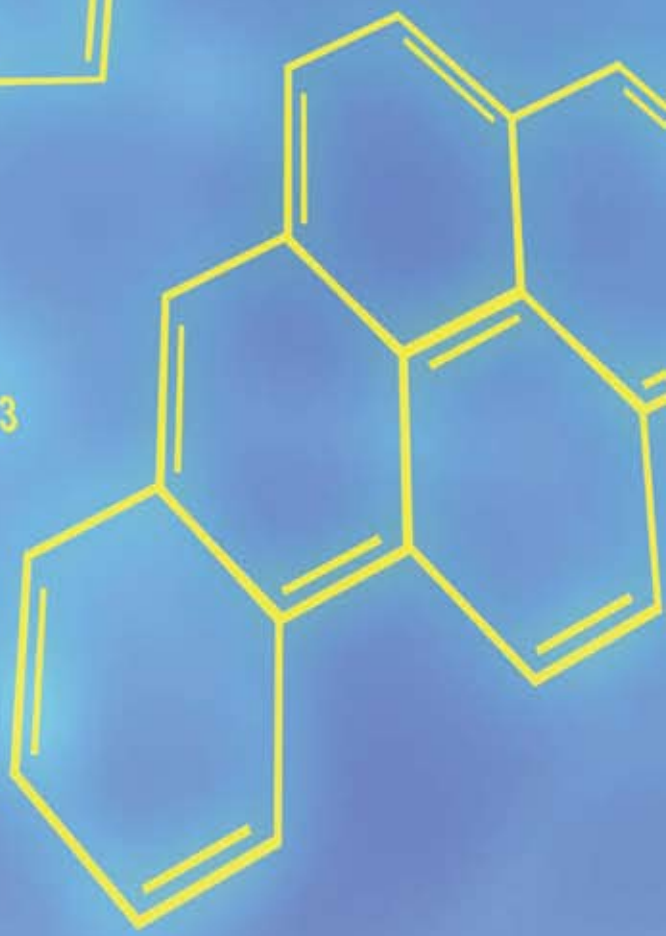
Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment



Committee on TOXICITY

Committee on CARCINOGENICITY

Committee on MUTAGENICITY

Annual Report 2010

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About the Committees

This is the twentieth joint annual report of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) and the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC).

The aim of these reports is to provide a brief toxicological background to the Committees' decisions. 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 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

This report contains summaries of the discussions and includes the Committees' published statements in full in order to fulfil the obligation to publish statements both electronically and in hard copy.

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 and Regulatory Authorities, and are published as statements on the Internet. Details of membership, agendas and minutes are also published on the Internet.

During 2010, the Committee agreed statements on possible health risks associated with exposure to chemicals emitted from landfill sites, and on mixed halogenated (chlorinated and brominated) dibenzo-p-dioxins (PXDDs), dibenzofurans (PXDFs) and biphenyls (PXBs) in fish, shellfish, meat and eggs. In addition, various other topics were discussed, without publication of a formal statement. These included phthalate esters, endocrine disrupting chemicals and mixtures toxicity. We also had a detailed discussion on methods of analysis for shellfish toxins, and the scope to replace use of the mouse bioassay in the UK monitoring programme for these toxins by alternative approaches that do not require testing in live animals. Many of the matters considered by COT require discussion at more than one meeting, and several items of business were still in progress at the end of 2010. Work on these was due to be completed early in 2011, and formal statements will be included in the 2011 Annual Report.

I would like to thank Dr David Tuthill, Professor Corinne De Vries, Ms Alison Ward, Ms Alma Williams and Dr Cliff Elcombe, who left the Committee during 2010 after valuable service. As always the administrative and scientific secretariats have given us excellent support.

Finally I would like pay tribute to Dr David Ray. Sadly David died in November 2010 after suffering from pneumoblastoma. David was an internationally renowned expert in neurotoxicology, and had been a member of COT from 2003 until he resigned in April 2010 because of his illness. He was a valued and much-liked member of the Committee, who contributed a wealth of knowledge on his specialism, and on the broader aspects of our discussions. His death is a sad loss to the COT and to the Scientific Community more widely.

Professor David Coggon (Chairman)
OBE MA PhD DM FRCP FFOM FFPH FMedSci

COT evaluations

Danish Environmental Protection Agency (EPA) report on health assessment of the exposure of 2 year-olds to chemical substances in consumer products'

1.1 As part of its consideration of mixtures of endocrine disrupting chemicals, in February 2010 the COT considered a summary of the Danish Environmental Protection Agency (EPA) report *'Survey and Health Assessment of the exposure of 2 year-olds to chemical substances in Consumer Products'*.

1.2 The COT subsequently discussed in more detail sections of the report relating to the calculation of the exposure estimates for each compound, and to the endpoints used as the basis for the no effect level (DNEL) for each compound. The DNEL is derived from No Observed Adverse Effect Levels (NOAELs) or Lowest Observed Adverse Effect Levels (LOAELs) by application of assessment factors to account for possible inter and intra-species differences in susceptibility to toxic effects. In addition, the COT requested information on time trends in exposure to a selection of the compounds investigated, since whilst some compounds had been withdrawn from use in certain applications, the use of others was growing, such trends might reduce or increase concerns about the risks of adverse effects.

Exposure assessment

1.3 The COT welcomed the approach taken in the EPA report of studying total exposures from a range of different scenarios, noting that 2-year old children are exposed to phthalates from a variety of sources, in and out of the home, through the diet, and through contact with clothes, consumer products and toys. The reported exposure calculations assumed high exposure to high concentrations of the chemicals by each route, and thus represented an extreme worst case. For some compounds the total calculated exposures were above the DNEL reference value. However, as assessment factors were used in deriving these reference values, the margins between exposures and the minimum effect levels in critical studies were likely to be substantial.

Endpoints used to derive DNELs

1.4 Since the report focused on substances with endocrine disrupting effects, the risk assessments were based on NOAELs and LOAELs from animal experiments that had shown such effects. Thus, the selected NOAELs and LOAELs did not necessarily relate to the critical adverse effects (normally those seen at the lowest concentrations or doses) of the compounds, which would generally be used in risk assessments. In many cases, the

NOAELs/LOAELs came from studies in which the effects were observed following *in utero* exposure to the substances, which the COT considered were likely to over-estimate risks in children.

1.5 The COT was presented with data from Scandinavia on exposure to dibutylphthalate (DBP) from rubber clogs, indicating that exposure would be above the DNEL. Members noted that it was unclear how relevant these data would be to the UK, and uncertain exactly how the exposure had been calculated. In addition Members questioned the basis for the DNEL derived by the Danish EPA, which was a study by Lee *et al*. (Toxicology 203, 221-238, 2004), and agreed to consider this study further as part of other items to be discussed during 2010 (see paragraphs 1.9-1.15).

Time trends

1.6 Phthalates were selected for closer consideration of time trends in exposure, as this was a group of endocrine disrupting chemicals for which the Danish EPA had estimated that exposures were higher than the DNELs.

1.7 A number of studies were identified which provided information on phthalate exposure through routes such as food, dust, indoor air, toys, consumer products, and medical devices/medications. These studies did not address changes in phthalate exposure over time. Some biomonitoring data were available which suggested both increases and decreases in exposure to different phthalates over time. However, 2003 was the last year for which there were time trend data, and Members concluded that it would be helpful to know current levels of usage, as these were likely to have changed. Ideally the validity of the modelled exposure levels would be assessed by comparison with biomonitoring data, but no UK biomonitoring data were available.

1.8 Members agreed that, before deciding whether more detailed consideration was required for other substances covered in the Danish EPA report, it would be best to wait for the results of studies being conducted under the European Union (EU) Framework Programme and a report on mixtures of endocrine disrupting chemicals being prepared for the European Commission (see paragraphs 1.33-1.37).

Dibutylphthalate (DBP) in clogs

1.9 In considering the report by the Danish EPA (see paragraphs 1.1 – 1.8), Members asked for further information on possible exposure to DBP from rubber clogs and on the basis of the DNEL for the compound that had been derived by the Danish EPA.

1.10 Subsequently, the COT considered in detail the interpretation of the critical toxicity study (Lee *et al*., Toxicology 203, 221-238, 2004) used to set the DNEL for DBP, taking into acount advice from additional experts in reproductive toxicity. Members agreed that a review should be undertaken of studies cited in a 2005 opinion of the European Food Safety Authority (EFSA) on DBP[a], and of other relevant studies on the compound, including toxicological, biomonitoring and epidemiological investigations, published since 2005. In addition, information on dermal absorption and exposure estimation was considered.

1.11 EFSA used the study by Lee *et al*. (Toxicology, 203, 221-238, 2004) as a basis for establishing a Tolerable Daily Intake (TDI) for DBP. In this study, maternal rats were fed DBP in the diet during the period from late gestation to the end of lactation. The LOAEL was 2 mg/kg bw/day, which was much lower than the NOAELs (in the region of 50 mg/kg bw/day) that had been observed in other studies. The COT noted that the study measured a lot of endpoints, not all of which were considered to be relevant, in rather small groups of animals. Effects at 2 mg/kg bw/day were on testicular spermatocyte development and mammary gland effects in male offspring. The effects on testicular spermatocyte development were reversible with continued dosing and lacked dose-dependence. The mammary gland effects seemed unlikely to be a manifestation of toxicity since they would be expected to be associated with an androgenic substance and not with the anti-androgenic mode of action of DBP. However the biological activity and some of the reported effects were plausible, and therefore the findings could not be discounted. Further work would be needed to confirm those effects at low doses, but meanwhile, the COT considered that the TDI proposed by EFSA was reasonable.

1.12 The COT agreed that, from the available dermal absorption studies, it was appropriate to assume a 2% absorption rate in humans, although it was noted that further empirical evidence on this would be helpful. Since the key study used to establish the TDI, involved exposure to DBP *in utero* and from lactation, it was not directly relevant to exposure of children to DBP from clogs. It was acknowledged that the worst-case risk characterisation ratio that had been proposed by the Danish EPA was likely to be an over-estimate, due to the conservative nature of the LOAEL and the long duration (10 hours) assumed for wearing clogs. Direct measurements of systemic uptake of DBP from clogs would be useful, together with information on the prevalence of DBP in the environment and on how commonly it occurs in clogs.

[a] http://www.efsa.europa.eu/en/efsajournal/pub/242.htm

1.13 COT noted that measurements of phthalates in urine samples taken as part of the US National Health and Nutrition Examination Survey (NHANES) project reflected exposures from a variety of sources. Some of the intakes estimated from such biomonitoring studies exceeded the EFSA TDI, but there was no information on whether and how levels were changing over time. The COT advised that the implications of exposures above the TDI and the potential contribution from wearing rubber clogs should be taken into account when considering different risk management options.

1.14 Epidemiological studies investigating the relationship of mono-butyl phthalate (MBP; the monoester of DBP) to cryptorchidism suggested possible hormonal effects. Similarly epidemiological studies investigating anogenital distance provided some evidence of endocrine disruption by DBP in humans.

1.15 The COT agreed that whilst small children were the critical population subgroup with regard to possible risks from DBP in rubber clogs, there was a need for biomonitoring studies in the UK with particular focus on women of childbearing age. This programme of work should explore the main sources of DBP exposure, and should investigate trends over time as well as patterns and determinants of exposure at baseline. Members agreed that an assumption of dose additivity would be appropriate when assessing the combined effects of phthalate esters.

Endocrine disrupting chemicals – definition for regulatory purposes

1.16 The classification of substances as endocrine disrupters has become important in a number of regulatory contexts. An example is the introduction into the new European Plant Protection Products (PPP) Regulations (1107/2009) of a requirement that an active substance, safener and synergist with endocrine disrupting properties that may cause adverse effects in humans cannot be approved for marketing and use unless the exposure of humans under realistic proposed conditions of use is negligible.

1.17 The COT was asked to comment on a paper that proposed a definition and method for determining whether a substance is an endocrine disrupter, which could be applied in the context of legislation relating to plant protection products, biocides, and the Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH). The COT's views would be used by the Health and Safety Executive to feed into and inform European Union discussions. It was noted that the discussions and recommendations from the meeting could have implications with respect to environmental chemicals more widely.

1.18 In European Union legislation, endocrine disruption, along with carcinogenicity, mutagenicity and teratogenicity, had been singled out as hazard triggers of special concern. However, the scientific basis for treating endocrine disruption differently from other toxic modes of action was debatable. In the view of the COT current evidence did not indicate special features of endocrine disruption that warranted a different approach from that for most other toxic modes of action. For example, there was strong evidence of monotonic dose/concentration-response relationships *in vitro* and *in vivo*, and non-monotonic effects seemed unlikely. Moreover, additivity at the estrogen receptor was in essence no different from that for other receptor-mediated effects. However, as COT has noted previously[b], there is stronger evidence from environmental studies that endocrine disrupters can adversely affect reproductive growth rates in populations of wild animals.

1.19 A number of definitions for endocrine disrupters have been proposed, some of which are ambiguous and, for regulatory purposes, are overly inclusive, in that they fail to discriminate between alterations of the endocrine system which fall within the physiological balance/homeostatic capabilities of the body, and adverse effects that disturb an organism's endocrine system to an extent beyond that compatible with normal function. This has led to the development of more restrictive definitions that account for the fact that many alterations of the endocrine system can be regarded as adaptive, falling within a range for which compensation can occur readily, and which pose no threat to the normal functioning of the organism.

1.20 The widely accepted scientific definition of an endocrine disrupter proposed by the World Health Organisation International Programme on Chemical Safety (WHO/IPCS) was considered as a starting point for the COT discussion: *"An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations."*

1.21 The COT suggested it might be considered to be too much of a "catch-all", and that it should capture concepts of potential to alter function based on mode of action and dose. Incorporating "*the potential* to alter function(s)" would allow for use of results of predictive systems or read across. However "potential" might be too broad a definition for regulatory purposes. The words "*, or (sub)populations*" were considered unnecessary.

1.22 The COT proposed the following revised definition for an endocrine disrupter: "*an exogenous substance or mixture that has the potential to alter function(s) of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny*"

[b] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2006/371075

1.23 The COT also considered the qualifying criteria that had been proposed by the WHO/IPCS. It was agreed that the use of the following four criteria would make it possible to confirm that a substance was an endocrine disrupter for regulatory purposes:

i. *"adverse effects to have been seen in one or more standard toxicity studies in which the substance was administered by a route relevant for human exposure"* More detailed information might need to be taken into account – for example the quality of the studies, the form of the substance and its stability

ii. *"the adverse effect(s) believed to be related to endocrine disruption to have been produced at a dose at or below the relevant guidance value for the application of Category 2 "Specific Target Organ Toxicity-Repeated Exposure, STOT-RE" classification & labelling"*

iii. *"a mode-of-action link between the toxic effects of concern and endocrine disruption to have been established*". In practice data gaps would need to be taken into account.

iv. *"the effects seen in experimental animals to be judged to be of potential relevance to human health"*

1.24 Members noted that the evidence required to conclude that a substance was not an endocrine disrupter would ultimately depend on the degree of certainty that risk managers required.

Landfill sites

1.25 In 2001, the COT published a statement on a major study of health outcomes in populations living around landfill sites[c]. The COT was largely reassured by the findings but considered that a small elevation of risk for all congenital anomalies in people living around special waste landfill sites merited further investigation. At that time, the COT had been informed that a programme of research and reviews was underway on congenital anomalies and landfill sites. This included a project by the Environment Agency (EA) 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).

1.26 The results of these studies were reviewed from 2007 to 2009. The COT welcomed the monitoring work by the EA and found no cause for concern for the health of families with infants, or for couples who live in the vicinity of landfill sites and who are considering having a baby. Based on the results of

[c] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2001/sahsulandfill

the monitoring, conclusions and recommendations were made in relation to specific chemicals and to future monitoring and research.

1.27 The COT statement can be found at: http://cot.food.gov.uk/pdfs/cotstatementlandfill201001.pdf

Mixed halogenated dioxins

1.28 The COT considered a recently completed Food Standards Agency (FSA) study that analysed 19 mixed halogenated (chlorinated and brominated) dibenzo-p-dioxins (PXDDs), dibenzofurans (PXDFs) and biphenyls (PXBs) in samples of fish, shellfish, meat and eggs consumed in the UK.

1.29 PXDDs, PXDFs and PXBs contain mixed bromine and chlorine substitutions in the hydrocarbon rings rather than exclusively chlorine or exclusively bromine substitutions. Theoretically 4600 individual PXDDs and PXDFs and 9180 PXBs are possible. Except for some PXBs produced for research purposes, mixed halogenated dioxins, furans and biphenyls have never been produced commercially.

1.30 The TEFs[d] developed for the polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and dioxin-like biphenyls (PCBs) were used as an indication of the dioxin-like activity of the corresponding PXDDs, PXDFs and dioxin-like PXBs congeners. This was the greatest source of uncertainty in assessing potential health risk for mixed halogenated dioxins, but the approach is conservative as available evidence overall suggests that PCDDs, PCDFs and dioxin-like PCBs have higher relative potencies and lower rates of clearance from the body than other structurally analogous compounds.

1.31 Based on the levels estimated per portion of the foods surveyed, the PCDDs, PCDFs and dioxin-like PCBs were likely to be the major contributors to the total TEQ. Assuming that the measured congeners were representative, PXDDs, PXDFs and dioxin-like PXBs were considered likely to be only a minor contributor to the total TEQ, and the measured levels were judged not to be a health concern.

[d] Toxicity Equivalency Factors (TEFs) allow concentrations of the less toxic dioxin-like compounds (16 PCDDs/PCDFs and 12 PCBs) to be expressed as a concentration equivalent to the most toxic dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). These toxicity-weighted concentrations are then summed to give a single value, which is expressed as a Toxic Equivalent (TEQ). The system of TEFs used in the UK and a number of other countries is that set by the World Health Organisation (WHO), and the resulting overall concentrations are referred to as WHO-TEQs.

1.32 The COT statement can be found at:
http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2010/cot201002

Mixtures – an appraisal of a report on "State of the Art on Mixture Toxicity"

1.33 In September 2010, the COT appraised a report entitled State of the Art Report on Mixture Toxicity by Professor Kortenkamp and colleagues[e]. The report summarised the output of a project commissioned by the European Commission (EC) Directorate General for the Environment. The COT was asked for comments in order to inform the UK's representatives in later discussions of mixture toxicity within the EU.

1.34 Members were not aware of any important literature on the concepts, frameworks and experimental strategies that had not been considered in the report, or of any omissions in the literature cited that could influence the conclusions drawn.

1.35 It was agreed that the report provided a reasonable representation of the literature describing the combined effects of chemicals on specific mammalian toxicity endpoints. However, Members considered that the literature did not support a concern about response addition at human exposure levels or the authors' claim that a default uncertainty factor of 100 was insufficient.

1.36 The COT approach to the risk assessment of mixtures of chemicals had evolved over time. The current default position for mixtures of chemicals that have a common target is as follows:

a. Where there is clear evidence that compounds act by different mechanisms, and on different biological pathways, independent action is assumed.

b. Where there is clear evidence that compounds act by the same mechanism, dose addition should be assumed.

c. Where there is clear evidence that compounds act on different elements of the same pathway, or where there is inadequate evidence on mechanism of action, dose addition should be assumed. Members elaborated that this may be highly conservative.

1.37 The European Food Safety Authority was expected to be producing a statement on mixtures during 2011, which Members felt they should also

[e] http://ec.europa.eu/environment/chemicals/pdf/report_Mixture%20toxicity.pdf

review. The published[f] minutes of the discussion set out the conclusions of the COT.

Mixtures – consideration of FSA-funded research on joint endocrine effects of multi-component mixtures of food contaminants and additives

1.38 The COT discussed pre-publication results of this FSA-funded research (T01045). Members considered it to be a well designed, executed and reported *in vitro* study into mixture effects of food additives and contaminants with endocrine effects. The results suggested that any deviation of the mixture effect from the prediction of dose additivity would be negative, and therefore, the COT's recommended approach of assuming dose additivity would be adequately protective of public health.

1.39 Members noted that as this work had been carried out *in vitro*, there were limitations, including the fact that the cells have limited homeostasis, the possibility that conformation of the receptor was altered by reporter attachment, and failure to include negative controls. In addition the assays were not thought to be predictive of the human hazard or the *in vivo* potency of the compounds.

1.40 Limitations in extrapolating the results to the *in vivo* situation included the involvement of the brain in feedback control of hormone levels, the presence of receptors in various tissues which have different responses to receptor activation, and the possibility of combined effects resulting from interactions at different sites. The COT advised that, due to these limitations, there would be limited value in pursuing further *in vitro* work.

National Health And Nutrition Examination Survey (NHANES)

1.41 The NHANES is a major program of the National Center for Health Statistics (NCHS). NCHS is a part of the Centers for Disease Control and Prevention (CDC) which has responsibility for producing vital and health statistics for the United States of America.

1.42 During the 2010 horizon-scanning session, a Member suggested that the outputs of the NHANES would be of interest to the COT. Members were provided with a paper giving information about the NHANES. At the May 2010 meeting and at the September 2010 meeting, a further paper was presented describing uses of NHANES data (with particular reference to

[f] http://cot.food.gov.uk/pdfs/cotmins14sept2010.pdf

endocrine disrupters considered in the 2010 Danish EPA report, see paragraphs 1.1-1.8).

1.43 Members commented that the outputs from the NHANES could provide a useful resource for epidemiologists and that the biomarker data were a particular strength. However, the data were largely cross-sectional, which limited their value in the investigation of causal relationships.

1.44 It was noted that NCHS go to great lengths to ensure that the survey reflects the demographics of the national population, with oversampling of specific sub-populations where appropriate. However, Members commented that no economically feasible survey could be fully representative.

1.45 Due to the nature and scope of the surveys it was inevitable that some associations would emerge by chance. Thus it was important to interpret reports that used NHANES data in the context of relevant scientific evidence from other sources.

1.46 It had been suggested that the NHANES data might be used to identify chemicals that were a priority for cumulative risk assessment due to evidence of simultaneous internal exposure. However, no published papers were identified that had taken this approach.

1.47 A literature search was undertaken to assess the uptake and use of NHANES genetic data. Forty two papers were identified as being of possible interest but only nine proved relevant. These were reviewed by the COT. Members noted that, given the data available, relatively few papers had been published that made use of the NHANES genetic datasets, and suggested this might be due to the need for much larger sample sizes than could be provided by the NHANES.

1.48 Members also observed that NHANES data appeared to have had limited impact on public health decisions; although it was noted that blood lead data had been instrumental in developing policy to reduce exposures.

1.49 In considering whether NHANES could be used to inform future COT risk assessments, Members noted that the data could provide a “reality check” when carrying out a mixture assessment. NHANES data could provide evidence as to which substances should be included in a combined risk assessment and could be used to demonstrate co-exposure. However, it would not be possible to confirm whether the exposure had been dietary. It was also noted that the distribution of biomarker levels and ethnic make-up would be specific to the US population, and there might be uncertainties in extrapolating to the UK population. A similar database covering the UK population would therefore be more useful for UK risk assessments. It was

noted that a biomarker study on exposure to 30 chemicals in a UK blood donor population was being conducted by the University of Newcastle.

1.50 Members agreed that the information provided on NHANES data did not indicate a need for full COT evaluation of any of the chemicals investigated.

Paralytic Shellfish Poisoning biotoxins

1.51 A number of marine phytoplankton produce biotoxins that can bioconcentrate in shellfish. Consumption of contaminated shellfish with sufficiently high levels of these toxins can result in human illness.

1.52 Paralytic Shellfish Poisoning (PSP) is a neurotoxic syndrome with symptoms that include tingling and numbness of extremities, respiratory distress and muscular paralysis leading to death by asphyxiation. The predominant toxin responsible for PSP is saxitoxin (STX), but at least 20 other related compounds have also been identified. The COT previously considered a risk assessment and monitoring of marine biotoxins associated with PSP towards the end of 2005, and published a statement in 2006. At that time the COT had concluded that High Performance Liquid Chromatography (HPLC) should be used for quantification of PSP toxins, subject to appropriate quality control measures and method validation.

1.53 At the March 2010 meeting Members were presented with a report of work commissioned by the FSA and carried out by the Centre for Environment, Fisheries & Aquaculture Science (Cefas) to validate of the HPLC methods for detection of PSP toxins in mussels, cockles, Pacific and native oysters, and king and queen scallops

1.54 Progress had already been made with replacement of a mouse bioassay (MBA) by HPLC in monitoring for PSP biotoxins in mussels. However the advice of the COT was sought on the public health implications of replacing the MBA with the HPLC method for monitoring of cockles, Pacific and native oysters, razor and hard clams, and king and queen scallops. Members noted that due to the major economic impacts on harvesting of closing shellfish beds, a robust scientific basis was needed for any method used to underpin decisions about closures.

1.55 It was recognised that whilst it was the current reference method, the MBA, had limitations with respect to limits of quantification and other performance characteristics. The best way of determining accuracy of any method was to carry out the analysis with a certified reference material comprising the shellfish matrix of interest with known concentrations of a range of toxins. If

certified reference material was not available, a well characterised material was the preferred option.

1.56 For mussels a well characterised material was available from Canada, and was used as part of the validation of the method. This material had been well characterised using HPLC and liquid chromatography with mass spectrometry (LC-MS). Accuracy was ensured through use of different quantitation methods as well as different extraction methods.

1.57 Neither certified reference material nor well characterised material was available for the other shellfish matrices under consideration. In the absence of these, samples spiked with known concentrations of toxins were used; however, these do not reflect the manner in which shellfish naturally accumulate PSP toxins, and thus provide an indication of recovery rather than accuracy. The homogenates used as a starting point for spiking were considered to be PSP-free as they were collected at a time of year when PSP toxins are not prevalent, and repeated analyses had shown these to be toxin-free.

1.58 Limits of detection (LoD) and quantitation (LoQ) were determined by Cefas for each toxin by establishing the amounts of toxins giving a signal to noise ratio on the chromatograms of 3:1 and 10:1 respectively. The LoDs and LoQs were determined for the whole method using the spiked homogenates rather than just representing instrument sensitivities by analysing extracts. Noise in the chromatograms was assessed from the results obtained by application of appropriate algorithms.

1.59 Cefas sought to ensure that the HPLC method for the detection of PSP toxins was precise, repeatable and reproducible. Members were informed that in assessment of the method, precision reflected short term variability in instrument performance, for example in retention time and peak size. Repeatability in the short term reflected the within batch replication of recovery variables by assessment of triplicate spiked homogenates. In the medium term, repeatability reflected the variation in concentrations measured over a longer period (2-3 weeks) and was influenced by a number of variables (e.g. change in operator, batch of reagents, etc). Reproducibility, while normally an assessment of the variability in performance between laboratories, applied in this single laboratory validation exercise to the long term repeatability (over time periods greater than 6 months) of the whole method. This was considered to provide a thorough assessment of how the method varied from day to day, taking into account factors such as different analysts performing the method, use of different instruments and carrying out the analysis on different days.

1.60 Recovery was an assessment of how much toxin was measured at the end of the analysis of a known amount of toxin present in the homogenate. Selectivity was the ability of the method to distinguish toxins, and an assessment of the effects of matrix interference. Linearity was a measure of how toxin concentration related to the detector measurement, the aim being a linear relationship.

1.61 The overall uncertainty of the total STX equivalent concentration had not been presented in the report as it would vary depending on the toxin profile of each sample. Not all the constituent uncertainties would necessarily operate in the same direction and therefore they could not be summed to obtain an overall value. Members suggested that the researchers could assess a number of samples in which the total STX equivalent concentration was close to the regulatory limit, to derive a distribution of overall uncertainties. These could then be compared with the uncertainty associated with the mouse bioassay method.

1.62 The report on cockles, Pacific oysters and native oysters showed the method to perform well, results comparing satisfactorily with those obtained in validation of the method in mussels. The recovery of the PSP bioxtoxin known as dcGTX2,3 was low in cockles but this had also been found in other laboratories, and it was noted that dcGTX2,3 does not appear to be frequently detected in United Kingdom shellfish samples, The low recovery was therefore considered to be of limited concern. Performance data for the HPLC method compared favourably with those of the mouse bioassay.

1.63 The HPLC results obtained for PSP-contaminated cockles, prepared by feeding cockles with toxic *Alexandrium* algae in the laboratory, showed good correlation with those obtained by the mouse bioassay, the measured levels by the HPLC method being 30-40% higher. This difference was thought to be due to use of the higher toxic equivalency factors (TEFs) where toxin epimer pairs are present. However, as HPLC resulted in a higher estimation of the toxin content than the mouse bioassay, there were no false negatives in the analysis and there would be no increased risks from its use. It was noted that, due to shortage of contaminated material, only a limited set of 19 cockle samples had been compared using the two methods.

1.64 HPLC results for contaminated Pacific and native oyster samples, most of which, like cockles, had been prepared in the laboratory, were 2-3 fold higher than those determined by the mouse bioassay. While up to 30% of this variation could be attributed to use of higher TEFs for toxin empimer pairs, no explanation had yet been found for the remaining variation. Members noted that whilst there would be no increased risks to public health, from using the HPLC method, there could be adverse implications for the shellfish industry.

1.65 The performance characteristics and standardised uncertainties determined for the method in razors and hard clams were reasonable and similar to those obtained for cockles and oysters. Analysis of contaminated samples showed that the HPLC and mouse bioassay methods compared well, but again only a small number of samples (8 razors and 8 hard clams) had been assessed.

1.66 The performance of the HPLC method for king and queen scallops was poor for N-hydroxylated toxins such as GTX1,4, NEO and dcNEO due to a lack of effectiveness at the periodate oxidation stage of the assay. The data for queen scallops indicated that the limit of detection for GTX1,4 in queen scallops was close to the regulatory limit.

1.67 No further work had been undertaken to validate the methodology for queen scallops due to the need for further optimisation to make it fit for purpose. As a result, Members considered the HPLC method was not appropriate, even as a qualitative screen for queen scallops, and in the monitoring programme all samples of queen scallops should continue to be assessed using the mouse bioassay. For king scallops however, it would be acceptable to use the HPLC method as a qualitative screen from which any positive results would be further assessed by the mouse bioassay. Poor recovery (less than 30%) for some of the toxins suggested that further work would be required on this method. Members noted that a number of N-hydroxylated toxins are prevalent in the United Kingdom, and therefore the potential for their underestimation was undesirable.

1.68 Despite poor performance characteristics, analysis of contaminated whole king scallops (some of which had been prepared in the laboratory), processed king scallops and Atlantic scallops showed good correlations between HPLC and the mouse bioassay. However, only a small number of samples of each were assessed. For queen scallops HPLC results showed concentrations approximately half of those seen by mouse bioassay, but it was emphasised that this was based on two samples only, so the results might be unrepresentative.

1.69 The COT noted that the work on validation had been performed in only one laboratory and on only a limited number of samples, and that these were sources of uncertainty. However, it was understood that other laboratories were also working on validation of the HPLC method, with some samples being analysed at more than one site to enable the assessment of between-laboratory variation.

1.70 Members questioned whether variations in storage conditions were likely to affect the results of the HPLC method. While work to evaluate this had been carried out, it was not considered relevant to the validation of the use of the

HPLC method in the monitoring programme because shellfish samples would all be processed within one day of receipt.

1.71 Members also discussed other available methods for analysis of PSP toxins in shellfish matrices for monitoring purposes. These included an HPLC method involving post-column oxidation which was currently being validated (the HPLC method undertaken by Cefas used pre-column oxidation), and LC-MS approaches that were in development.

1.72 The COT considered that use of the HPLC method as described in the report by Cefas would offer greater public health protection than the mouse bioassay when used for oysters, though it was noted that there was likely to be an increase in the number of positive results found. For cockles and hard and other clams, similar levels of public health protection would be achieved through use of the HPLC method as from use of the mouse bioassay. For razors, public health protection might be slightly less with the HPLC method as compared with the mouse bioassay. The methodology was not yet considered acceptable for king and queen scallops.

Committee procedures

Horizon Scanning

1.73 At the February 2010 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. Items scheduled for future discussion were:

- Risk assessment of bystander/resident exposure to pesticides – joint working group with the Advisory Committee on Pesticides
- Review of epidemiological literature of para-occupational exposure to pesticides and health outcomes in cooperation with the Committee on Carcinogenicity (COC).
- Psychological aspects of Idiopathic Environmental Intolerance.
- Detection of biotoxins responsible for paralytic shellfish poisoning.
- Literature related to tobacco, following discussions at the Committee on Mutagenicity (COM) and the COC.
- A paper reviewing toxicogenomics techniques and applications.

- Review of research commissioned as a result of the COT Report on risk assessment of mixtures of pesticides and similar substances.

1.74 In discussing the balance of expertise on the COT, Members identified a number of areas in which additional expertise would be advantageous: environmental exposure assessment; epidemiology; experimental toxicology, including respiratory toxicology; mathematical modelling of dose-response relationships; dietary exposure assessment. The COT would continue where necessary to invite persons with special expertise on an *ad hoc* basis, to assist with evaluations by supplementing the expertise of Members. The need was recognised also to ensure sufficient overlap of expertise in the future as individual Members came to the end of their terms.

1.75 A Member suggested that the outputs of the NHANES of the United States Centers for Disease Control and Prevention would be of interest to the COT. These data were publicly available[g]. Noting recent publications involving NHANES data, and the potential for data-mining, it was proposed that it would be useful for the COT to receive an overview of NHANES. Such a review would cover publications that had made use of the NHANES data, the sorts of data available online and the kinds of samples that are available to researchers. The COT asked to be involved in setting the scope for a review of the NHANES and that the review focus on the inter-relation of biomarkers and health outcomes.

1.76 COT members expressed an interest in reviewing draft toxicological guidelines such as those prepared by the Organisation for Economic Co-Operation and Development. It was pointed out that comments from the COT would be most effective during the earlier stages of guideline preparation. Relevant draft guidelines are emailed to Members for comment when they become available, and Members were encouraged to respond.

1.77 The Chairman reminded Members that topics of emerging interest relevant to the work of the COT could be suggested at any point throughout the year, to either himself or the Secretariat.

Consultation document for updating the Code of Practice for Scientific Advisory Committees (CoPSAC)

1.78 At the November 2010 meeting, the COT was asked to comment on the contents of the Code of Practice for Scientific Advisory Committees (CoPSAC), produced by the Government Office for Science (GO-Science). COT members had previously discussed consultation drafts of a first version

[g] http://www.cdc.gov/nchs/nhanes.htm

of the CoPSAC in 2000 and 2001 and a revised version in 2007. The 2007 version of the CoPSAC was being reviewed to take into account the Principles on Scientific Advice to Government that were issued in March 2010. Members were invited to comment on the specific consultation questions and on any other aspects of the draft code. Members were reminded that CoPSAC had originally been written in a context in which most scientific advisory committees were Non-Departmental Public Bodies (NDPBs), but the consultation indicated that "all Scientific Advisory Committees – whether or not formal Non-Departmental Public Bodies – are covered by this guidance".

1.79 Members questioned the requirement that a committee's advice should be understandable by lay readers. When reporting, committees needed to communicate with Government and the scientific community, as well as the wider public. Inevitably, the rationale underpinning advice was sometimes quite technical, but it needed to be clearly documented and open to scrutiny. Important nuances could be lost if advice were simplified to make it more understandable by the lay reader. An alternative was to provide a "lay summary" to accompany more detailed technical advice, and Members agreed that 'lay summaries' of the COT's conclusions should be included in its future published statements.

1.80 Consultation question 1 related to "Maintaining strong relationships" A Member questioned whether a change in status from independent scientific advisory committee to departmental committee would result in "unpalatable" advice being retained within departments and not reaching ministers. The Chair emphasised that if a chair or members of a committee had concerns about this in a specific case, they should contact first the relevant Department's Chief Scientist and if necessary, the Government's Chief Scientific Advisor.

1.81 Consultation question 2 related to "Openness and Transparency". Para 106 of the CoPSAC was considered to address adequately the issue of communication with the media. Communication should be the responsibility of the chair, delegating to members if appropriate.

1.82 Consultation question 3 related to "Engaging the Scientific Community and Succession Planning". Members discussed the balance of expertise in committees. It was agreed that this would largely depend on the function of the advisory committee. It was suggested that a reduced incentive for younger scientists to get involved with committee work might lead to a decline in available expertise in some areas of science. In addition, the Chair reported that several chairs of scientific advisory committees and other interested parties had recently produced a report highlighting concerns about an impending generation gap in applied scientific expertise relevant to risk

assessment for chemical and physical hazards. A meeting had been arranged with the Government's Chief Scientific Advisor to discuss the problem.

1.83 Consultation question 4 asked "Is there any other information that could be usefully included in the Code of Practice?". The Committee highlighted a need for further guidance on declarations of interests, particularly regarding interests that would not normally present a conflict (e.g. membership of another independent committee that had discussed a topic under consideration).

1.84 A response was sent to GO-Science.

Working Groups and Workshops

Bystander Risk Assessment Working Group (BRAWG)

1.85 The BRAWG is a joint Working Group with the Advisory Committee on Pesticides (ACP). The COT agreed in 2009 to form this joint working group with the ACP in order to explore issues related to the assessment of risks to bystanders and residents from the application of pesticides. The Group's terms of reference are:

- To agree a definition of operators, workers, bystanders and residents
- To agree the nature of the exposures that require consideration
- To review the current approach to modelling these exposures for bystanders and residents in the light of current knowledge
- To review the approach to assessing the risk arising from these exposures in the light of current knowledge

1.86 The BRAWG held two meetings during 2010. The Group aims to complete its work and to report back to the COT and the ACP during 2011.

Lowermoor Subgroup

1.87 Members had previously been informed that the deaths of two individuals who had lived in the area that received contaminated water following the 1988 Lowermoor Water Pollution Incident had been referred to the West Somerset coroner. The two individuals both had neurodegenerative disease and had been reported to have higher than usual levels of aluminium in the brain.

1.88 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 into the death of one individual was held in 2008 and recorded a verdict of death by natural causes. The second inquest began in November 2010 but was adjourned. Therefore the final Subgroup report will not be published until 2011.

Workshop on expression of uncertainty

1.89 In March 2007, the COT published a report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment[h]. The report concluded that the development of a framework for transparent expression of uncertainty in hazard characterisation would enable the COT and other committees that perform toxicological evaluations to improve communication of the sources of variability and uncertainty in their risk assessments.

1.90 The FSA subsequently commissioned a research project to review existing approaches to qualitative evaluation and expression of uncertainties and assess their suitability for routine use by the COT and other committees. As part of this project the COT held a one-day workshop in February 2010, at which COT Members and invited guests participated in discussions exploring the evaluation and expression of uncertainties in risk assessment. Participants considered examples of risk assessments previously published by the COT and used a draft framework to consider whether this could make the steps of the risk assessment process easier and more transparent. The potential utility of the framework for COT work was also considered.

1.91 At a subsequent meeting the COT discussed the draft report of the project and a further draft of the framework, which had been revised following the workshop. Members commented that the challenges for the COT in expressing uncertainty are not easily addressed by a simple mathematical approach, and reiterated the reluctance they had expressed at the Workshop to put numerical values on uncertainties regarding qualitative conclusions, as they might easily be misinterpreted. It was decided that it would be helpful to develop a scale of terms describing different levels of uncertainty, with input from the FSA Social Science Research Committee (SSRC).

1.92 The report, including a revised framework, was finalised by the project team. The agreed draft framework will be tested in the course of COT evaluations and may require further modification before being adopted for use by the COT.

[h] http://cot.food.gov.uk/cotreports/cotwgreports/cotwgvut

Ongoing work

Dietary exposure to phthalates – data from the Total Diet Study

1.93 The COT was presented with the results of a recent FSA-funded study of phthalate diesters, a few phthalate monoesters and phthalic acid in Total Diet Study (TDS) samples from 2007. Members considered recent toxicological studies on phthalates identified in a literature review and concluded that these did not indicate a need to revise TDIs set by EFSA (2005) or WHO CICAD (2003), which should therefore be used in assessing possible risks from dietary exposure to phthalates.

1.94 Estimates of dietary exposure to phthalates have been calculated from the results of the study. The COT concluded that a cumulative risk assessment for phthalates should be undertaken based on an assumption of dose-addition. Furthermore a full risk assessment would require non-dietary exposures also to be taken into account.

1.95 Further discussion will take place in 2011 and the statement will be published.

Gluten - timing of introduction into the infant diet

1.96 In 2010, the Department of Health and Food Standards Agency asked the Scientific Advisory Committee on Nutrition (SACN) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) to assess the evidence on timing of introduction of gluten into the infant diet and subsequent risk of developing coeliac disease or type 1 diabetes mellitus (T1DM).

1.97 The COT considered the relevant evidence and provisional conclusions have been forwarded to SACN. Further discussions will take place during 2011 and a joint SACN/COT statement will be published.

Idiopathic Environmental Intolerance: Evidence for a toxicological mechanism

1.98 In 2006, the COT discussed a report of the Royal Commission on Environmental Pollution (RCEP) report on crop spraying and health of residents and bystanders, and recommended that a further review of Idiopathic Environmental Intolerance (IEI, also described as Multiple Chemical Sensitivity) be undertaken[i].

[i] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2006/cotstatementrcep0605

1.99 In 2010, the COT considered a discussion paper on the evidence for toxicological mechanisms for IEI, and subsequently considered psychological aspects of IEI in consultation with experts in psychology. Further discussions will take place during 2011 and a statement will published.

Methanol - chronic toxicity

1.100 Methanol is produced endogenously and also occurs in a number of foods notably fruit and vegetables and their juices.In addition some people are exposed to methanol vapours occupationally. In humans, acute exposure to very high levels of methanol, for example from illegally distilled or counterfeit spirits, has resulted in well characterised toxic effects including metabolic acidosis and neurotoxicity, particularly in the visual system.

1.101 Less is known about whether chronic exposure to methanol at lower levels can result in adverse effects. In response to consumer concerns that methanol arising from the breakdown of the sweetener aspartame could be harmful, the COT has been conducting a review of possible health effects of chronic oral methanol exposure.

1.102 Various data have been considered by the COT including information on the effects of oral exposure to methanol in the diet and of occupational exposure via inhalation. Further discussion will take place in 2011 and a statement will be produced.

Para-occupational exposure to pesticides and health outcomes - systematic review of epidemiological literature

1.103 ‘Para-occupational exposure’ is the term given to exposures that result from living in the same household as a person who is occupationally exposed to a substance For example the wife of a farm worker might be exposed to pesticide contamination that he brought home from work on his person or clothes. It is different from the scenario in which people live in the vicinity of land where pesticides are applied (residential exposure).

1.104 On the 22nd September 2009 Members discussed a systematic review of epidemiological literature reporting health effects associated with para-occupational exposures to pesticides, herbicides, fungicides and insecticides. The COT requested an assessment of publication bias to assist them with their evaluation of the epidemiological data, and this was considered on 14th September 2010.

1.105 In parallel with this the COC has assessed possible associations of para-occupational and residential exposures to pesticides with the occurrence of cancers. The COT and COC will produce a joint statement on para-occupational exposure to pesticides in 2011.

Toxicogenomics in toxicology – design, analysis and statistical issues

1.106 The term toxicogenomics refers to applications in toxicology of genomics, proteomics and metabonomics. The Committees on Toxicology, Mutagenicity and Carcinogenicity jointly considered toxicogenomic tools in 2002 and 2004, and they were discussed again at 2009 COT Workshop[j,k,l].

1.107 On the 22nd of June 2010 the COT began reviewing further progress in the field, considering aspects of study design, and statistical approaches to this analysis of results. Papers will be presented at future meetings on topics such as applications in risk assessment, and a COT statement will be produced.

Waste And Resources Action Programme (WRAP)

1.108 In February Members discussed the two risk assessments carried out under the Waste And Resources Action Programme **(**WRAP) Confidence in Compost Programme. The draft risk assessments were on use of green composts in the Scottish livestock sector study and all composts in all agricultural sectors. The COT provided comments and observations on the two reports. These indicated a need for substantial modifications to the draft report, and the COT wished to see the final versions of the reports before agreeing its conclusions. The Advisory Committee on the Microbiological Safety of Food (ACMSF) were also considering these two risk assessments plus a further one which only dealt with microbiological risks. The ACMSF comments were finalised in the Autumn. WRAP have commissioned revised reports and it is expected that these will be available in 2011.

[j] http://cot.food.gov.uk/pdfs/JointCOT-COM-COCStatement.pdf
[k] http://cot.food.gov.uk/pdfs/cotstatementtoxicogen0410.pdf
[l] http://cot.food.gov.uk/pdfs/cotstatementwkshp200903.pdf

2010 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

CHAIRMAN

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Professor of Occupational & Environmental Medicine, University of Southampton

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Mr Derek Bodey MA (from 1st April 2010)
Public Interest Representative

Professor Alan Boobis BSc PhD CBiol FIBiol
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Professor Janet Cade BSc PhD (from 1st September 2010)
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Professor of Pharmacoepidemiology, University of Bath

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Dr Clifford Elcombe BSc PhD FBTS (up to 4th November 2010)
Co-founder and Research Director of CXR Biosciences,
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Dr John Foster BSc PhD FRCPath
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Professor Justin Konje MBBS MD MRCOG
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Head of Molecular Sciences Department, Leatherhead Food Research

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Professor Robert Smith BA MSc PhD (from 1st April 2010)
Public Interest Representative
Emeritus Professor, University of Huddersfield

Dr John Thompson BM BS BMedSc FRCP FBTS (from 1st April 2010)
Senior Lecturer in Clinical Pharmacology, Cardiff University
Director, National Poisons Information Service, Cardiff

Dr David Tuthill MB BCh MRCP MRCPCH (up to 23rd June 2010)
Consultant Paediatrician, Children's Hospital for Wales

Miss Alison Ward BA (up to 31st March 2010)
Public Interest Representative

Mrs Alma Williams OBE BA (Hons) (up to 31st March 2010)
Public Interest Representative

SECRETARIAT

Dr D Benford BSc(Hons) PhD	Scientific Secretary
Mrs J Shroff BA(Hons)	Administrative Secretary
Mr J Battershill BSc MSc	Scientific – HPA
Dr D Gott BSc(Hons) PhD	
Mr D Renshaw BSc EurBiol CBiol MIBiol	*(upto 22 October 2010)*
Ms C A Mulholland BSc(Hons)	
Dr C Baskaran BSc MSc PhD	*(from 1 November 2010)*
Dr D Key BSc(Hons) PhD	*(from 1 June 2010)*
Ms B Gadeberg BSc MSc	*(up to 12 April 2010)*
Mrs F Hill BSc	
Ms R Harrison BSc MSc	*(up to 16 July 2010)*
Dr N Thatcher BSc(Hons) PhD	
Mr T Chandler BSc(Hons) MSc	*(from 1July 2010)*
Mr B Maycock BSc(Hons) MSc	
Dr D Parker BSc(Hons) MSc PhD	
Mr G Welsh BSc(Hons)	
Miss T Gray BA(Hons)	
Miss J Murphy BA(Hons)	*(up to 22 October 2010)*

Declaration of COT members' interests during (2010) 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 OBE	Halifax Standard Life	Shareholder	Colt Foundation British Occupational Health Research Foundation Faculty of Occupational Medicine Public Health Commission	Trustee Trustee President and Trustee Member
Mr D Bodey (from 1st April 2010)	Centre for Alternative Technology Institute of Physics	Shareholder Membership		
Dr R Brimblecombe (from 1st September 2010)	Vertex Pharmaceuticals, Inc MVM Life Sciences Partnership LLP	Shareholder Advisor		

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) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) 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
Professor J Cade (from 1st September 2010)			Kellogg	PhD student

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 (upto 31st March 2010)	NONE	NONE	Schering AG Yamanouchi	Research Grant
Dr C Elcombe (upto 4th November 2010)	CXR Biosciences Ltd	Salaried Director Shareholder	Various Pharmaceutical and chemical companies	Contract Research at CXR
Dr J Foster	AstraZeneca	Shareholder	NONE	
Dr M Graham (from 1st September 2010)	AstraZeneca	Employee		
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	University of Florida University of Canberra The Forensic Institute Avipero	Consultant Consultant Shareholder Shareholder	Melville Trust Medical Research Scotland Office of the Scottish Charity Regulator Myriad Genetics	Trustee Trustee Board Member Research collaboration
Professor B Houston (from 1st April 2010)	Simcyp Xenotech SK Pfizer ISSX BPS BTS	Consultancies and Direct Employment Membership	GSK Pfizer Lilly Servier	Support by Industry

Professor J Konje				
Professor B Lake	Leatherhead Food Research (LFR)	Employee	British Toxicology Society Society of Toxicology Various Pharmaceutical, agrochemical and other companies	Member Member Contract research and consultancy at LFR
Dr G McNeill (upto 31st March 2010)	Smith & Nephew Diageo Café Direct BHP Biliton	Shareholder	Word 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		Xenobiotica British Toxicology Society Pfizer GlaxoSmithKline AstraZeneca	Associate Editor Member of Education sub-committee Research Funding
Dr D Ray (upto 31st March 2010)	University of Nottingham ZLB Behring (Switzerland) Astellas pharmaceuticals CEFIC ESAP	Employee Consultancy Consultancy Independent advisor		
Professor R Smith (from 1st April 2010)	Research Programme Advisor (Defra) Rodenticide Resistance Action Group	Consultancy Member	Student monitoring rodenticide resistance	Support by Industry - Research costs

Dr J Thompson (from 1st April 2010)	NONE		NONE	
Dr D Tuthill (upto 23rd June 2010)	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 (upto 31st March 2010)	NONE		Farm Animal Welfare Council	Member
Mrs A Williams (upto 31st March 2010)	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 2010, the Committee's work focussed the development of a new approach to publishing guidance on assessment strategies and genotoxicity tests. The Committee completed its review of thresholds for mutagens and produced a consultation document on a revised strategy for testing and mutagen assessment.

The Committee also undertook a further review of the utility of the GADD45a GFP genotoxicity assay and initiated reviews on the development and validation of a mutation assay using the PIG-A gene.

The Committee heard two presentations. Professor David Kirkland (COM Member) gave a presentation entitled '*Which mammalian cell tests best complement the Ames test in terms of detecting rodent carcinogens and in vivo genotoxins*.' Dr Nabil Hajii (Imperial College, London) gave a presentation on the '*Cytokinesis-block (CBMN) assay for the measurement and comparison of carcinogenic and in vivo genotoxicity potency estimates*.' Dr Andrew Olaharski (Roche) gave a presentation on the *GADD45a 'Green screen' assay*

The COM also advised on a biomonitoring study undertaken as part of the Government funded research on organophosphate pesticides. Horizon scanning was discussed at the October 2010 meeting.

Professor P B Farmer Chair
MA DPhil CChem FRSC

COM evaluations

Organophosphates

2.1 In 1999 the COT published a report on organophosphates (OPs) which considered whether prolonged or repeated low level exposure to OPs or acute exposures to OPs at levels sufficient to cause overt toxicity, can cause long-term adverse health effects. In the report, the COT had drawn conclusions from the available data and made recommendations for further research to address issues relating to potential chronic ill health such neuropyschiatric, neuropsychological effects and evidence for the occurrence of sheep dippers flu.' The research had been funded jointly by a number of Government Departments with the Veterinary Medicines Directorate taking a coordinating role. The COT has considered research projects as they have been published. The most recent consideration was in September 2009.

2.2 One study conducted as part of the Government funded research was project VM02301, which examined evidence for genotoxic effects of OPs exposure in horticultural workers. Part of this study had recently been published as: Atherton K *et al*., 2009. Biomarkers, 14 (7), 443 – 451. The overall project aims were to investigate whether there is a causal relationship between chronic OP exposure and DNA damage. The project reported results of a bio-monitoring investigation which aimed to address the hypothesis that OPs can cause DNA damage in humans following low-level chronic exposure. It was noted that the COM had previously undertaken detailed reviews of the published literature on the evidence for genotoxicity of pesticides in pesticide applicators and on the factors influencing the background incidence of genotoxicity biomarkers. These additional papers were also provided for members' information. Members were asked for their views on the recently published study by Atherton K *et al*., 2009.

2.3 The COM noted that exposed workers in southern Spain had been compared with University workers in the North East of England. Members questioned the suitability of the control group as there could be differences between the two comparison groups which could affect the COMET assay such as, exposure to UV light, physical exercise/manual work and exposure to other chemicals.

2.4 The study design as reported was insufficient to allow any conclusions to be reached regarding the results reported and association with exposure to pesticides.

Publication of COM Guidance Statements on assessment strategies and genotoxicity tests

2.5 The COM has a general remit to advise on important general principles or new scientific discoveries in connection with mutagenic and genotoxic hazards (the inherent property of the substance) or risk (the likelihood of mutagenic or genotoxic effects occurring after a given exposure) and to present recommendations for genotoxicity testing. The committee agreed that the proposed approach to publishing Guidance Statements allowed for the development of statements on individual genotoxicity tests and the overall testing strategy and components of the testing strategy. One particular advantage was that Guidance Statements could be rapidly updated in the light of new scientific developments. The COM would continue to publish individual statement on chemicals or referrals for Government Departments and Agencies as requested.

2.6 Further information on the new structure for guidance statements can be found at http://www.iacom.org.uk/guidstate/index.htm

Thresholds for *in vivo* mutagens

2.7 The general advice of the COM when considering the risk assessment of chemicals which are mutagenic *in vivo* has been that it is prudent to assume a non threshold dose response. Thus it is assumed that any exposure to an *in vivo* mutagen is associated with some damage to DNA and consequently an increased risk of mutation leading to an increased risk of adverse health effects albeit that this may be small. In such instances the Committee has recommended that exposures be reduced to a low as is reasonably practicable. The Committee has previously considered specific chemicals, on a case-by-case basis, with regard to deviations from its general approach to *in vivo* mutagens (see COM 2001 statement on risk assessment of *in vivo* mutagens http://www.iacom.org.uk/statements/COM01S3.htm).

2.8 The Committee considered draft guidance statements at its June and October meetings in 2009 and its March 2010 meeting.

2.9 The Committee agreed that evidence for a plausible threshold mode of action for genotoxicity was a prerequisite before conducting studies to identify threshold doses. Mutagenic effects that have been reported only at dose levels inducing a high level of toxicity or mortality should not be included in any evaluation for threshold dose levels, as the observed genotoxicity may not reflect a true mutagenic mode of action for the chemical under consideration. The biological significance of high dose positive *in vivo* mutagenic effects needs to be assessed on a case-by-case basis.

2.10 The COM reached the following conclusions.

(i) The COM reaffirmed the default position that for *in vivo* mutagens, in the absence of mechanistic data to infer a threshold, it is prudent to assume that there is no threshold for mutagenicity.

(ii) If there is good reason to consider that a threshold mode of action is appropriate, then it is necessary to investigate the biologically meaningful threshold for all genotoxic effects that have been reported.

(iii) An appropriate strategy should be devised for each chemical under consideration to identify threshold dose levels or NOELs for all potential thresholded modes of action of genotoxicity, which may include either *in vitro* or *in vivo* studies.

2.11 A copy of the link to the full statement is appended at the end of this annual report.

GADD45a GFP 'Green Screen' assay

2.12 At the COM meeting in October 2009, members evaluated reports on the development of the GADD45a-GFP genotoxicity assay. It was generally agreed that the assay may be useful as a high throughput pre-screening tool similar to QSAR using DEREK, but that it could not be used as part of a regulatory mutagenicity testing strategy at present. It was felt that further analysis of the low sensitivity reported by the study by Olaharski et al., 2009, (Mutation Research, 672, 10-16, 2009) for Roche proprietary compounds would provide a better understanding of the performance of this assay. Previously, members had noted the presentation of the data could have affected the reported results. The COM also noted that not all genotoxic substances are carcinogenic. Dr Olaharski (Roche) had provided a presentation on an analysis for the sensitivity, specificity and concordance of the GADD45a-GFP genotoxicity assay with *in vitro* genotoxicity and rodent carcinogenicity bioassay data for 91 Roche compounds. Out of the 91 compounds, 50 had been tested in a two year carcinogenicity assays, with 33 identified as rodent carcinogens and 17 as non-carcinogens. The reported sensitivity and specificity using the GADD45a-GFP 'GreenScreen HC' genotoxicity assay for genotoxicity (based on combined Ames and *in vitro* MN data) was 30% and 97% respectively (17/57 and 33/34) when a GFP induction of 1.5-fold was used as the criterion for a positive result. Its sensitivity and specificity for rodent carcinogenicity prediction was 30% and 80% respectively (10/33 and 15/17). The available data suggested a high concordance between laboratories indicating that the assay was both robust and reproducible.

2.13 Subsequently, Dr Olaharski agreed to make a presentation providing more detail regarding the genotoxicity data for the 41 proprietary Roche compounds that were used in the analysis. (An overview of the main points raised by Dr Olaharski can be found at http://www.iacom.org.uk/meetings/documents/COMminsMarch2010finalforinternet_000.pdf

2.14 Members concurred that Dr Olaharski had provided a valuable assessment of the 41 Roche proprietary compounds. However more information would be needed to assess the mode of action for the positive results in the *in vitro* genotoxicity assays conducted with these compounds (e.g. the degree of cytotoxicity in the MN assays).

2.15 Professor Walmsley (Genotrix Ltd) provided some additional analyses of the GADD45a 'Green Screen' assay data and in particular the 41 Roche proprietary compounds reported by Olaharski et al 2009. This was supplied as a manuscript to be submitted for publication entitled 'Interpretation of correlations between data sets from different *in vitro* genotoxicity tests.' In respect of the new data presented by Professor Walmsley, members commented that it was critical to assess the *in vitro* genotoxicity data on the 41 Roche compounds and in particular the mode of action for compounds with reported positive results in genotoxicity tests.

2.16 The COM also considered the paper by L Birrel *et al* (Mutation Research 695, 87 – 95, 2010) which assessed the 'Green Screen HC' assay results for a list of chemicals recommended by ECVAM. This study concluded that the GADD45a GFP 'Green Screen' assay demonstrated sensitivity for genotoxins comparable with other *in vitro* mammalian cell assays with a high specificity. This paper had been previously reviewed by the COM and members agreed that there were still only limited information regarding compounds which required exogenous metabolic activation.

2.17 The COM was also asked to consider a paper from the US EPA ToxCast programme by A Knight et al (Regulatory Toxicology and Pharmacology, 55, 188-199, 2009). This study was part of the US EPA ToxCast programme and reported data from three high-throughput screening (HTS) genotoxicity assays including the GADD45a GFP 'Green Screen' assays. Around 320 compounds with a large number of pesticides had been included in this initial part of this research programme. The sensitivity of the GADD45a GFP 'Green Screen' assay for a variety of end points including Ames positive, and rodent carcinogens was 11.6%-22.4% whilst specificity was reported to be 90-94.4%. Members noted that the GADD45a GFP 'Green Screen' assays had been conducted without exogenous metabolic activation. Thus, it was assumed that a proportion of the compounds that were negative in the 'Green Screen HC'

assay were pro-carcinogens that would require metabolic activation to produce a positive result in an *in vitro* genotoxicity test. This would reduce the sensitivity substantially. The authors of the ToxCast study also suggested the possibility that the limited concentration used (maximum test concentration of 200 µM) could have reduced the sensitivity. This research examined HTS assays in general and not the 'Green Screen HC' assay specifically and therefore may not have been sufficiently detailed to critically evaluate the performance of this assay.

2.18 Overall the committee agreed that the GADD45a-GFP genotoxicity assay was most suited as part of a battery of high throughput screening and noted it would still be useful in this respect even if sensitivity was low, as long as specificity was high.

In vivo PIG-A mutagenicity assay

2.19 The PIG-A gene codes for one subunit of a glycosylphosphatidyl inositol (GPI) anchor protein. Mutation of GPI (+) to GPI (-) results in loss of protein anchorage which can be evaluated using immunohistochemical approaches. The PIG-A assay has been shown to work in a number of experimental animals using a variety of blood cells and splenocytes. The method is easily adapted to flow cytometry approaches. It can potentially be used as an adjunct investigation in conventional rodent toxicology studies and could potentially be developed for use in biomonitoring investigations.

2.20 The potential role that this assay might play in a genotoxicity testing strategy needed to be better defined before further validation. There were already transgenic assays that also detected gene mutation *in vivo*, which had been extensively validated and could be used to assess mutagenicity in a wide range of tissues. Furthermore, the haematopoietic system was already a target tissue in the bone marrow MN *in vivo* assay. However, the *in vivo* PIG-A assay had potential to be an alternative to transgenic *in vivo* gene mutation assays in the future as it had the advantage of easy access; simpler method; a relative quick response time; and potentially could be used for more species and standard animal strains

2.21 The Committee was aware of a Health and Environmental Sciences Institute (HESI) presentation on the ongoing approaches to validation of the PIG-A assay
http://www.hesiglobal.org/files/public/2010%20Annual%20Meeting/Presentations/IVGT_Sessioin/1_jkim_intro.pdf

2.22 The PIG-A assay was an *in vivo* mutation assay using easily accessible sampling of blood which might potentially be incorporated into routine

toxicology studies. Participants in the HESI validation study were initially investigating the dynamics of PIG-A response with known *in vivo* mutagens. There was evidence to suggest that the mutagenic response in the assay accumulated with repeated exposure to *in vivo* mutagens and that inter-laboratory response was good. A number of participants in the HESI project were considering investigation of PIG-A response in the liver and gastrointestinal tract. One possible approach would be to undertake immunohistochemistry of tissue slices.

2.23 Members agreed there were many aspects of the PIG-A assay which needed investigation including identification of the optimum GPI-linked protein to use and the need for confirmatory DNA sequencing to confirm mutations.

2.24 Overall members felt that the PIG-A mutagenicity assay was an interesting development in genotoxicity testing, but that further work would be required before validation and there was a need to identify its role within a genotoxicity testing strategy.

Presentations to COM

'*Which mammalian cell tests best complement the Ames test in terms of detecting rodent carcinogens and in vivo genotoxins*.'
Professor David Kirkland (COM Member)

2.25 Professor Kirkland had provided a short paper for the March 2010 meeting entitled 'Is an *in vitro* battery of Ames plus micronucleus sufficient?' Subsequently, Professor Kirkland agreed to make a presentation to the COM to update the committee with additional analyses of rodent carcinogens and *in vivo* genotoxins.

2.26 Professor Kirkland outlined that most genotoxicity test guidelines recommended three *in vitro* genotoxicity tests i.e. gene mutations in bacteria; a test for induction of gene mutations in mammalian cells (usually the mouse lymphoma assay (MLA); and chromosomal aberration (CA) or micronucleus test.

2.27 It was agreed in various genotoxicity guidelines that there was a requirement for bacterial and mammalian tests and that the endpoints of gene mutation; chromosomal damage; and aneuploidy needed to be investigated. However, Professor Kirkland examined whether two mammalian cell tests were necessary to achieve this aim i.e. whether both bacterial and mammalian cell tests were required to investigate the endpoint of gene mutation. It was

suggested that the *in vitro* micronucleus test (MNvit) included in a test battery would be sufficient to detect both chromosomal aberrations and aneuploidy.

2.28 Published carcinogenicity data were analysed to address two questions: 1) Are there Ames negative rodent carcinogens that are not positive in the mouse lymphoma assay (MLA) that are not detected in the MNvit or CA assays?; and
2) Are there rodent carcinogens that are not detected in either Ames or MNvit, but might be uniquely positive in the MLA?

2.29 These two questions were addressed using a database of 756 rodent carcinogens and 461 *in vivo* genotoxins. A detailed paper summarising the evaluation has been published on the COM internet site http://www.iacom.org.uk/papers/documents/POSTMTGNOTEKirklandRevisedproposalfor2testbatterymut201014_000.pdf

2.30 Professor Kirkland reached a number of conclusions.

(i) From the available data, no genotoxic rodent carcinogens would be "missed" by using an *in vitro* battery consisting of Ames and *in vitro* micronucleus tests.

(ii) Thus, a 2-test battery consisting of Ames + MNvit is comparable to a 3-test battery consisting of Ames + MLA + MNvit in terms of detecting genotoxic rodent carcinogens as positive.

(iii) There is no notable advantage achieved by adding MLA to a battery consisting of Ames + MNvit. Based on the above analysis there are no examples of *in vivo* genotoxins for which it is essential to include the MLA in addition to Ames plus MNvit in order to detect genotoxic potential.

(iv) Thus, a 2-test battery consisting of Ames + MNvit is comparable to a 3-test battery consisting of Ames + MLA + MNvit in terms of detecting *in vivo* genotoxins as positive. There is no notable advantage achieved by adding MLA to a battery consisting of Ames + MNvit.

Cytokinesis-block (CBMN) assay for the measurement and comparison of carcinogenic and in vivo genotoxicity potency estimates.'

2.31 Dr Nabil Hajji from Imperial College, London gave a presentation on developing a generic approach to ranking *in vivo* mutagens where there is no carcinogenicity data. An approach using only a single end point from an *in vivo* genotoxicity test was suggested to be preferable as this would be relatively simple and readily comparable. An approach to ranking *in vivo* mutagens, which did not have carcinogenicity data, using the lowest effective dose (LED) had already been developed by Sanner and Dybing 2005 (Basic & Clinical Pharmacology & Toxicology 2005,96, 131 – 139)**).**

2.32 Dr Hajji had identified three potentially useful database sources. A published evaluation of the rodent MN tests undertaken as part of the US EPA Gene Tox program during the 1980s and 1990s was suggested as a useful source of information. Under this program, 506 chemicals had been assessed, but not all the current data were available in the public domain or readily accessible for the derivation of LED values. Another potentially useful data source was the 6th Collaborative Study Group on the Micronucleus Test (CSGMT) available from the Japanese Environmental Mutagen Society (JMS). This identified approximately 100 mouse MN assays predominantly undertaken by using the intraperitoneal dosing. A third suggested data source was the International Programme on Chemical Safety (IPCS) INCHEM database.

2.33 It was proposed that the data sources would be used to obtain *in vivo* genotoxicity potency estimates such as the LED or the Benchmark Dose (BMD) (i.e. where there were at least 3 dose-response data points). These could then be compared with available carcinogenicity potency estimates such as the TD50 (the chronic daily dose that will give rise to 50% of the test animals having tumours above background at a specific site).

2.34 The Committee recommended that Dr Hajji contact other research groups who were already undertaking similar work and that it may be useful to liaise with them. For example, RIVM and ILSI/HESI Members noted that the ILSI/HESI group were looking at extrapolating from *in vitro* genotoxicity potency to *in vivo* potency. Whereas the RIVM group, were considered to be mainly looking at *in vivo* data for prioritising mutagens and to examine what could be learned about carcinogenic potential without carcinogenicity data.

2.35 The committee agreed that where possible, the use of BMD would be preferable to the LED, and that it would be important to define the biologically significant response level e.g. 1% or 10% above the control response

Horizon Scanning

2.36 A horizon scanning exercise is conducted every year, where new and emerging topics in the field of genotoxicity are identified that may require review. The horizon scanning process provides an opportunity for members and advisors from Government Departments and regulatory agencies to suggest topics for further work. This year, most of the committee's work had involved updating the current COM guidance and resources had not been available to undertake all of the projects identified in the 2009 horizon scanning exercise. Some topics raised during the 2009 horizon scanning exercise were considered as part of the drafting of the revised genotoxicity testing strategy and generation of new guidance documents. These included:

- Does the mouse lymphoma assay detect aneugens?
- Which mammalian cell test best complements the Ames test in terms of detecting rodent carcinogens and *in vivo* genotoxins?
- An evaluation of the GADD45a-GFP 'GreenScreen HC' genotoxicity assay.

2.37 Additionally, the COM agreed a format for separating the guidance into separate statements. Progress was also made on consideration of the validation of the mutation assay using the PIG-A gene. A review of expanded simple tandem repeat (ESTR) mutation had been initiated, but not completed.

2.38 Topics not addressed in 2010 included a review of the mutagenicity of nanomaterials; mutational spectra in the investigation of chemical mutagenesis; the role of epigenetics in mutagenesis; and mitochondrial mutagenesis. The genotoxicity of nanomaterials was suggested as a priority topic. The Chair noted that the secretariat would have to complete a review of the significance of chemical induced mutation for human health and a review of genotoxicity testing of impurities which had been identified as priorities during the consideration of a revised strategy for testing for genotoxicity.

2.39 The committee was also informed that some funding was available to the HPA for research projects relevant to public health. This included initial funding for a one year project of around 25K as well as larger two to three year projects of up to a maximum of 250K per year. There was also scope to fund PhD's. Members were asked for suggestions for suitable projects which could also involve collaborative work between different organisations.

2.40 Some initial suggestions included research into low dose genotoxicity effects compared with higher doses; non-DNA targets; systems biology approach to key gene suppression and expression; and the sequencing of whole genomes for different cancers.

Ongoing work

Consultation on a strategy for genotoxicity testing and mutagenic Hazard assessment of chemical substances

2.41 The draft paper on Guidance on a strategy for Genotoxicity testing and mutagenic hazard assessment of chemical substances was issued for consultation in early December 2010, together with associated diagrams and a copy of the consultation list. These are available on the Publications page of the COM internet site. Comments were invited by 12th February 2011. The finalisation of COM guidance on a strategy for testing and assessment of

mutagenicity of chemical substances will be a major item for completion during 2011.

Published Statement
http://www.iacom.org.uk/guidstate/documents/Thresholdsforinternetfinal.pdf

2010 Membership of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment

CHAIR

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Dr Elizabeth M Parry BSc DPhil
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Professor David H Phillips BA PhD DSc FRCPath
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SECRETARIAT

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

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

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Prof P B Farmer (Chairman)	Santander Foreign & Colonial Friends Provident Tototrak ILSI HESI EFSA	Shareholder Shareholder Shareholder Shareholder Committee Member Member of Scientific Panel	Van Geest Foundation	Research support
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 B M Elliott	Syngenta AstraZeneca Elliott GT Ltd Regulatory Science Associates	Pension & Shareholder Shareholder Director Associate	NONE	NONE
Dr D Gatehouse	GlaxoSmithKline	Pension Share Option Holder Shareholder	NONE	NONE
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr G Jenkins	NONE	NONE	Hoffman-LaRoche Unilever Hoffman-LaRoche CEFIC/ECETOC	Research Grant 2008 – 2010 Consultancy 2008 Honorarium 2008
Dr D Kirkland	Kirkland Consulting	Principal	NONE	NONE

Dr D P Lovell	National Grid Plc Pfizer	Shareholder Pension	AstraZeneca National Grid Plc	Spouse is Shareholder
Dr A Lynch	GlaxoSmithKline	Salary & Shareholder	NONE	NONE
Dr E M Parry	F & C M & S Compass BP	Shareholder Shareholder Shareholder Shareholder	NONE	NONE
Prof D H Phillips	Aviva Banco Santander BG Group Bradford & Bingley Centrica National Grid	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder	AstraZeneca	Research Support

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 2010, the Committee again considered a varied range of items. For example, advice was provided to the Health and Safety Executive on the carcinogenicity of the pesticide dichlorvos, and we heard an interesting presentation of work on carbon nanotubes, which is of relevance to assessing their carcinogenicity. We also began a review of the way in which our guidance on the risk assessment of carcinogens is presented and this topic is likely to occupy much of the Committee's time over the next two years. I am grateful to the members of the Committee for their input on these and the other topics considered and to the secretariat for the continued provision of high quality papers.

During the year, we were informed by the Departmental of Health that, by March 2012, the COC will no longer be an advisory Non-Departmental Public Body reporting jointly to the Chief Medical Officer and the Chairman of the Food Standards Agency but would be reconstituted by the Department of Health as a Departmental Expert Committee reporting through Departmental officials. I have been assured that the Committee will retain its independence and, indeed, it is essential that this continues to be the case.

Professor David H Phillips
BA PhD DSc FRCPath

COC evaluations

Carcinogenicity of mixtures

3.1 In 2010, the COC concluded its consideration of the carcinogenicity of mixtures. "Mixtures" was defined as combined exposure to more than one carcinogen, or to a carcinogen and other chemical(s) with potentially modifying effects, either simultaneously or at different times. The purpose of the review was to examine the data in the scientific literature on this topic, with a view to providing advice on the potential carcinogenic action of these combined exposures and on methods for testing and assessment of such effects.

3.2 This proved to be a large and difficult topic with a lack of experimental data from which to draw conclusions. The Committee concluded that it is not possible for the risk assessment process to account for the combined action of every possible mixture of carcinogens at all possible levels of exposures over all possible time frames. Nevertheless, Members considered that some general principles could be stated as follows:

(i) Mixtures of chemicals which act via the same Mode of Action (MOA) and which do not react chemically with one another, such as polychlorinated dibenzo-*p*-dioxins, can be assessed using the concept of dose additivity and relative potency factors/toxic equivalency factors.

(ii) Although there may be a substantial margin between exposure to a carcinogen and either its no observed adverse effect level (in the case of a non genotoxic carcinogen) or another point of departure (in the case of a genotoxic carcinogen), it is possible that simultaneous exposure to two carcinogens which have the same MOA may result in a lower margin of exposure. Risk assessors should be alert to this possibility when assessing a chemical which commonly occurs together with one or more other chemicals which have the potential to cause cancer.

(iii) There are several stages in the carcinogenic process at which carcinogens might interact, for example: ADME processes, DNA adduction, mutagenicity, early preneoplastic changes, proliferation, apoptosis and neoplastic transformation. MOA analysis may be of value here, in determining critical steps at which interaction might be anticipated. Potential interactions in genotoxic MOAs have been addressed in a statement by the COM.

(iv) It is postulated that otherwise non-carcinogenic chemicals, such as anti-apoptotic chemicals or chemicals which interfere with cell cycle

regulation, which alter ADME processes or which increase permeability of the skin or oral mucosa, might have the potential to interact synergistically with known carcinogens.

(v) The assessment of potential interactions in the context of carcinogenicity is complex due to the multistage nature of the process. However, we do not advocate standard carcinogenicity studies on mixtures of chemicals except in exceptional circumstances. Such studies would be costly and would require ethical consideration in view of the high number of animals required.

(vi) *In vitro* studies of interactions should be hypothesis driven, attempt to characterize the dose-response and use models relevant to *in vivo* carcinogenicity. These studies should adhere to the criteria laid out in Borgert et al (2001). Models used to evaluate the synergistic interactions between PAHs and between HCAs were, in general, complex and may not truly reflect the situation for carcinogenesis. Thus extrapolation of results for risk assessment in humans is difficult.

(vii) Overall*, in vitro* studies can be used to confirm molecular targets or provide insight into MOA identification but are not of value for the evaluation of relative potencies of chemicals or interactions at environmentally relevant exposure levels.

(viii) In terms of the risk assessment of potential interactive effects of carcinogens, exposure to a non-genotoxic carcinogen at or below the no-effect level for the critical effect contributing to the interaction is unlikely to result in an interaction with a chemical which has a different MOA. In the case of genotoxic carcinogens, in principle, effects could occur at any level of exposure which could lead to interaction. This supports the view that exposure to genotoxic carcinogens should be as low as reasonably practicable.

3.3 The COC statement can be found at http://www.iacoc.org.uk/statements/index.htm#I

Horizon scanning

3.4 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 2010 exercise. From these and Committee members’

own proposals, the COC decided that the following items should be taken forward:

- The role of epigenetics in cancer
- New developments in the Mode of Action framework
- Alternative test strategies to conducting a 2-year rat bioassay
- COC/COM joint meeting on thresholds of genotoxicity
- Endogenous DNA adducts
- The cancer risk of exposure to environmental tobacco smoke in childhood
- Dose-response modelling in epidemiology studies
- The use of Zebrafish in mechanistic studies
- Common strain specific tumour types

3.5 The Committee confirmed that it wished to discuss the output of the workshop held by the International Life Sciences Institute Health and Environmental Sciences Institute on Intermittent/Short-Term Exposure to Carcinogens held in December 2009 when the final report was available and would then decide whether to pursue this topic further.

3.6 Also, the Committee decided that it should consider updating existing COC statements on specific topics if new data had become available, as resources permit.

Ongoing topics

Interaction between genotype and chemicals in the environment on the induction of cancer in risk assessment

3.7 The COC has considered previously the question of whether the genetic code for individuals (genotype) is important in determining the risk of cancer from exposure to chemicals. The Committee concluded in a 2002 statement that the data then available provided no evidence of a consistent or strong interaction between the genotype of an individual and chemical induced cancer. However, it could not discount the possibility that important interactions might be discovered in the future. It added that it was important to keep this subject under review, particularly in the light of developments expected from the Environmental Genome Project and other intiatives.

3.8 At its July meeting, the COC considered a scoping paper which reported ongoing activity in the area of genomics, environmental exposure assessment and gene-environment interaction (GEI). It included details of the relevant genomic projects and noted that, since establishment of the Human Genome Epidemiology Network (HuGEnet), 25 reviews/meta-analyses have been

published which discuss the association of particular gene variants and cancer, including data on interactions among genes and environmental exposures. The paper also discussed the advent of Genome-Wide Association Studies (GWAS). These are non-hypothesis driven studies that examine genetic variation across a given genome and relate these variants to disease. It was suggested these studies could be discussed separately from other GEI studies, where specific genetic changes are examined and a priori hypotheses should be tested. The Committee decided that, while it may be inappropriate for it to make recommendations on the conduct of GWAS studies, it should have an opinion on their interpretation, in order to provide advice to Government departments and agencies on how to evaluate these studies as part of a weight of evidence.

3.9 Since the topic is broad, Members decided that further discussions should focus on determining to what extent concerns expressed in the previous COC statement have been resolved. It was agreed that the next step should be to compare, for a specific endpoint, GWAS studies and good quality studies investigating specific GEIs. As there are several studies of both types on the bladder, this was selected as the endpoint.

3.10 It was also proposed that other areas for further review might include the metrics used to assess exposure; studies assessing known rodent genetic variants that are similar to humans; and any HuGENet reviews that are within the Committee's terms of reference, paying particular attention to those where there is robust exposure information.

The carcinogenicity of carbon nanotubes

3.11 Carbon nanotubes (CNT) are rolled up sheets of carbon atoms only one-atom thick which are densely packed in a honeycomb crystal lattice. They are extremely strong, biopersistent materials which have good thermal and electrical conductivity. The COC considered an overview of nanomaterial toxicology in 2005 and discussed whether, because of their essentially fibrous structure, they might have carcinogenic potential analogous to asbestos. Subsequently, one study had provided evidence that CNT may cause asbestos like pathology when injected into the abdominal cavity of mice. However, the COC had noted that there was some debate about the validity of models used in such studies and had asked to hear a presentation on the subject. At the July meeting, the COT heard a presentation from Professor Ken Donaldson of Edinburgh University on his work on CNT.

3.12 Professor Donaldson initially discussed the potential mechanisms of asbestos carcinogenicity. He went on to describe his work on long nanotubes, which employed direct injection into the pleural cavity as this was considered a more

physiologically relevant route of exposure than injection into the abdominal cavity.

3.13 Following the presentation, the Committee discussed a number of issues with Professor Donaldson including the risk assessment of nanomaterials. It was noted that, at present, they are assessed by existing standard risk assessment methods in Europe. Nanotubes may form part of a variety of products, such as sports racquets, bike frames, display screens and may be used to strengthen cloth. There should be limited potential for exposure during normal use of many of these products, but it is possible.

3.14 The Committee discussed how best to take this issue forward but decided that a thorough review of the available literature on nanotube carcinogenicity might be unfeasibly large. Instead, the Committee will review the relatively small number of papers reporting bioassays.

Dichlorvos

3.15 Dichlorvos (2,2-dichlorovinyl dimethyl phosphate) is an insecticide acting by acetylcholinesterase inhibition. The genotoxicity and carcinogenicity of dichlorvos were evaluated by the COM, with coopted COC members, in 2002. Since then, evaluations of dichlorvos have been performed by the US Environmental Protection Agency (EPA) and the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR) of the European Food Safety Authority (EFSA) and there are some differences between the three groups in the conclusions on carcinogenicity.

3.16 At the November meeting, the Health and Safety Executive (HSE) sought the view of the COC as to whether a threshold could be assumed for the carcinogenicity of dichlorvos. The advice was to be used in formulating a position for the ongoing EU discussions on the use of dichlorvos as a biocide.

3.17 The COC heard a presentation from representatives of AMVAC Chemical Company on a possible MOA for forestomach tumours seen in a US National Toxicology Programe (NTP) gavage study in the mouse. This proposed that there is an interaction between dichlorvos and the corn oil vehicle used in the study. It was noted that there was no evidence of carcinogenicity by other routes of administration. It was also proposed that there is a threshold for tumour induction when dichlorvos is administered in corn oil.

3.18 Members agreed that there seems to be some interaction between corn oil and the test chemical, so it was plausible that the vehicle has some influence on the results of the NTP study and that dichlorvos could cause cancer through a threshold based mechanism. However, there were not sufficient data to

support the proposed MOA. The uncertainties in this case meant that the weight of evidence that dichlorvos was a potential human carcinogen was not strong. Nevertheless, the Committee's position on the risk assessment of carcinogens is that there needs to be clear evidence of a mode of action for tumour formation before it can move away from the default non-threshold assumption for substances that are genotoxic and carcinogenic. The Committee considered that the evidence was insufficient in this case and that, therefore, exposure should be as low as reasonably practicable (ALARP).

Systematic review of the epidemiological literature on para-occupational exposure to pesticides and cancer

3.19 In 2005, the Royal Commission on Environmental Pollution (RCEP) published a report on crop spraying and the health of residents and bystanders. This recommended a "…systematic review of the literature on pesticide spraying and human health…" The COT and COC commented on the RCEP report at the request of the Department for Environment Food and Rural Affairs and the Advisory Committee on Pesticides and published a joint statement in 2006. In this, the COT agreed that an epidemiological review of paraoccupational exposure to pesticides should be undertaken. The COC was therefore asked to review the relevant epidemiological literature on cancer.

3.20 In 2010, the COC considered a systematic review of the relevant literature which included a detailed meta-analysis of the available case-control studies. A number of different cancer types and exposure scenarios were reported in the case-control studies, which made comparison of these papers difficult in meta-analysis A meta-analysis was also performed for a small group of studies reporting on 'haematopoietic cancers' in children.

3.21 After reviewing the available data and analyses, the Committee considered that there was limited evidence for a weak positive association with maternal para-occupational exposure to pesticides and childhood leukaemia. There was insufficient evidence to determine whether this is causal, nor the likely candidate pesticides.

3.22 The COC noted that, although beyond the scope of the present review, studies investigating occupational exposure to pesticides, where exposure would be higher and better characterised, would be of great benefit in interpreting the significance of the weak effect suggested by this meta analysis. However, one Member noted that even the occupational studies suffered from poor exposure assessment.

3.23 A detailed statement is expected in 2011.

Guidance statements

3.24 During 2010, the COC adopted a proposal to change the way in which technical guidance on the risk assessment of carcinogens is presented on the COC website. At present, guidance is presented in a stand-alone booklet and is also spread throughout minutes and certain statements. The drawbacks of this approach are that valuable advice can be difficult to access and it is not always apparent when it is out of date. Furthermore, it can be time-consuming to reach a consensus on complex and comprehensive guidance booklets and specific elements of the guidance may soon become out of date; these elements will remain out-of-date until the next opportunity arose to review and revise the entire document. The proposed changes aim to improve accessibility of up-to-date advice, ease timely review, and make it easier to reference specific parts of COC guidance.

3.25 The new system will comprise an overarching statement which will provide an 'executive summary' of the advice, and a series of guidance statements on specific aspects of the risk assessment of carcinogens. The overarching statement will undergo regular updates as each detailed guidance statement is revised to reflect the best available scientific practice as it evolves. The Committee recognises that there will be a need to identify old versions of statements which have been updated and these may be kept in an archive. It also recognises that, currently, it provides no advice on the interpretation of epidemiology studies, and how these contribute to the weight of evidence in a carcinogenicity risk assessment, and intends to include such advice in one of the guidance statements.

2010 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
Consultant Pathologist and Honorary Senior Lecturer Department of Cancer Studies & Molecular Medicine, University of Leicester

Ms Denise M Howel BSc MSc CStat FIS
Senior Lecturer in Epidemiological Statistics, Institute of Health and Society, Newcastle University

Dr David P Lovell PhD BSc (Hons) FSS FIBiol CStat CBiol
Reader in Medical Statistics, Division of Medical Sciences, St George's, University of London

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

Dr Christopher J Powell BSc MSc PhD Dip RC Path MRC Path FRC Path FBTS
European Registered Toxicologist, Director Non-clinical Development Europe, GlaxoSmithKline

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
Team Leader in General Toxicology Sciences, Therapy Area Toxicologist for Infection Therapy Area, Project Team Representative, AstraZeneca

SECRETARIAT

Ms F Pollitt MA DipRCPath	Joint Scientific Secretary – Health Protection Agency
Dr D Benford BSc PhD	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
(an up-to-date version can be found on the COC website)

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	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder	AstraZeneca	Research Support
Dr C Allen	NONE	NONE	NONE	NONE
Professor A Boobis OBE	BanK Santander SA Barclays Bank BG Group BT Group Centrica Iberdrola SA National Grid Lloyds Endura Fine Chemicals	Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Shareholder Consultancy	GlaxoSmithKlin FSA DoH HPA Commission of the EU (FP6) Medical Research Council CEFIC - LRI ESRC PhD Elsevier JMPR JECFA (vet drugs) EFSA PPR Panel (Panel on Plant Protection Products & their Residues) EFSA CONTAM Panel (Panel on chemical contaminants in the food chain) ECETOC Task Force on Guidance for Classification of Carcinogens under GHS EFSA Scientific Committee	Research Support Studentship Editor-in-Chief Food & Chemical Toxicology Member Member of

			Working Group on Risk-Benefit Assessment EFSA Scientific Committee Working Group on the Benchmark Dose ILSI HESI, ILSI Europe & ILSI Research Foundation Working Groups on generic risk assessment issues	 Unpaid member of Board of Trustees
Dr P Carthew	Unilever	Salary	Gwathmey(USA)	Consultant
Professor P B Farmer	Santander Foreign & Colonial Friends Provident Tototrak ILSI HESI EFSA	Shareholder Shareholder Shareholder Shareholder Committee Member Member of Scientific Panel	Van Geest Foundation	Research support
Mrs R Glazebrook	BT Group Lloyds TSB National Grid	Shareholder Shareholder Shareholder	NONE	NONE
Dr P Greaves	Actelion Pharmaceuticals Ltd (Switzerland) Astellas Pharma AstraZeneca INEOS Healthcare Nono Nordisk (Denmark) Pfizer Shire Pharmaceutical Synosia Therapeutics (USA) Teva Pharmaceuticals (Israel)	Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant Consultant		
Ms D Howel	NONE	NONE	NONE	NONE
Dr D Lovell	National Grid Plc Pfizer	Shareholder Share Options & Pension	AstraZeneca National Grid Plc	Spouse is shareholder
Dr C Powell	GlaxoSmithKline	Salary & Shareholder		
Dr P Vineis	NONE	NONE	NONE	NONE

Dr N Wallis	Pfizer	Salary & Shareholder	NONE	NONE
Dr L Wright	AstraZeneca	Salary & 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, Innovation & Skills
Department of Transport, Local Government and the Regions
Health and Safety Executive
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 and Healthcare products Regulatory Agency;

   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[13]

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.
- follow the Seven Principles of Public Life set out by the Committee on Standards in Public Life[14];

[13] 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

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

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.

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[15]
- 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.

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.

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

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)

Declaration of Members' Interests

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.

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 [16] 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.

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.

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

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."*[17] 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[18] 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.

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

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

[18] 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.

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

(iii) 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 to be brought.

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[19] 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

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

considerations include 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. In the financial year 2009/10 the budget for the COT, excluding Secretariat resources was £80,000.00. Costs were met by the Food Standards Agency (FSA).

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 the 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*[20] 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*[21] (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*[22] 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[23]
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[24]

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

Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment[25]
Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment[26]
Scientific Advisory Committee on Nutrition[27]
Spongiform Encephalopathy Advisory Committee[28]

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

[24] Joint FSA/HPA Secretariat, HPA lead
[25] Joint FSA/HPA Secretariat, HPA lead
[26] Joint FSA/HPA, FSA lead
[27] Joint FSA/DH Secretariat
[28] Joint Defra/FSA/DH Secretariat

external/additional scientific experts who may know of relevant unpublished or pre-publication data.

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[29].

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.

[29] 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).

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

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 bodyweight 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.

ARfD: see Acute reference dose

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 or plant (literally “in glass”).

***In vivo**:* A Latin term used to describe effects in living animals or plants (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.

LC_{50}: The theoretical lethal concentration for 50% of a group of organisms

LD_{50}: 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.

LOAEL: Lowest observed adverse effect level. The lowest administered dose at which an adverse effect has been observed.

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.

µg: Microgram

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.

NOAEL: No observed adverse effect level. 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

Safener: A substance which reduces or eliminates the phytotoxic effects of a plant protection product on certain plant species.

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 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 $\rightarrow$ carcinoma sequence in the large bowel in humans, and the papilloma $\rightarrow$ 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

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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[++]

2009 Annual Report of Committees on Toxicity, Mutagenicity and Carcinogenicity of Chemicals in Food, Consumer Products and the Environment. Food Standards Agency/Department of Health, July 2010[++]

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.

Guidelines for the Preparation of Summaries of Data on Chemicals in Food, Consumer Products and the Environment submitted to DHSS Report on Health and Social Subjects 30 HMSO ISBN 0 11 321063 9 Price £2.70.

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