identify mRNA from actively transcribed genes.

Transfer RNA (tRNA): RNA molecules which bond with amino acids and transfer them to ribosome's, where protein synthesis is completed.

Transfection: A process by which the genetic material carried by an individual cell is altered by incorporation of exogenous DNA into its genome.

Transgenic: Genetically modified to contain genetic material from another species (see also genetically modified organism).

Transgenic animal models: Animals which have extra (exogenous) fragments of DNA incorporated into their genomes. This may include reporter genes to assess *in-vivo* effects such as mutagenicity in transgenic mice containing a recoverable bacterial gene (lacZ or *lac I*). Other transgenic animals may have alterations of specific genes believed to be involved in disease processes (e.g. cancer). For example strains of mice have been bred which carry an inactivated copy of the p53 tumour suppressor gene (qv) -, or an activated form of the *ras* oncogene which may enhance their susceptibility of the mice to certain types of carcinogenic chemicals.

Translation: In molecular biology, the process during which the information in mRNA molecules is used to construct proteins.

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. **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 recognisable features of their tissue of origin but these characteristics 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.

Tumour initiation: A term originally used to describe and explain observations made in laboratory models of multistage carcinogenesis, principally involving repeated applications of chemicals to the skin of mice. Initiation, in such contexts, was the first step whereby small numbers of cells were irreversibly changed, or initiated. Subsequent, separate events (see tumour promotion) resulted in the development of tumours. It is now recognised that these early, irreversible heritable changes in initiated cells were due to genotoxic damage, usually in the form of somatic mutations and the initiators used in these experimental models can be regarded as genotoxic carcinogens (qv).

Tumour promotion: An increasingly confusing term, originally used, like 'tumour initiation' to describe events in multistage carcinogenesis in experimental animals. In that context, promotion is regarded as the protracted process whereby initiated cells undergo clonal expansion to form overt tumours. The mechanisms of clonal expansion are diverse, but include direct stimulation of cell proliferation, repeated cycles of cell damage and cell regeneration and release of cells from normal growth-controlling mechanisms. Initiating and promoting agents were originally regarded as separate categories, but the distinction between them is becoming increasingly hard to sustain. The various modes of promotion are non-genotoxic, but it is incorrect to conclude that 'non-genotoxic carcinogen' (qv) and 'promoter' are synonymous.

Uncertainty factor: Value used in extrapolation from experimental animals to man (assuming that man may be more sensitive) or from selected individuals to the general population: for example, a value applied to the NOAEL to derive an ADI or TDI. The value depends on the size and type of population to be protected and the quality of the toxicological information available.

Unscheduled DNA Synthesis (UDS): DNA synthesis that occurs at some stage in the cell cycle other than the S period (the normal or 'scheduled' DNA synthesis period), in response to DNA damage. It is usually associated with DNA repair.

Volume of distribution: Apparent volume of fluid required to contain the total amount of a substance in the body at the same concentration as that present in the plasma, assuming equilibrium has been attained.

WHO-TEQs: The system of Toxic Equivalency Factors (TEFs) used in the UK and a number of other countries to express the concentrations of the less toxic dioxin-like compounds (16 PCDDs/PCDFs and 12 PCBs) as a concentration equivalent to the most toxic dioxin 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is that set by the World Health Organisation (WHO), and the resulting overall concentrations are referred to as WHO-TEQs (Total toxic equivalents).

Xenobiotic: A chemical foreign to the biologic system.

Xenoestrogen: A 'foreign' compound with estrogenic activity (see estrogen).

Annex 6 – Index to Subjects and Substances considered in previous annual reports of the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Working Group on Variability and Uncertainty in Toxicology	2004 2005 2006 2007	15, 18 14 19 23
Workshop on		
evolving approaches to chemical risk assessment	2007	23, 38
Transgenerational Epigenetics	2008	19, 36
Xylanase preparation from Aspergillus niger	2001	13
Zearalenone	1998	29
2006 UK Total Diet Study of metals and other elements	2008	16, 170

Annex 7 – Previous Publications

Publications produced by the Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

1991 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321529 0 Price £9.50.

1992 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321604-1 Price £11.70.

1993 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321808-7 Price £11.95.

1994 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321912-1 Price £12.50.

1995 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. HMSO ISBN 0 11 321988-1 Price £18.50.

1996 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. The Stationery Office ISBN 0 11 322115-0 Price £19.50.

1997 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health.*

1998 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health*.

1999 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health*.

2000 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Department of Health.*

2001 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/0681/0802.[++]

2002 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/0838/0803.++

2003 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/0900/0504.++

2004 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/0992/0804.++

2005 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/1098/0906.++

2006 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/1184/0707++

2007 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/1260/0608++

2008 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, FSA/1410/0709++

Guidelines for the Testing of Chemicals for Toxicity DHSS Report on Health and Social Subjects 27 HMSO ISBN 0 11 320815 4 Price £4.30.

Guidelines for the Evaluation of Chemicals for Carcinogenicity DH Report on Health and Social Subjects 42 HMSO ISBN 0 11 321453 7 Price £7.30.

Guidelines for the Testing of Chemicals for Mutagenicity DH Report on Health and Social Subjects 35 HMSO ISBN 0 11 321222 4 Price £6.80.

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Published by Food Standards Agency/Department of Health
July 2010